THE STATE OF SOUTH CAROLINA
In The Supreme Court

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APPEAL FROM SPARTANBURG COUNTY
Court of Common Pleas

Roger L. Couch, Circuit Court Judge

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Case No. 2007-CP-42-1438

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State of South Carolina ex. rel. Alan Wilson in his capacity as Attorney General of the State of South Carolina, ..... Respondent,

v.

Ortho-McNeill-Janssen Pharmaceuticals, Inc., f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P., and Johnson & Johnson, Inc., ..... Defendants.

Of whom Ortho-McNeill-Janssen Pharmaceuticals, Inc. is ..... Appellant.

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# RECORD ON APPEAL - VOLUME XIX

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**VII. CERTIFICATE OF COUNSEL**

| | | |
|---|---|---|
| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | ) | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | ) | Civil Action No. 2007-CP-42-1438<br><br>**DEFENDANTS' OFFER OF PROOF FOR THE POST-2007 FDA-APPROVED PACKAGE INSERT FOR ZYPREXA AND THE 2010 FDA-APPROVED PACKAGE INSERT FOR LATUDA** |

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby submit this Offer of Proof in response to the Court's Order of March 7, 2011 and pursuant to South Carolina Rule of Evidence 103. The Court's Order excluded post-2004 evidence relating to weight gain, diabetes, and other metabolic risks associated with Risperdal® and other atypical antipsychotics. If Defendants had been allowed to offer post-2004 evidence related to weight gain, diabetes, and other metabolic risks associated with atypical antipsychotics, Defendants would have offered evidence that the U.S. Food and Drug Administration ("FDA") has acknowledged there are differences in the diabetes-related side effects associated with the various atypical antipsychotics. Specifically, Defendants would have offered evidence that the FDA has required Eli Lilly & Co., Inc., which manufactures Zyprexa®,

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and Sunovion Pharmaceuticals Inc., which manufactures Latuda®, to add language to the warning sections of their package inserts acknowledging these differences.

**The Zyprexa Package Insert**

In 2007, the FDA required Eli Lilly to add a stronger diabetes-related warning to the Zyprexa package insert. Specifically, the Warnings and Precautions section of the post-2007 Zyprexa label provides:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. **While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.**

D4011 at 8 (2009 Zyprexa Package Insert) (emphasis added), attached as Ex. A.

**The Latuda Package Insert**

Similarly, in October 2010, when the FDA approved a new atypical antipsychotic, Latuda, the FDA required Sunovion to include language in the Warnings and Precautions section of the Latuda label that recognized the differences in the metabolic-related side effects associated with the various atypical antipsychotics:

> Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. **While all of the drugs in the class have been**

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**shown to produce some metabolic changes, each drug has its own specific risk profile.**

D6367 at 5 (2010 Latuda Package Insert) (emphasis added), attached as Ex. B.

Respectfully submitted,

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March 21, 2011.

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# EXHIBIT A

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use ZYPREXA safely and effectively. See full prescribing information for ZYPREXA.**

**ZYPREXA (olanzapine) Tablet for Oral use**
**ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use**
**ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use**

**Initial U.S. Approval: 1996**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

***See full prescribing information for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 5.14, 17.2)**
- **When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## RECENT MAJOR CHANGES

| | |
|---|---|
| Indications and Usage: | |
| Schizophrenia (1.1) | MM/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (1.2) | MM/2009 |
| Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder (1.3) | MM/2009 |
| ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania (1.4) | MM/2009 |
| Indications and Usage, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (1.5) | 03/2009 |
| Treatment Resistant Depression (1.6) | 03/2009 |
| Dosage and Administration: | |
| Schizophrenia (2.1) | MM/2009 |
| Bipolar I Disorder (Manic or Mixed Episodes) (2.2) | MM/2009 |
| Dosage and Administration, *ZYPREXA and Fluoxetine in Combination:* | |
| Depressive Episodes Associated with Bipolar I Disorder (2.5) | 03/2009 |
| Treatment Resistant Depression (2.6) | 03/2009 |
| Warnings and Precautions: | |
| Hyperglycemia (5.4) | 03/2009 |
| Hyperlipidemia (5.5) | 03/2009 |
| Weight Gain (5.6) | 03/2009 |
| Leukopenia, Neutropenia, and Agranulocytosis (5.9) | 08/2009 |
| Use in Patients with Concomitant Illness (5.14) | 03/2009 |
| Hyperprolactinemia (5.15) | 03/2009 |
| Use in Combination with Fluoxetine, Lithium, or Valproate (5.16) | 03/2009 |
| Laboratory Tests (5.17) | 03/2009 |

## INDICATIONS AND USAGE

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

*As oral formulation for the:*

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and hyperlipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

*As ZYPREXA IntraMuscular for the:*

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

*As ZYPREXA and Fluoxetine in Combination for the:*

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.
- Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode). (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

## DOSAGE AND ADMINISTRATION

| | |
|---|---|
| Schizophrenia in adults (2.1) | Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days |
| Schizophrenia in adolescents (2.1) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) in adults (2.2) | Oral: Start at 10 or 15 mg once daily |
| Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2) | Oral: Start at 10 mg once daily |
| Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) | IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart) |
| Depressive Episodes associated with Bipolar I Disorder in adults (2.5) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Treatment Resistant Depression in adults (2.6) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

*ZYPREXA and Fluoxetine in Combination:*

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated. (2.5, 2.6)

## DOSAGE FORMS AND STRENGTHS

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg (3)

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- Intramuscular Injection: 10 mg vial (3)

## CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

## WARNINGS AND PRECAUTIONS

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Hyperglycemia:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.4)
- *Hyperlipidemia:* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.5)
- *Weight Gain:* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.6)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.7)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.8)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

## ADVERSE REACTIONS

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

*Oral Olanzapine Monotherapy:*

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity (6.1)

*Combination of ZYPREXA and Lithium or Valproate:*

- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia (6.1)

*ZYPREXA and Fluoxetine in Combination:* Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

*ZYPREXA IntraMuscular for Injection:*

- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

## DRUG INTERACTIONS

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination:* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

## USE IN SPECIFIC POPULATIONS

- *Pregnancy:* ZYPREXA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)
- *Nursing Mothers:* Breast-feeding is not recommended. (8.3)
- *Pediatric Use:* Safety and effectiveness of ZYPREXA in children <13 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide**

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*Sections or subsections omitted from the full prescribing information are not listed

## FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1, 5.14) and Patient Counseling Information (17.2)]*.**

**When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

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**1.2 Bipolar I Disorder (Manic or Mixed Episodes)**

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5, 5.6)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

**1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder**

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

**1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania**

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

**1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder**

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

**1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression**

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

## 2 DOSAGE AND ADMINISTRATION

**2.1 Schizophrenia**

**Adults**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been

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demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Adolescents

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

**2.2 Bipolar I Disorder (Manic or Mixed Episodes)**

**Adults**

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The physician who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

**2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)**

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

**2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania**

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.8)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

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If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL |
|---|---|
| 10 | Withdraw total contents of vial |
| 7.5 | 1.5 |
| 5 | 1 |
| 2.5 | 0.5 |

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

**2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder**

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine**

| For Symbyax (mg/day) | Use in Combination | |
|---|---|---|
| | ZYPREXA (mg/day) | Fluoxetine (mg/day) |
| 3 mg olanzapine/25 mg fluoxetine | 2.5 | 20 |
| 6 mg olanzapine/25 mg fluoxetine | 5 | 20 |
| 12 mg olanzapine/25 mg fluoxetine | 10+2.5 | 20 |
| 6 mg olanzapine/50 mg fluoxetine | 5 | 40+10 |
| 12 mg olanzapine/50 mg fluoxetine | 10+2.5 | 40+10 |

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

*While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in* combination should remain on it, it is generally accepted that bipolar I disorder, including the depressive episodes associated with bipolar I disorder, is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

**2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression**

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When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination should remain on it, it is generally accepted that treatment resistant depression (major depressive disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode) is a chronic illness requiring chronic treatment. The physician should periodically reexamine the need for continued pharmacotherapy.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

### 2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. ZYPREXA and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients <18 years of age *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

## 5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### 5.1 Elderly Patients with Dementia-Related Psychosis

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Increased Mortality — **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.14), and Patient Counseling Information (17.2)]*.**

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17.2)]*.

**5.2 Suicide**

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

**5.3 Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17.3)]*.

**5.4 Hyperglycemia**

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug *[see Patient Counseling Information (17.4)]*.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose

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level ≥126 mg/dL). Olanzapine-treated patients had a greater mean HbA1c increase from baseline of 0.04% (median exposure 21 days), compared to a mean HbA1c decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

**Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies**

| | | | Up to 12 weeks exposure | | At least 48 weeks exposure | |
|---|---|---|---|---|---|---|
| Laboratory Analyte | Category Change (at least once) from Baseline | Treatment Arm | N | Patients | N | Patients |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 543 | 2.2% | 345 | 12.8% |
| | | Placebo | 293 | 3.4% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 178 | 17.4% | 127 | 26.0% |
| | | Placebo | 96 | 11.5% | NA[a] | NA[a] |

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

**Table 3: Changes in Fasting Glucose Levels from Adolescent Olanzapine Monotherapy Studies**

| | | | Up to 12 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| Laboratory Analyte | Category Change (at least once) from Baseline | Treatment Arm | N | Patients | N | Patients |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 124 | 0% | 108 | 0.9% |
| | | Placebo | 53 | 1.9% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 14 | 14.3% | 13 | 23.1% |
| | | Placebo | 13 | 0% | NA[a] | NA[a] |

[a] Not Applicable.

### 5.5 Hyperlipidemia

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17.5)]*.

Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

**Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies**

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| Laboratory Analyte | Category Change (at least once) from Baseline | Treatment Arm | Up to 12 weeks exposure N | Up to 12 weeks exposure Patients | At least 48 weeks exposure N | At least 48 weeks exposure Patients |
|---|---|---|---|---|---|---|
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6% | 487 | 61.4% |
| | | Placebo | 402 | 26.1% | NA[a] | NA[a] |
| | Normal to High (<150 mg/dL to ≥200 mg/dL) | Olanzapine | 457 | 9.2% | 293 | 32.4% |
| | | Placebo | 251 | 4.4% | NA[a] | NA[a] |
| | Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 135 | 39.3% | 75 | 70.7% |
| | | Placebo | 65 | 20.0% | NA[a] | NA[a] |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6% | 489 | 32.9% |
| | | Placebo | 402 | 9.5% | NA[a] | NA[a] |
| | Normal to High (<200 mg/dL to ≥240 mg/dL) | Olanzapine | 392 | 2.8% | 283 | 14.8% |
| | | Placebo | 207 | 2.4% | NA[a] | NA[a] |
| | Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | Olanzapine | 222 | 23.0% | 125 | 55.2% |
| | | Placebo | 112 | 12.5% | NA[a] | NA[a] |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7% | 483 | 39.8% |
| | | Placebo | 304 | 14.1% | NA[a] | NA[a] |
| | Normal to High (<100 mg/dL to ≥160 mg/dL) | Olanzapine | 154 | 0% | 123 | 7.3% |
| | | Placebo | 82 | 1.2% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL) | Olanzapine | 302 | 10.6% | 284 | 31.0% |
| | | Placebo | 173 | 8.1% | NA[a] | NA[a] |

[a] Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

**Table 5: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies**

| Laboratory Analyte | Category Change (at least once) from Baseline | Treatment Arm | Up to 6 weeks exposure N | Up to 6 weeks exposure Patients | At least 24 weeks exposure N | At least 24 weeks exposure Patients |
|---|---|---|---|---|---|---|
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 138 | 37.0% | 122 | 45.9% |
| | | Placebo | 66 | 15.2% | NA[a] | NA[a] |
| | Normal to High (<90 mg/dL to >130 mg/dL) | Olanzapine | 67 | 26.9% | 66 | 36.4% |
| | | Placebo | 28 | 10.7% | NA[a] | NA[a] |
| | Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL) | Olanzapine | 37 | 59.5% | 31 | 64.5% |
| | | Placebo | 17 | 35.3% | NA[a] | NA[a] |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 138 | 14.5% | 122 | 14.8% |
| | | Placebo | 66 | 4.5% | NA[a] | NA[a] |
| | Normal to High (<170 mg/dL to ≥200 mg/dL) | Olanzapine | 87 | 6.9% | 78 | 7.7% |
| | | Placebo | 43 | 2.3% | NA[a] | NA[a] |
| | Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 36 | 38.9% | 33 | 57.6% |
| | | Placebo | 13 | 7.7% | NA[a] | NA[a] |

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| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 137 | 17.5% | 121 | 22.3% |
| | | Placebo | 63 | 11.1% | NA[a] | NA[a] |
| | Normal to High (<110 mg/dL to ≥130 mg/dL) | Olanzapine | 98 | 5.1% | 92 | 10.9% |
| | | Placebo | 44 | 4.5% | NA[a] | NA[a] |
| | Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL) | Olanzapine | 29 | 48.3% | 21 | 47.6% |
| | | Placebo | 9 | 0% | NA[a] | NA[a] |

[a] Not Applicable.

### 5.6 Weight Gain

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17.6)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

**Table 6: Weight Gain with Olanzapine Use in Adults**

| Amount Gained kg (lb) | 6 Weeks (N=7465) (%) | 6 Months (N=4162) (%) | 12 Months (N=1345) (%) | 24 Months (N=474) (%) | 36 Months (N=147) (%) |
|---|---|---|---|---|---|
| ≤0 | 26.2 | 24.3 | 20.8 | 23.2 | 17.0 |
| 0 to ≤5 (0-11 lb) | 57.0 | 36.0 | 26.0 | 23.4 | 25.2 |
| >5 to ≤10 (11-22 lb) | 14.9 | 24.6 | 24.2 | 24.1 | 18.4 |
| >10 to ≤15 (22-33 lb) | 1.8 | 10.9 | 14.9 | 11.4 | 17.0 |
| >15 to ≤20 (33-44 lb) | 0.1 | 3.1 | 8.6 | 9.3 | 11.6 |
| >20 to ≤25 (44-55 lb) | 0 | 0.9 | 3.3 | 5.1 | 4.1 |
| >25 to ≤30 (55-66 lb) | 0 | 0.2 | 1.4 | 2.3 | 4.8 |
| >30 (>66 lb) | 0 | 0.1 | 0.8 | 1.2 | 2 |

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

**Table 7: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials**

| | Olanzapine-treated patients | Placebo-treated patients |
|---|---|---|
| Mean change in body weight from baseline (median exposure = 3 weeks) | 4.6 kg (10.1 lb) | 0.3 kg (0.7 lb) |
| Percentage of patients who gained at least 7% of baseline body weight | 40.6% (median exposure to 7% = 4 weeks) | 9.8% (median exposure to 7% = 8 weeks) |
| Percentage of patients who gained at least 15% of baseline body weight | 7.1% (median exposure to 15% = 19 weeks) | 2.7% (median exposure to 15% = 8 weeks) |

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

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Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

**Table 8: Weight Gain with Olanzapine Use in Adolescents**

| Amount Gained kg (lb) | 6 Weeks (N=243) (%) | 6 Months (N=191) (%) |
|---|---|---|
| ≤0 | 2.9 | 2.1 |
| 0 to ≤5 (0-11 lb) | 47.3 | 24.6 |
| >5 to ≤10 (11-22 lb) | 42.4 | 26.7 |
| >10 to ≤15 (22-33 lb) | 5.8 | 22.0 |
| >15 to ≤20 (33-44 lb) | 0.8 | 12.6 |
| >20 to ≤25 (44-55 lb) | 0.8 | 9.4 |
| >25 to ≤30 (55-66 lb) | 0 | 2.1 |
| >30 to ≤35 (66-77 lb) | 0 | 0 |
| >35 to ≤40 (77-88 lb) | 0 | 0 |
| >40 (>88 lb) | 0 | 0.5 |

### 5.7 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

### 5.8 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties *[see Patient Counseling Information (17.7)]*.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

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Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is therefore not recommended. If use of intramuscular olanzapine in combination with parenteral benzodiazepines is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

**5.9 Leukopenia, Neutropenia, and Agranulocytosis**

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm$^3$) should discontinue ZYPREXA and have their WBC followed until recovery.

**5.10 Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

**5.11 Seizures**

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

**5.12 Potential for Cognitive and Motor Impairment**

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17.8)]*.

**5.13 Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

**5.14 Use in Patients with Concomitant Illness**

Clinical experience with olanzapine in patients with certain concomitant systemic illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Olanzapine exhibits in vitro muscarinic receptor affinity. In premarketing clinical trials with olanzapine, olanzapine was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations from olanzapine, but olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus or related conditions.

In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following treatment-emergent adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17.2)]*.

Olanzapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with olanzapine, caution should be observed in cardiac patients *[see Warnings and Precautions (5.8)]*.

**5.15 Hyperprolactinemia**

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As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and a modest elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In clinical studies, elevated plasma prolactin concentrations were observed in 34% of adults treated with olanzapine compared to 13.1% of placebo-treated patients. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations such as galactorrhea (14/8136; 0.2%), gynecomastia (8/4896; 0.2% of males), and breast enlargement (2/3240; 0.06% of females) were reported.

In placebo-controlled olanzapine monotherapy studies in adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), elevated prolactin concentrations compared to baseline occurred in 47.4% of olanzapine-treated patients compared to 6.8% of placebo-treated patients. In long-term clinical trials of olanzapine in adolescents, gynecomastia occurred in 2.4% of males (7/286) and galactorrhea occurred in 1.8% of females (3/168) *[see Use in Specific Populations (8.4)]*.

### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

### 5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended *[see Warnings and Precautions (5.4, 5.5) and Patient Counseling Information (17.4, 17.5)]*.

## 6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect or predict the rates observed in practice.

**Clinical Trials in Adults**

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 8661 adult patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 patients from 88 additional oral olanzapine clinical trials as of December 31, 2001; and (5) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. In addition, information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure, is included below.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

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The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reactions incidence in the population studied.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials*

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials*

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

*Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials*

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

**Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Adverse Reaction | Olanzapine (N=248) | Placebo (N=118) |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[a] | 8 | 4 |
| Akathisia | 5 | 1 |

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

**Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Adverse Reaction | Olanzapine (N=125) | Placebo (N=129) |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |

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|---|---|---|
| 16 | | |
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |

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|---|---|---|
| 17 | | |
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

*Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate*

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

**Table 12: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Adverse Reaction | Olanzapine with lithium or valproate (N=229) | Placebo with lithium or valproate (N=115) |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate*

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 13: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Body System/Adverse Reaction | Olanzapine with lithium or valproate (N=229) | Placebo with lithium or valproate (N=115) |
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

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| | | |
|---|---|---|
| 18 | | |
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |
| Dysmenorrhea[a] | 2 | 0 |
| Vaginitis[a] | 2 | 0 |

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Body System/Adverse Reaction | Olanzapine (N=415) | Placebo (N=150) |
| **Body as a Whole** | | |
| Asthenia | 2 | 1 |
| **Cardiovascular System** | | |
| Hypotension | 2 | 0 |
| Postural hypotension | 1 | 0 |
| **Nervous System** | | |
| Somnolence | 6 | 3 |
| Dizziness | 4 | 2 |
| Tremor | 1 | 0 |

**Additional Findings Observed in Clinical Trials**

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

*Extrapyramidal Symptoms:* The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 15: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo | Olanzapine 5 ± 2.5 mg/day | Olanzapine 10 ± 2.5 mg/day | Olanzapine 15 ± 2.5 mg/day |
| Parkinsonism[a] | 15 | 14 | 12 | 14 |
| Akathisia[b] | 23 | 16 | 19 | 27 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

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The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Dystonic events[a] | 1 | 3 | 2 | 3 |
| Parkinsonism events[b] | 10 | 8 | 14 | 20 |
| Akathisia events[c] | 1 | 5 | 11 | 10 |
| Dyskinetic events[d] | 4 | 0 | 2 | 1 |
| Residual events[e] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Categories[a] | Placebo (N=89) | Olanzapine (N=179) |
| Dystonic events | 0 | 1 |
| Parkinsonism events | 2 | 1 |
| Akathisia events | 4 | 6 |
| Dyskinetic events | 0 | 1 |
| Nonspecific events | 0 | 4 |
| Any extrapyramidal event | 6 | 10 |

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo | Olanzapine IM 2.5 mg | Olanzapine IM 5 mg | Olanzapine IM 7.5 mg | Olanzapine IM 10 mg |
| Parkinsonism[a] | 0 | 0 | 0 | 0 | 3 |
| Akathisia[b] | 0 | 0 | 5 | 0 | 0 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

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The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo (N=45) | Olanzapine IM 2.5 mg (N=48) | Olanzapine IM 5 mg (N=45) | Olanzapine IM 7.5 mg (N=46) | Olanzapine IM 10 mg (N=46) |
| Dystonic events[a] | 0 | 0 | 0 | 0 | 0 |
| Parkinsonism events[b] | 0 | 4 | 2 | 0 | 0 |
| Akathisia events[c] | 0 | 2 | 0 | 0 | 0 |
| Dyskinetic events[d] | 0 | 0 | 0 | 0 | 0 |
| Residual events[e] | 0 | 0 | 0 | 0 | 0 |
| Any extrapyramidal events | 0 | 4 | 2 | 0 | 0 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

*Dystonia, Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with olanzapine use.

*Other Adverse Reactions:* The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

**Table 20: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| Adverse Reaction | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

Differences among Fixed-Dose Groups Observed in Other Olanzapine Clinical Trials

In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in patients with schizophrenia or schizoaffective disorder, differences among 3 dose groups were observed for the following safety outcomes: weight gain, prolactin elevation, fatigue and dizziness. Mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day. Incidence of treatment-emergent prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) with significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day; fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) with significant differences between 10 vs 40 and 20 vs 40 mg/day; and dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) with significant differences between 20 vs 40 mg, was observed.

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Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

**Cardiovascular System** — *Infrequent:* cerebrovascular accident, vasodilatation.

**Digestive System** — *Infrequent:* nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

**Hemic and Lymphatic System** — *Infrequent:* leukopenia, thrombocytopenia.

**Metabolic and Nutritional Disorders** — *Infrequent:* alkaline phosphatase increased, bilirubinemia, hypoproteinemia.

**Musculoskeletal System** — *Rare:* osteoporosis.

**Nervous System** — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

**Respiratory System** — *Infrequent:* epistaxis; *Rare:* lung edema.

**Skin and Appendages** — *Infrequent:* alopecia.

**Special Senses** — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

**Urogenital System** — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

[1] These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

**Body as a Whole** — *Frequent:* injection site pain.

**Cardiovascular System** — *Infrequent:* syncope.

**Digestive System** — *Infrequent:* nausea.

**Metabolic and Nutritional Disorders** — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

*Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

**Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | 6 Week Trial % Schizophrenia Patients | | 3 Week Trial % Bipolar Patients | |
| Adverse Reactions | Olanzapine (N=72) | Placebo (N=35) | Olanzapine (N=107) | Placebo (N=54) |
| Sedation[a] | 39 | 9 | 48 | 9 |
| Weight increased | 31 | 9 | 29 | 4 |
| Headache | 17 | 6 | 17 | 17 |
| Increased appetite | 17 | 9 | 29 | 4 |
| Dizziness | 8 | 3 | 7 | 2 |
| Abdominal pain[b] | 6 | 3 | 6 | 7 |
| Pain in extremity | 6 | 3 | 5 | 0 |
| Fatigue | 3 | 3 | 14 | 6 |
| Dry mouth | 4 | 0 | 7 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

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*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

**Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Adverse Reaction | Olanzapine (N=179) | Placebo (N=89) |
| Sedation[a] | 44 | 9 |
| Weight increased | 30 | 6 |
| Increased appetite | 24 | 6 |
| Headache | 17 | 12 |
| Fatigue | 9 | 4 |
| Dizziness | 7 | 2 |
| Dry mouth | 6 | 0 |
| Pain in extremity | 5 | 1 |
| Constipation | 4 | 0 |
| Nasopharyngitis | 4 | 2 |
| Diarrhea | 3 | 0 |
| Restlessness | 3 | 2 |
| Liver enzymes increased[b] | 8 | 1 |
| Dyspepsia | 3 | 1 |
| Epistaxis | 3 | 0 |
| Respiratory tract infection[c] | 3 | 2 |
| Sinusitis | 3 | 0 |
| Arthralgia | 2 | 0 |
| Musculoskeletal stiffness | 2 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.

[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.

[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

**6.2 Vital Signs and Laboratory Studies**

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes — An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In 2 of these patients, liver enzymes decreased toward normal despite continued treatment and, in 2 others, enzymes decreased upon discontinuation of olanzapine. In the remaining 2 patients, 1, seropositive for hepatitis C, had persistent enzyme elevations for 4 months after discontinuation, and the other had insufficient follow-up to determine if enzymes normalized.

Within the larger premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevation to >200 IU/L was 2% (50/2381). Again, none of these patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

Among 2500 adult patients in oral olanzapine clinical trials, about 1% (23/2500) discontinued treatment due to transaminase increases.

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times the upper limit of normal at baseline to ≥3 times the upper limit of the normal range) were observed in 12% (21/174) of patients exposed to olanzapine compared to 2% (2/87) of the placebo-treated patients. Discontinuation due to transaminase increases occurred in 3.4% (6/179) of patients exposed to olanzapine.

Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period.

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Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

Given the concern about neutropenia associated with other psychotropic compounds and the finding of leukopenia associated with the administration of olanzapine in several animal models *[see Nonclinical Toxicology (13.2)]*, careful attention was given to examination of hematologic parameters in premarketing studies with olanzapine. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database for this drug.

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3 X ULN in patients with ALT at baseline <3 X ULN), (12.1% vs 2.3%); elevated AST (27.6% vs 3.8%); low total bilirubin (22.1% vs 6.7%); elevated GGT (10.1% vs 1.2%); and elevated prolactin (47.4% vs 6.8%).

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.8)]*.

### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), jaundice, neutropenia, pancreatitis, priapism, rash, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

## 7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

### 7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

*Fluvoxamine:* Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

*Fluoxetine:* Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

### 7.2 Potential for Olanzapine to Affect Other Drugs

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CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.8)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

Biperiden — Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

## 8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C — In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the maximum recommended human daily oral dose on a mg/m$^2$ basis, respectively) no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). Gestation was prolonged at 10 mg/kg/day (5 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). In an oral rabbit teratology study, fetal toxicity (manifested as increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 mg/kg/day (30 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental transfer of olanzapine occurs in rat pups.

There are no adequate and well-controlled trials with olanzapine in pregnant females. Seven pregnancies were observed during clinical trials with olanzapine, including 2 resulting in normal births, 1 resulting in neonatal death due to a cardiovascular defect, 3 therapeutic abortions, and 1 spontaneous abortion.

### 8.2 Labor and Delivery

The effect of olanzapine on labor and delivery in humans is unknown. Parturition in rats was not affected by olanzapine.

### 8.3 Nursing Mothers

In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal olanzapine dose. It is recommended that women receiving olanzapine should not breast-feed.

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic transaminase levels *[see Warnings and Precautions (5.5, 5.6, 5.15, 5.17) and Adverse Reactions (6.2)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and hyperlipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

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Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17.13)]*.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children and adolescents <18 years of age have not been established.

### 8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the maximum recommended human daily oral dose (20 mg) and rhesus monkeys administered oral doses up to 8 times the maximum recommended human daily oral dose on a mg/m$^2$ basis.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

### 10.2 Management of Overdose

The possibility of multiple drug involvement should be considered. In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation, which may include intubation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to olanzapine. Therefore, appropriate supportive measures should be initiated. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. (Do not use epinephrine, dopamine, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of olanzapine-induced alpha blockade.) Close medical supervision and monitoring should continue until the patient recovers.

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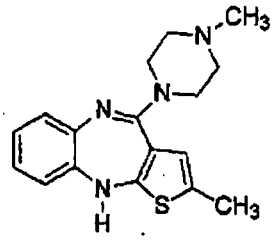
For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the package inserts for these products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax package insert.

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine and serotonin type 2 (5HT2) antagonism. The mechanism of action of olanzapine in the treatment of acute manic or mixed episodes associated with bipolar I disorder is unknown.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i$=4, 11, and 5 nM, respectively), dopamine $D_{1-4}$ ($K_i$=11-31 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i$=57 nM) and muscarinic $M_{1-5}$ ($K_i$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds weakly to $GABA_A$, BZD, and β-adrenergic receptors ($K_i$>10 µM).

Antagonism at receptors other than dopamine and $5HT_2$ may explain some of the other therapeutic and side effects of olanzapine. Olanzapine's antagonism of muscarinic $M_{1-5}$ receptors may explain its anticholinergic-like effects. Olanzapine's antagonism of histamine $H_1$ receptors may explain the somnolence observed with this drug. Olanzapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

### 12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

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Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of $^{14}C$ labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4'-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

*Specific Populations*

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the maximum recommended human daily oral dose on a mg/m$^2$ basis) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the maximum recommended human daily oral dose on a mg/m$^2$ basis, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice dosed at 8 mg/kg/day (2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis). These tumors were not increased in another mouse study in females dosed at 10 or 30/20 mg/kg/day (2-5 times the maximum recommended human daily oral dose on a mg/m$^2$ basis); in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the maximum recommended human daily oral dose on a mg/m$^2$ basis, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has

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been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.15)]*.

Mutagenesis — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the maximum recommended human daily oral dose on a $mg/m^2$ basis). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the maximum recommended human daily oral dose on a $mg/m^2$ basis); therefore olanzapine may produce a delay in ovulation.

### 13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the maximum recommended human daily oral dose on a $mg/m^2$ basis), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 3 months or 16 mg/kg (8 times the maximum recommended human daily oral dose on a $mg/m^2$ basis) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

### 14.1 Schizophrenia

**Adults**

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months. however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

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**Adolescents**

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

**14.2 Bipolar I Disorder (Manic or Mixed Episodes)**

**Adults**

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

**Adolescents**

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

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The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.3 Agitation Associated with Schizophrenia and Bipolar I Mania

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |
| NDC Codes: | | | | | | |
| Bottles 30 | NDC 0002-4112-30 | NDC 0002-4115-30 | NDC 0002-4116-30 | NDC 0002-4117-30 | NDC 0002-4415-30 | NDC 0002-4420-30 |
| Blisters – ID[a] 100 | NDC 0002-4112-33 | NDC 0002-4115-33 | NDC 0002-4116-33 | NDC 0002-4117-33 | NDC 0002-4415-33 | NDC 0002-4420-33 |
| Bottles 1000 | NDC 0002-4112-04 | NDC 0002-4115-04 | NDC 0002-4116-04 | NDC 0002-4117-04 | NDC 0002-4415-04 | NDC 0002-4420-04 |

[a] Identi-Dose® (unit dose medication, Lilly).

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ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets* | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.

ZYDIS is a registered trademark of Catalent Pharma Solutions.

*ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is manufactured for Eli Lilly and Company by Catalent Pharma Solutions, United Kingdom, SN5 8RU.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

**16.2 Storage and Handling**

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

**17 PATIENT COUNSELING INFORMATION**

*See FDA-approved Medication Guide for the oral formulations.*

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for Symbyax.

**17.1 Information on Medication Guide**

Prescribers or other health professionals should inform patients, their families, and their caregivers about the potential benefits and potential risks associated with treatment with ZYPREXA, and should counsel them in its appropriate use. A patient Medication Guide is available for ZYPREXA. Prescribers or other health professionals should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. When using ZYPREXA and fluoxetine in combination, also refer to the Medication Guide for Symbyax.

**17.2 Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke**

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

**17.3 Neuroleptic Malignant Syndrome (NMS)**

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including ZYPREXA. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

**17.4 Hyperglycemia**

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.4)]*.

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**17.5 Hyperlipidemia**

Patients should be counseled that hyperlipidemia has occurred during treatment with ZYPREXA. Patients should have their lipid profile monitored regularly *[see Warnings and Precautions (5.5)]*.

**17.6 Weight Gain**

Patients should be counseled that weight gain has occurred during treatment with ZYPREXA. Patients should have their weight monitored regularly *[see Warnings and Precautions (5.6)]*.

**17.7 Orthostatic Hypotension**

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.8) and Drug Interactions (7)]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heart beat, or fainting.

**17.8 Potential for Cognitive and Motor Impairment**

Because ZYPREXA has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

**17.9 Body Temperature Regulation**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see Warnings and Precautions (5.13)]*.

**17.10 Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, Symbyax. Patients should also be advised to inform their physicians if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions *[see Drug Interactions (7)]*.

**17.11 Alcohol**

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

**17.12 Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

**17.13 Use in Specific Populations**

Pregnancy — Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ZYPREXA *[see Use in Specific Populations (8.1)]*.

Nursing Mothers — Patients should be advised not to breast-feed an infant if they are taking ZYPREXA *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic transaminase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <18 years of age have not been established *[see Warnings and Precautions (5.5, 5.6) and Use in Specific Populations (8.4)]*.

**17.14 Need for Comprehensive Treatment Program in Pediatric Patients**

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

Literature revised Month dd, 2009

Eli Lilly and Company, Indianapolis, IN 46285, USA

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# Medication Guide

ZYPREXA® (zy-PREX-a)

(olanzapine)

Tablet

ZYPREXA® ZYDIS® (zy-PREX-a ZY-dis)

(olanzapine)

Tablet, Orally Disintegrating

Read the Medication Guide that comes with ZYPREXA before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or treatment. Talk with your doctor or pharmacist if there is something you do not understand or you want to learn more about ZYPREXA.

## What is the most important information I should know about ZYPREXA?

**Serious side effects may happen when you take ZYPREXA, including:**

**Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ZYPREXA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ZYPREXA is not approved for treating psychosis in the elderly with dementia.

**High blood sugar (hyperglycemia):** High blood sugar can happen if you have diabetes already or even if you have never had diabetes. In rare cases, this could lead to ketoacidosis (build up of acid in the blood due to ketones), coma, or death. Your doctor should do lab tests to check your blood sugar before you start taking ZYPREXA and during treatment. In people who do not have diabetes, sometimes high blood sugar goes away when ZYPREXA is stopped. People with diabetes and some people who did not have diabetes before taking ZYPREXA need to take medicine for high blood sugar even after they stop taking ZYPREXA.

If you have diabetes, follow your doctor's instructions about how often to check your blood sugar while taking ZYPREXA.

**Call your doctor** if you have any of these symptoms of high blood sugar (hyperglycemia) while taking ZYPREXA:

- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity.

**High cholesterol and triglyceride levels in the blood (fat in the blood)** may happen in people treated with ZYPREXA, especially in teenagers (13-17 years old). You may not have any symptoms, so your doctor should do blood tests to check your cholesterol and triglyceride levels before you start taking ZYPREXA and during treatment.

**Increase in weight (weight gain):** Weight gain is very common in people who take ZYPREXA. Teenagers (13-17 years old) are more likely to gain weight and to gain more weight than adults. Some people may gain a lot of weight while taking ZYPREXA, so you and your doctor should check your weight regularly. Talk to your doctor about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.

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**Increased risk in teenagers (13-17 years old):** Possible serious risks of weight gain and increases in cholesterol and triglycerides are more common in teenagers than in adults. You and your doctor should decide if other available treatments should be used first. Before your teenager takes ZYPREXA, talk with your doctor about the possible long-term risks of teenagers taking ZYPREXA.

## What is ZYPREXA?

**ZYPREXA is a prescription medicine used to treat:**

- schizophrenia in people age 13 or older.
- bipolar disorder, including:
  - manic or mixed episodes that happen with bipolar I disorder in people age 13 or older.
  - manic or mixed episodes that happen with bipolar I disorder, when used with the medicine lithium or valproate, in adults.
  - long-term treatment of bipolar I disorder in adults.
- episodes of depression that happen with bipolar I disorder, when used with the medicine fluoxetine (Prozac®), in adults.
- episodes of depression that do not get better after 2 other medicines, also called treatment resistant depression, when used with the medicine fluoxetine (Prozac), in adults.

ZYPREXA has not been approved for use in children under 13 years of age.

The symptoms of schizophrenia include hearing voices, seeing things that are not there, having beliefs that are not true, and being suspicious or withdrawn.

The symptoms of bipolar I disorder include alternating periods of depression and high or irritable mood, increased activity and restlessness, racing thoughts, talking fast, impulsive behavior, and a decreased need for sleep.

The symptoms of treatment resistant depression include decreased mood, decreased interest, increased guilty feelings, decreased energy, decreased concentration, changes in appetite, and suicidal thoughts or behavior.

Some of your symptoms may improve with treatment. If you do not think you are getting better, call your doctor.

## What should I tell my doctor before taking ZYPREXA?

ZYPREXA may not be right for you. Before starting ZYPREXA, tell your doctor if you have or had:

- heart problems
- seizures
- diabetes or high blood sugar levels (hyperglycemia)
- high cholesterol or triglyceride levels in your blood
- liver problems
- low or high blood pressure
- strokes or "mini-strokes" also called transient ischemic attacks (TIAs)
- Alzheimer's disease
- narrow-angle glaucoma
- enlarged prostate in men
- bowel obstruction
- phenylketonuria, because ZYPREXA ZYDIS contains phenylalanine

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- breast cancer
- thoughts of suicide or hurting yourself
- any other medical condition
- are pregnant or plan to become pregnant. It is not known if ZYPREXA will harm your unborn baby.
- are breast-feeding or plan to breast-feed. ZYPREXA can pass into your breast milk and may harm your baby. You should not breast-feed while taking ZYPREXA. Talk to your doctor about the best way to feed your baby if you take ZYPREXA.

Tell your doctor if you exercise a lot or are in hot places often.

The symptoms of bipolar I disorder, treatment resistant depression, or schizophrenia may include **thoughts of suicide** or of hurting yourself or others. If you have these thoughts at any time, tell your doctor or go to an emergency room right away.

**Tell your doctor about all the medicines that you take,** including prescription and nonprescription medicines, vitamins, and herbal supplements. ZYPREXA and some medicines may interact with each other and may not work as well, or cause possible serious side effects. Your doctor can tell you if it is safe to take ZYPREXA with your other medicines. Do not start or stop any medicine while taking ZYPREXA without talking to your doctor first.

## How should I take ZYPREXA?

- Take ZYPREXA exactly as prescribed. Your doctor may need to change (adjust) the dose of ZYPREXA until it is right for you.
- If you miss a dose of ZYPREXA, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ZYPREXA at the same time.
- **To prevent serious side effects, do not stop taking ZYPREXA suddenly. If you need to stop taking ZYPREXA, your doctor can tell you how to safely stop taking it.**
- **If you take too much ZYPREXA, call your doctor or poison control center at 1-800-222-1212 right away, or get emergency treatment.**
- ZYPREXA can be taken with or without food.
- ZYPREXA is usually taken one time each day.
- Take ZYPREXA ZYDIS as follows:
  - Be sure that your hands are dry.
  - Open the sachet and peel back the foil on the blister. Do not push the tablet through the foil.
  - As soon as you open the blister, remove the tablet and put it into your mouth.
  - The tablet will disintegrate quickly in your saliva so that you can easily swallow it with or without drinking liquid.
- Call your doctor if you do not think you are getting better or have any concerns about your condition while taking ZYPREXA.

## What should I avoid while taking ZYPREXA?

- ZYPREXA can cause sleepiness and may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how ZYPREXA affects you.
- Avoid drinking alcohol while taking ZYPREXA. Drinking alcohol while you take ZYPREXA may make you sleepier than if you take ZYPREXA alone.

## What are the possible side effects of ZYPREXA?

***Serious side effects may happen when you take ZYPREXA, including:***

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- **See "What is the most important information I should know about ZYPREXA?", which describes the increased risk of death in elderly people with dementia-related psychosis and the risks of high blood sugar, high cholesterol and triglyceride levels, and weight gain.**
- **Increased incidence of stroke or "mini-strokes" called transient ischemic attacks (TIAs) in elderly people with dementia-related psychosis** (elderly people who have lost touch with reality due to confusion and memory loss). ZYPREXA is not approved for these patients.
- **Neuroleptic Malignant Syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including ZYPREXA. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have any of these symptoms:
  - high fever
  - excessive sweating
  - rigid muscles
  - confusion
  - changes in your breathing, heartbeat, and blood pressure.
- **Tardive Dyskinesia:** This condition causes body movements that keep happening and that you can not control. These movements usually affect the face and tongue. Tardive dyskinesia may not go away, even if you stop taking ZYPREXA. It may also start after you stop taking ZYPREXA. Tell your doctor if you get any body movements that you can not control.
- **Decreased blood pressure when you change positions, with symptoms of dizziness, fast or slow heartbeat, or fainting.**
- **Difficulty swallowing, that can cause food or liquid to get into your lungs.**
- **Seizures: Tell your doctor if you have a seizure during treatment with ZYPREXA.**
- **Problems with control of body temperature:** You could become very hot, for instance when you exercise a lot or stay in an area that is very hot. It is important for you to drink water to avoid dehydration. Call your doctor right away if you become severely ill and have any of these symptoms of dehydration:
  - sweating too much or not at all
  - dry mouth
  - feeling very hot
  - feeling thirsty
  - not able to produce urine.

**Common side effects of ZYPREXA include:** lack of energy, dry mouth, increased appetite, sleepiness, tremor (shakes), having hard or infrequent stools, dizziness, changes in behavior, or restlessness.

**Other common side effects in teenagers (13-17 years old) include:** headache, stomach-area (abdominal) pain, pain in your arms or legs, or tiredness. Teenagers experienced greater increases in prolactin, liver enzymes, and sleepiness, as compared with adults.

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the possible side effects with ZYPREXA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## How should I store ZYPREXA?

- Store ZYPREXA at room temperature, between 68°F to 77°F (20°C to 25°C).

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- Keep ZYPREXA away from light.
- Keep ZYPREXA dry and away from moisture.

**Keep ZYPREXA and all medicines out of the reach of children.**

## General Information about ZYPREXA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ZYPREXA for a condition for which it was not prescribed. Do not give ZYPREXA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about ZYPREXA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ZYPREXA that was written for healthcare professionals. For more information about ZYPREXA call 1-800-Lilly-Rx (1-800-545-5979) or visit www.zyprexa.com.

## What are the ingredients in ZYPREXA?

**Active ingredient:** olanzapine

**Inactive ingredients:**

**Tablets** — carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains: Titanium Dioxide, FD&C Blue No. 2 Aluminum Lake, or Synthetic Red Iron Oxide.

**ZYDIS** — gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

*This Medication Guide has been approved by the U.S. Food and Drug Administration.*

Medication Guide revised Month dd, 2009

**Eli Lilly and Company**
**Indianapolis, IN 46285, USA**

**www.zyprexa.com**

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# EXHIBIT B

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# LATUDA® (lurasidone HCl) Tablets

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information (FPI) for LATUDA.

LATUDA (LURASIDONE HCL) tablets for oral administration,
Initial U.S. Approval: 2010

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

*See full prescribing information for complete boxed warning.*

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis. *(5.1)*

### INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia *(1)*. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia *(14.1)*.

### DOSAGE AND ADMINISTRATION

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. The maximum recommended dose is 80 mg once daily. LATUDA should be taken with food *(2.2)*.

### DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg and 80 mg *(3)*.

### CONTRAINDICATIONS

Any known hypersensitivity to LATUDA or any components in the formulation *(4)*. Coadministration with a strong CYP3A4 inhibitor (e.g., ketoconazole) and inducer (e.g., rifampin) *(4)*.

### WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions:** An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. *(5.2)*.
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring *(5.3)*.
- **Tardive Dyskinesia:** Discontinue if clinically appropriate *(5.4)*.
- **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain *(5.5)*.
  - **Hyperglycemia and Diabetes Mellitus:** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
  - **Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.
  - **Weight Gain:** Gain in body weight has been observed, clinical monitoring of weight is recommended.
- **Hyperprolactinemia:** Prolactin elevations may occur *(5.6)*.
- **Leukopenia, Neutropenia, and Agranulocytosis** have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors *(5.7)*.
- **Orthostatic Hypotension and Syncope:** Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naive patients *(5.8)*.
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold *(5.9)*.
- **Potential for Cognitive and Motor Impairment:** Use caution when operating machinery *(5.10)*.
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia. Closely supervise high-risk patients *(5.12)*.
- See Full Prescribing Information for additional WARNINGS and PRECAUTIONS

### ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and at least twice the rate for placebo) included somnolence, akathisia, nausea, parkinsonism and agitation *(6.2)*.

**To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### DRUG INTERACTIONS

- LATUDA is not recommended to be used in combination with strong CYP3A4 inhibitors, e.g., ketoconazole. *(4 and 7.1)*
- Dose adjustment is recommended for moderate CYP3A4 inhibitors (e.g. diltiazem) *(7.1)*
- LATUDA is not recommended to be used in combination with strong CYP3A4 inducers, e.g., rifampin. *(4 and 7.1)*

### USE IN SPECIFIC POPULATIONS

- **Geriatric Use:** No dose adjustments required. *(8.5)*
- **Pregnancy:** Use LATUDA during pregnancy only if the potential benefit justifies the potential risk. *(8.1)*
- **Nursing Mothers:** Breast feeding is not recommended. *(8.3)*
- **Pediatric Use:** Safety and effectiveness have not been established. *(8.4)*
- **Renal Impairment:** Dose adjustment is recommended. *(8.6)*
- **Hepatic Impairment:** Dose adjustment is recommended. *(8.7)*

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FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.**

**Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.**

**LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1 )]*.**


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## 1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in four 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

## 2. DOSAGE AND ADMINISTRATION

### 2.1. Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 120 mg/day *[see Clinical Studies (14.1)]*. In the 6-week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 80 mg/day.

### 2.2. Administration Instructions

LATUDA should be taken with food (at least 350 calories) *[see Clinical Pharmacology (12)]*.

### 2.3. Dosage in Special Populations

Dosage adjustments are not recommended on the basis of age, gender, and race *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe renal impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe hepatic impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

**Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inhibitors:** When coadministration of LATUDA with a moderate CYP3A4 inhibitor such as diltiazem is considered, the dose should not exceed 40 mg/day. LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole) *[see Contraindications (4); Drug Interactions (7.1)]*.

**Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inducers:** LATUDA should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin) *[see Contraindications (4); Drug Interactions (7.1)]*.

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## 3. DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing: 40 mg (white to off-white, round, "L40"), or 80 mg (pale green, oval, "L80").

**Table 1: LATUDA Tablet Presentations**

| Tablet Strength | Tablet Color/Shape | Tablet Markings |
|---|---|---|
| 40 mg | white to off-white round | "L40" |
| 80 mg | pale green oval | "L80" |

## 4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.6)*].

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) [*see Drug Interactions (7.1)*].

## 5. WARNINGS AND PRECAUTIONS

### 5.1. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of dementia-related psychosis [*see Boxed Warning*].**

### 5.2. Cerebrovascular Adverse Reactions, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

### 5.3. Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g. pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

## 5.4. Tardive Dyskinesia

Tardive Dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

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## 5.5. Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

**Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However,

epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Pooled data from short-term, placebo-controlled studies are presented in Table 2.

**Table 2: Change in Fasting Glucose**

| | Placebo | LATUDA 20 mg/day | LATUDA 40 mg/day | LATUDA 80 mg/day | LATUDA 120 mg/day |
|---|---|---|---|---|---|
| | | | **Mean Change from Baseline (mg/dL)** | | |
| | n=438 | n=71 | n=352 | n=270 | n=283 |
| Serum Glucose | -0.7 | -0.6 | 2.5 | -0.9 | 2.5 |
| | | | **Proportion of Patients with Shifts to ≥ 126 mg/dL** | | |
| Serum Glucose (≥ 126 mg/dL) | 8.6% (34/397) | 11.7% (7/60) | 14.3% (47/328) | 10.0% (24/241) | 10.0% (26/260) |

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n = 186), +0.3 mg/dL at week 36 (n = 236) and +1.2 mg/dL at week 52 (n = 244).

**Dyslipidemia**

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 3.

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**Table 3: Change in Fasting Lipids**

| | Placebo | LATUDA 20 mg/day | LATUDA 40 mg/day | LATUDA 80 mg/day | LATUDA 120 mg/day |
|---|---|---|---|---|---|
| | | | Mean Change from Baseline (mg/dL) | | |
| | n=418 | n=71 | n=341 | n=263 | n=268 |
| Total cholesterol | -8.5 | -12.3 | -9.4 | -9.8 | -3.8 |
| Triglycerides | -15.7 | -29.1 | -6.2 | -14.2 | -3.1 |
| | | | Proportion of Patients with Shifts | | |
| Total Cholesterol (≥ 240 mg/dL) | 6.6% (23/350) | 13.8% (8/58) | 7.3% (21/287) | 6.9% (15/216) | 3.8% (9/238) |
| Triglycerides (≥ 200 mg/dL) | 12.5% (39/312) | 14.3% (7/49) | 14.0% (37/264) | 8.7% (17/196) | 10.5% (22/209) |

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n = 238) and -3.5 (n = 238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

**Weight Gain**

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Pooled data from short-term, placebo-controlled studies are presented in Table 4. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 [*see Clinical Studies (14.1)*] change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

**Table 4: Mean Change in Weight (kg) from Baseline**

| | Placebo (n=450) | LATUDA 20 mg/day (n=71) | LATUDA 40 mg/day (n= 358) | LATUDA 80 mg/day (n= 279) | LATUDA 120 mg/day (n=291) |
|---|---|---|---|---|---|
| All Patients | 0.26 | -0.15 | 0.67 | 1.14 | 0.68 |

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n = 531), -0.47 kg at week 36 (n = 303) and -0.71 kg at week 52 (n = 244).

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## 5.6. Hyperprolactinemia

As with other drugs that antagonize dopamine $D_2$ receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was - 0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 5).

**Table 5: Median Change in Prolactin (ng/mL) from Baseline**

| | Placebo | LATUDA 20 mg/day | LATUDA 40 mg/day | LATUDA 80 mg/day | LATUDA 120 mg/day |
|---|---|---|---|---|---|
| All Patients | -0.6 (n=430) | -1.1 (n=70) | 0.3 (n=351) | 1.1 (n=259) | 3.3 (n=284) |
| Females | -1.5 (n=102) | -0.7 (n=19) | -0.9 (n=99) | 2.0 (n=78) | 6.7 (n=70) |
| Males | -0.5 (n=328) | -1.2 (n=51) | 0.5 (n=252) | 0.9 (n=181) | 3.1 (n=214) |

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n = 188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n = 243).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

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## 5.7. Leukopenia, Neutropenia and Agranulocytosis

Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm$^3$) should discontinue LATUDA and have their WBC followed until recovery.

## 5.8. Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2 % (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by vital sign changes (≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

LATUDA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

## 5.9. Seizures

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

## 5.10. Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

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## 5.11. Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17.9)]*.

## 5.12. Suicide

The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

## 5.13. Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

## 5.14. Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6, 8.7)]*. LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see Warnings and Precautions (5.1, 5.8)]*.

# 6. ADVERSE REACTIONS

## 6.1. Overall Adverse Reaction Profile

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*

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- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

## 6.2. Clinical Studies Experience

The following findings are based on the short-term placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n = 1004).

**Commonly Observed Adverse Reactions:** The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea, parkinsonism and agitation.

**Adverse Reactions Associated with Discontinuation of Treatment:** A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

**Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:** Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6-weeks in patients with schizophrenia) are shown in Table 6.

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**Table 6: Adverse Reaction in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies**

| Body System or Organ Class<br>Dictionary-derived Term | Percentage of Patients Reporting Reaction<br>Placebo<br>(N = 455) | <br>All LATUDA<br>(N = 1004) |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Nausea | 6 | 12 |
| Vomiting | 6 | 8 |
| Dyspepsia | 6 | 8 |
| Salivary hypersecretion | <1 | 2 |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 3 | 4 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Back Pain | 3 | 4 |
| **Nervous System Disorders** | | |
| Somnolence* | 10 | 22 |
| Akathisia | 3 | 15 |
| Parkinsonism** | 5 | 11 |
| Dystonia*** | 1 | 5 |
| Dizziness | 3 | 5 |
| **Psychiatric Disorders** | | |
| Insomnia | 7 | 8 |
| Agitation | 3 | 6 |
| Anxiety | 3 | 6 |
| Restlessness | 2 | 3 |

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
*** Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

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## 6.3. Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 7).

**Table 7: Dose-Related Adverse Events**

| Adverse Event Term | Percentage of Subjects Reporting Reaction | | | | |
|---|---|---|---|---|---|
| | Placebo (N = 455) (%) | LATUDA 20 mg/day (N = 71) (%) | LATUDA 40 mg/day (N = 360) (%) | LATUDA 80 mg/day (N = 282) (%) | LATUDA 120 mg/day (N = 291) (%) |
| Akathisia | 3 | 6 | 11 | 15 | 22 |
| Somnolence* | 10 | 15 | 19 | 23 | 26 |

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

## 6.4. Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 8).

**Table 8: Percentage of EPS Compared to Placebo**

| Adverse Event Term | Placebo (N = 455) (%) | LATUDA 20 mg/day (N = 71) (%) | LATUDA 40 mg/day (N = 360) (%) | LATUDA 80 mg/day (N = 282) (%) | LATUDA 120 mg/day (N = 291) (%) |
|---|---|---|---|---|---|
| **All EPS events** | 9 | 10 | 24 | 26 | 39 |
| **All EPS events, excluding Akathisia/Restlessness** | 5 | 6 | 13 | 11 | 22 |
| Akathisia | 3 | 6 | 11 | 15 | 22 |
| Dystonia* | 1 | 0 | 4 | 5 | 7 |
| Parkinsonism** | 5 | 6 | 10 | 7 | 17 |
| Restlessness | 2 | 1 | 4 | 1 | 3 |

Note: Figures rounded to the nearest integer
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

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In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

**Dystonia**

*Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events – 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

## 6.5. Laboratory Test Abnormalities and ECG Changes in Clinical Studies

**Laboratory Test Abnormalities**

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint [*see Warnings and Precautions (5.5)*]. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration [*see Warnings and Precautions (5.6)*]

*Creatinine:* In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Population (2.3); Use in Specific Populations (8)*].

*Transaminases:* The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

**ECG Changes**

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

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## 6.6. Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 6 are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

*Blood and Lymphatic System Disorders:* ***Infrequent:*** *anemia;* ***Rare:*** *leukopenia, neutropenia*

*Cardiac Disorders:* ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

*Ear and Labyrinth Disorders:* ***Infrequent:*** *vertigo*

*Eye disorders:* ***Frequent:*** *blurred vision*

*Gastrointestinal Disorders:* ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis, dysphagia*

*General Disorders and Administrative Site Conditions:* ***Rare:*** *Sudden death*

*Investigations:* ***Frequent:*** *CPK increased*

*Metabolic and Nutritional System Disorders:* ***Frequent:*** *decreased appetite*

*Musculoskeletal and Connective Tissue Disorders:* ***Rare:*** *rhabdomyolysis*

*Nervous System Disorders:* ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*

*Psychiatric Disorders:* ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*

*Renal and Urinary Disorders:* ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

*Reproductive System and Breast Disorders:* ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

*Skin and Subcutaneous Tissue Disorders:* ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

*Vascular Disorders:* ***Infrequent:*** *hypertension, orthostatic hypotension*

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## 7. DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

### 7.1. Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 9). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

**Table 9: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia**

| Coadministered drug | Dose schedule | | Effect on LATUDA pharmacokinetics | | Recommendation |
|---|---|---|---|---|---|
| | Coadministered drug | LATUDA | $C_{max}$ | AUC | |
| Ketoconazole (strong CYP3A4 inhibitor) | 400 mg/day for 5 days | 10 mg single dose | 6.9-times LATUDA alone | 9-times LATUDA alone | Should not be coadministered with LATUDA |
| Diltiazem (moderate CYP3A4 inhibitor) | 240 mg/ day for 5 days | 20 mg single dose | 2.1- times LATUDA alone | 2.2- times LATUDA alone | LATUDA dose should not exceed 40 mg/day if coadministered |
| Rifampin (strong CYP3A4 inducer) | 600 mg/day for 8 days | 40 mg single dose | 1/7th of LATUDA alone | 1/5th of LATUDA alone | Should not be coadministered with LATUDA |
| Lithium | 600 mg BID for 8 days | 120 mg/day for 8 days | 0.9-times LATUDA alone | 1.1- times LATUDA alone | No LATUDA dose adjustment required. |

## 7.2. Potential for LATUDA to Affect Other Drugs

**Digoxin (P-gp substrate):** Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased $C_{max}$ and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

**Midazolam (CYP3A4 substrate):** Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam Cmax and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

**Oral Contraceptive (estrogen/progesterone):** Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and $C_{max}$ of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

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## 8. USE IN SPECIFIC POPULATIONS

### 8.1. Pregnancy

**Teratogenic Effects**

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately equal to the MRHD based on body surface area.

**Non-teratogenic Effects**

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### 8.2. Labor and Delivery

The effect of LATUDA on labor and delivery in humans is unknown.

### 8.3. Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

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### 8.4. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5. Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology (12.3)]*. No dose adjustment is necessary in elderly patients.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

## 8.6. Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment ($Cl_{cr} \geq 10$ mL/min to $< 50$ mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean $C_{max}$ increased by 40%, 92% and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

## 8.7. Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{(0-last)}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean $C_{max}$ was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

## 8.8. Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean $C_{max}$ of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

## 8.9. Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of LATUDA, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of LATUDA. No dosage adjustment of LATUDA is recommended based on race.

## 8.10. Smoking Status

Based on in vitro studies utilizing human liver enzymes, LATUDA is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of LATUDA.

# 9. DRUG ABUSE AND DEPENDENCE

## 9.1. Controlled substance

LATUDA is not a controlled substance.

## 9.2. Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

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## 10. OVERDOSAGE

### 10.1. Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

### 10.2. Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

## 11. DESCRIPTION

LATUDA is a psychotropic agent belonging to the chemical class of benzoisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S \cdot HCl$ and its molecular weight is 529.14.

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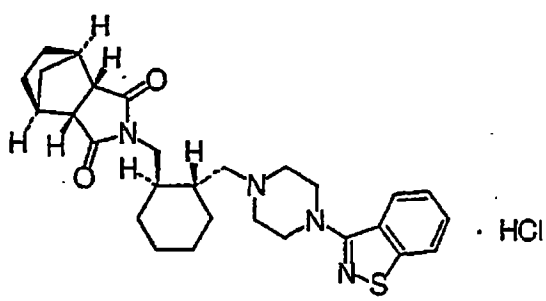
The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.

LATUDA tablets are intended for oral administration only. Each tablet contains 40 mg, or 80 mg of lurasidone hydrochloride.

Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No.2 Aluminum Lake.

## 12. CLINICAL PHARMACOLOGY

### 12.1. Mechanism of Action

The mechanism of action of lurasidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 ($D_2$) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

### 12.2. Pharmacodynamics

In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine $D_2$ receptors (Ki = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (Ki = 0.47 nM) and $5\text{-}HT_7$ (Ki = 0.495 nM), is an antagonist with moderate affinity at human $\alpha_{2C}$ adrenergic receptors (Ki = 10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (Ki = 6.38 nM) receptors, and is an antagonist at $\alpha_{2A}$ adrenergic receptors (Ki = 40.7 nM). Lurasidone exhibits little or no affinity for histamine $H_1$ and muscarinic $M_1$ receptors ($IC_{50} \geq 1{,}000$ nM and > 1,000 nM, respectively).

### 12.3. Pharmacokinetics

The activity of lurasidone is primarily due to the parent drug. The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

**Absorption and Distribution:** Lurasidone is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (57.2) Lurasidone is highly bound (~99%) to serum proteins.

In a food effect study, lurasidone mean $C_{max}$ and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. Lurasidone exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content [see *Dosage and Administration (2.2)*].

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food [*see Dosage and Administration (2.2)*].

**Metabolism and Elimination:** Lurasidone is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. Lurasidone is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220).

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Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [$^{14}$C]-labeled lurasidone.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

## 13. NONCLINICAL TOXICOLOGY

**Carcinogenesis:** Lifetime carcinogenicity studies were conducted in ICR mice and Sprague-Dawley rats. Lurasidone was administered orally at doses of 30, 100, 300, or 650 (the high dose was reduced from 1200 in males) mg/kg/day to ICR mice and 3, 12, or 36 (high dose reduced from 50) mg/kg/day to Sprague-Dawley rats.

In the mouse study, there were increased incidences of malignant mammary gland tumors and pituitary gland adenomas in females at all doses; the lowest dose tested produced plasma levels (AUC) 2 times those in humans receiving the maximum recommended human dose (MRHD) of 80 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 15-25 times those in humans receiving the MRHD.

In rats, an increased incidence of mammary gland carcinomas was seen in females at the two higher doses; the no-effect dose of 3 mg/kg produced plasma levels (AUC) 0.7 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to highest dose tested, which produced plasma levels (AUC) 10 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents in terms of human risk is unknown *[see Warnings and Precautions (5.6)]*.

**Mutagenesis:** Lurasidone was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in Chinese Hamster Lung (CHL) cells, or the *in vivo* mouse bone marrow micronucleus test.

**Impairment of Fertility:** Lurasidone was administered orally to female rats at doses of 0.1, 1.5, 15, or 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through day 7 of gestation. Estrus cycle irregularities were seen at 1.5 mg/kg and above; the no-effect dose of 0.1 mg/kg is approximately 0.01 times the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area. Fertility was reduced only at the highest dose and this was shown to be reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is 1.8 times the MRHD based on body surface area.

Fertility was not affected in male rats treated orally with lurasidone for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (12 times the MRHD based on body surface area).

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## 14. CLINICAL STUDIES

### 14.1. Schizophrenia

The efficacy of LATUDA for the treatment of schizophrenia was established in four short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.8 years, range 18-72) who met DSM-IV criteria for schizophrenia. One study included an active-control arm (olanzapine) to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a validated clinician-rated scale that measures the subject's current illness state on a 1 to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80 and 120 mg/day was established in two studies for each dose. However, the 120 mg dose did not appear to add additional benefit over the 40 mg dose (Table 10).

**Table 10: Summary of Results for Primary Efficacy Endpoints**

| Study Number | Primary Endpoint | LS Mean (SE)[a] Difference from Placebo in Change from Baseline | | | |
|---|---|---|---|---|---|
| | | LATUDA 40 mg/day | LATUDA 80 mg/day | LATUDA 120 mg/day | Olanzapine 15 mg/day |
| 1 | BPRSd | -5.6* (2.1) | - | -6.7* (2.2) | - |
| 2 | BPRSd | - | -4.7* (1.8) | - | - |
| 3 | PANSS | -9.7* (2.9) | - | -7.5* (3.0) | -12.6* (2.8) |
| 4 | PANSS | -2.1 (2.5) | -6.4* (2.5) | -3.5 (2.5) | - |

*adjusted p-value <0.05 (except for olanzapine)
[a] Least Squares Mean (Standard Error)

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Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

## 16. HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (40 mg), or pale green, oval (80 mg) and identified with strength specific one-sided debossing , "L40" (40 mg), or "L80" (80 mg). Tablets are supplied in the following strengths and package configurations (Table 11):

**Table 11: Package Configuration for LATUDA Tablets**

| Tablet Strength | Package Configuration | NDC Code |
|---|---|---|
| 40 mg | Bottles of 30 | 63402-304-30 |
| | Bottles of 90 | 63402-304-90 |
| | Bottles of 500 | 63402-304-50 |
| | Box of 28<br>4 blister cards, 7 tablets each | 63402-304-04 Carton<br>63402-304-07 Blister |
| | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-304-10 Carton<br>63402-304-01 Blister |
| 80 mg | Bottles of 30 | 63402-308-30 |
| | Bottles of 90 | 63402-308-90 |
| | Bottles of 500 | 63402-308-50 |
| | Box of 28<br>4 blister cards, 7 tablets each | 63402-308-04 Carton<br>63402-308-07 Blister |
| | Box of 100 (Hospital Unit Dose)<br>10 blister cards, 10 tablets each | 63402-308-10 Carton<br>63402-308-01 Blister |

**Storage**

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) *[See USP Controlled Room Temperature]*.

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## 17. PATIENT COUNSELING INFORMATION

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

### 17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis [*see Boxed Warning; Warnings and Precautions (5.1)*].

### 17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

### 17.3 Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [*see Warnings and Precautions (5.5)*].

### 17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.8)]*.

### 17.5 Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking LATUDA [*see Warnings and Precautions (5.7)*].

### 17.6 Interference with Cognitive and Motor Performance

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.10)]*.

### 17.7 Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA *[see Use in Specific Populations (8.1)]*.

### 17.8 Concomitant Medication and Alcohol

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be advised to avoid alcohol while taking LATUDA *[see Drug Interactions (7)]*.

### 17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.11)]*.

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC. f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**DEFENDANTS' RENEWED MOTION FOR A DIRECTED VERDICT** |

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TO: JOHN B. WHITE, JOHN S. SIMMONS, AND FLETCHER V. TRAMMELL
ATTORNEYS FOR PLAINTIFF

Pursuant to Rule 50 of the South Carolina Rules of Civil Procedure, Defendants Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby renew their previously filed Motion for a Directed Verdict and again ask this Court to enter an Order directing a verdict for Defendants on the claim of Plaintiff, the State of South Carolina, under the South Carolina Unfair Trade Practices Act ("SCUTPA"). In addition to the grounds outlined in Defendants' Motion for a Directed Verdict, Memorandum of Law in Support of Defendants' Renewed Motion for a Directed Verdict, and the Reply in Support of Defendants' Motion for a Directed Verdict, all of which are incorporated herein by reference, a directed verdict is appropriate for four additional reasons.

**First**, when ruling on Defendants' first Motion for a Directed Verdict, the Court declined to apply SCUTPA's regulated activity exemption, S.C. Code Ann. § 39-5-40, because there was evidence of "off-label promotion" and "nondisclosures to the FDA."

However, the State has not based its claim on alleged off-label promotion or alleged nondisclosures to the FDA. Rather, it argued – and the Court held – that this type of evidence was admissible only as to the element of "willfulness."

**Second**, the State's SCUTPA claim based on the Risperdal package insert is preempted by federal law. The State did not offer evidence to show with the requisite specificity what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence" of any association, "causal" or not, or exactly "when" the inadequacy existed as a result of the "newly acquired information." The State's claim therefore does not fall within the exception to preemption recognized by *Wyeth v. Levine*, 129 S. Ct. 1187 (2009). To the extent the State's claim is based on the purported failure to disclose to the FDA information regarding the results of two Janssen "studies," it is a "fraud on the FDA claim" preempted under *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 348 (2001). Additionally, to the extent the State's claim is based on the supposed "off-label promotion" of Risperdal, it is expressly preempted by the Food, Drug, and Cosmetic Act. *See* 21 U.S.C. § 337(a).

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**Third**, "[w]hether an act or practice is unfair or deceptive within the meaning of the [S]CUTPA depends upon the surrounding facts and the impact of the transaction on the marketplace." *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (2000). The only evidence regarding the "impact" of the November 10, 2003 mailing on the marketplace in South Carolina is evidence presented by Defendants. That evidence consists of: (1) the testimony of the present and former medical directors of the South Carolina Department of Mental Health, and (2) a stipulation between the parties that there was no change in Risperdal's South Carolina Medicaid and State Health Plan market share when the November 2003 mailing was sent *or* when Janssen sent a follow-up letter in July

2004. A directed verdict is appropriate because there is no evidence that the November 2003 mailing had any impact whatsoever on the South Carolina marketplace.

**Fourth**, there are no facts of record that would support a jury finding that (i) Johnson & Johnson itself violated SCUTPA, or (ii) Defendants disregarded the independent corporate existence of Johnson & Johnson, a separate legal entity that functions solely as a holding company. Although there are documents and testimony relating to Johnson & Johnson Pharmaceutical Research & Development, L.L.C., the only conclusion supported by the evidence is that Johnson & Johnson Pharmaceutical Research & Development, L.L.C., like Janssen, is a subsidiary of Johnson & Johnson with an entirely separate corporate identity.

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WHEREFORE, for the reasons stated herein, in the accompanying Memorandum of Law, and in Defendants' original Motion for a Directed Verdict, Memorandum of Law in Support of Defendants' Renewed Motion for a Directed Verdict, and the Reply in Support of motion for a Directed Verdict, the Court should grant Defendants' Motion in its entirety.

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March 21, 2011.

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC. f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' RENEWED MOTION FOR A DIRECTED VERDICT** |

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Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through their undersigned counsel, hereby submit this Memorandum of Law in support of their Renewed Motion for a Directed Verdict.

## I. INTRODUCTION

Plaintiff, the State of South Carolina, has chosen to pursue a single claim against Defendants – a claim under the South Carolina Unfair Trade Practices Act ("SCUTPA"). As its sole remaining claim, the State asserts that Defendants engaged in certain allegedly unfair or deceptive trade practices: (1) the dissemination of a November 10, 2003 mailing by Janssen to South Carolina physicians; and (2) the distribution of a package insert, or product label, for Risperdal (the "Risperdal package insert" or the "package insert"), which was approved repeatedly by the U.S. Food and Drug Administration ("FDA") over a fifteen-year period.

Defendants' Motion for a Directed Verdict, which is incorporated herein by reference (and attached hereto, along with the Memorandum of Law in Support of Defendants' Renewed Motion for a Directed Verdict, as Ex. A, and Reply in Support of Defendants' Motion for a Directed Verdict, as Ex. B), set forth eight grounds for a directed verdict based on insufficiency of the evidence. In Defendants' renewed motion, Defendants incorporate those original eight grounds and set forth four additional reasons why a directed verdict is necessary here.

## II. THE STATE'S SCUTPA CLAIM BASED ON THE FDA-APPROVED RISPERDAL PACKAGE INSERT FAILS BECAUSE, ON THIS RECORD, THE STATE CANNOT AVOID APPLICATION OF THE REGULATED ACTIVITY EXEMPTION

### A. The State's SCUTPA Claim Is Not Based On Alleged Nondisclosures To The FDA Or Alleged Off-Label Promotion.

In denying Defendants' Motion for a Directed Verdict as to application of SCUTPA's regulated activity exemption, S.C. Code Ann. § 39-5-40, the Court stated:

> Secondly, the motion concerning the regulated activity exemption contained in the code Section [39-5-40] – and, again, for reasons previously stated by the Court in other rulings, pretrial in this case, of the actions which are complained of by the State in this matter do not fall into the areas protected by the safe harbor provisions of SCUTPA.
>
> The allegations and evidence presented or the inferences that can be drawn do establish a cause of action that is not covered by the regulatory safe harbor in that some of the actions which have been described in the evidence are not permitted by state law – by federal law or federal regulation. **That would include withholding of pertinent information concerning representations made to the FDA and potential off-label promotions.** Therefore, my prior ruling will stand on this, and that motion is denied as well.

Trial Tr. vol. VIII, 1803:8-1804:1, Mar. 16, 2011 (emphasis added).

Defendants respectfully maintain that the evidence identified by the Court as sufficient to avoid application of the regulated activity exemption is not relevant to the threshold issue of whether there is an unfair or deceptive trade practice. In particular, by

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the State's own admission, the evidence cited by the Court is not the alleged deceptive or unfair conduct upon which the State bases its claim under SCUTPA. Rather, this evidence was introduced – and ruled admissible – only to establish willfulness, which is an entirely separate SCUTPA element. For example, the State argued that documents and testimony relating to promotional materials were relevant only to the issue of "willfulness":

> And I would submit to the Court that these promotional materials, what they say and when they say it, when taken in juxtaposition with what the regulatory people were telling them and what the science was telling them, shows that this was not a mistake, this was not a whoops, this was not some rogue employee, this was a corporate strategy.
>
> And so for the purpose of establishing willfulness and intentional conduct, we will be proposing or presenting evidence along those lines, but it will go to that corporate intent, that corporate motivation, that willfulness aspect.
>
> . . . .
>
> So for those reasons, those things will be presented to show motive and to show intent and intentional conduct.
>
> THE COURT: I think the issue is willfulness; is it not?
>
> MR. COGGINS: Yes, sir. And so we have to show willfulness. That's one of the ways we'll be going about doing it. We have no quarrel with the defense in that we're not going to be asking the Court to assess any damages based on that conduct.
>
> . . . .
>
> . . . All we'll do with the promotional material is identify corporate strategies for purposes of demonstrating willfulness.

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Trial Tr. vol. I, 69:14-71:10, 78:3-5, Mar. 7, 2011 (argument by Mr. Coggins, counsel for the State). The State further argued that it was necessary to introduce internal Janssen documents – which include documents said by the State to be related to alleged off-label promotion and alleged nondisclosures to the FDA – solely to prove "willfulness":

> MR. COGGINS: Just very briefly, Your Honor. As with a lot of cases – and I try a fair number of discrimination cases where

> you have to try to show that something was an intentional act, that somebody was fired because of their age or race or whatever, I would simply point out what I know is obvious to the Court. If you cannot use the internal documents of the Defendant to establish willfulness, to establish what they knew and when they knew it, you can never sue an organization or corporate entity and prove those things.
>
> Absent somebody having an attack of conscience and a Perry Mason moment and admitting in open court.
>
> The only way you can go back and prove that is to use internal documents, internal communications, to show what the people were saying and thinking and doing when their idea was to make a profit, not to defend a lawsuit. It's nothing new. The defense knows that. And I would, with respect to the specific answer that Mr. Posner pointed the Court to, I would make this point.

*Id.* at 84:10-85:7 (argument by Mr. Coggins, counsel for the State). When ruling on the admissibility of these categories of evidence, the Court specifically limited the admissibility of the documents and testimony to the question of "willfulness":

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> THE COURT: And the parameters are going to be limited to willfulness?
>
> MR. COGGINS: Yes, sir.
>
> THE COURT: Won't be any, as you said, cards, promotional materials, things of that nature. I'm not going to allow it, but I will allow it on the issue of willfulness in terms of internal documents that you referenced.

*Id.* at 86:23-87:5. Accordingly, Defendants are entitled to a directed verdict on the State's claim based on the FDA-approved Risperdal package insert because evidence as to alleged improper off-label promotion or the alleged nondisclosure of information, regardless of whether such activities are "permitted," cannot be the basis for a recovery on the State's SCUTPA claim.

### B. The Undisputed Evidence In The Record Shows That The FDA Never Found The Risperdal Label Inadequate.

The regulated activity exemption also is a bar to the State's claim on the Risperdal package insert because the record at the close of the case shows that the FDA never found the Risperdal label inadequate. *See* Trial Tr. vol. VII, 1518:23-1520:2, Mar. 15, 2011 (testimony of Dr. Mahmoud). Even when it requested a class-wide label change in September 2003, the FDA never said that the existing package insert was inadequate, i.e., that Janssen should have updated its package insert to add a warning earlier. Rather, the FDA simply requested, on a going forward basis, that the package insert be revised to add additional warning language. *See* Ex. C, P0520 (Letter from R. Katz to C. McGowan). The evidence thus shows that the Risperdal package insert was always "allowed" and "permitted" by the FDA.

### C. The Record Does Not Establish That Janssen Could Or Should Have Updated The Label Using the "Changes Being Effected" Procedures.

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In addition, Defendants previously moved for a directed verdict based on the part of this Court's February 25, 2011 Opinion discussing the regulated activity exemption. In the Court's February 25, 2011 Opinion, the Court held that the State could avoid application of the exemption by showing that Janssen possessed the requisite information to update the label. Slip op. at 7-8 (Feb. 25, 2011) ("This Court has previously noted that drug manufacturers have a continuing duty to update its labels so as to include new more stringent warnings concerning the use and efficacy of it drugs and the warning associated therewith. *See* 21 C.F.R. Section 314.70 (c)(6)(iii)(A), (C)).") Despite being given this opportunity, the State did not present evidence sufficient to establish that Janssen had a duty to update because the testimony of the State's experts did not show there was a

relevant "reasonable association" between Risperdal use and any serious risk that was not already in the label.[1]

According to Dr. Wirshing, the State's expert, a duty to update purportedly exists when:

> Q. And what does it say about when a warning should be revised or when a warning should be added?
>
> A. It uses the language – something called reasonable evidence in association, which means that there needs to be some kind of scientific data or experience that indicates the drug is associated with the event. But you don't have to have actually proven there's a cause-and-effect relationship, just the two things appear to be related or associated.
>
> Q. Okay. You don't have to prove – in order to add a safety risk to a drug's warning, you don't have to prove – the manufacturer doesn't have to prove to itself that the drug caused that safety risk, right?
>
> . . . .
>
> Q. Just describe briefly the level of evidence that a drug company needs to add a warning to its label.
>
> A. Um, the language here that I just read that says "reasonable evidence of association" and then it says later "a causal relationship need not have been proved," what that means is, you don't have to have definitive proof. For example, if you have experience from patients and you've tried to identify that the two things are related but you may not definitively know, you don't have to have that level of proof. You have to know that you have reasonable understanding that the two events are related. So in this case, for Risperdal, reasonable evidence that diabetes in

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[1] In their Request for Corrective Instruction as to the Sheldon Bradshaw testimony, Defendants have shown that the regulations actually required a "causal association." The point here, however, is that the proof did not even meet the arguably lower standard proposed by plaintiff's experts – there was no showing of newly discovered scientific evidence of a reasonable association between Risperdal and a previously undisclosed risk.

someone was associated with ingestion of the drug, or weight gain is associated with ingestion of the drug.

Trial Tr. vol. IV, 670:21-672:13, Mar. 10, 2011. However, Dr. Wirshing and Dr. Plunkett, the State's experts, could not even satisfy their own purported standard. Neither could they identify with any specificity exactly what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence" of any association, or exactly "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing). For this reason as well, the regulated activity exemption bars the State's package insert claim, and the claim should not be submitted to the jury.

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## III. THE STATE'S PACKAGE INSERT CLAIM IS PREEMPTED BY FEDERAL LAW.

*Wyeth v. Levine*, 129 S. Ct. 1187, 1196 (2009), provides a narrow exception to principles of federal preemption when a plaintiff alleges that a pharmaceutical manufacturer had "newly acquired" information sufficient to conclude that the manufacturer had an obligation to update its label under the Changes Being Effected ("CBE") regulations. *Wyeth*, 129 S. Ct. at 1196-97. As noted above, the testimony of the State's experts did not state with the required specificity exactly what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence" of any association, or exactly "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing). For at least this reason, the *Wyeth* exception does not apply, and the State's package insert claim is preempted by federal law.

The State's claim also is preempted to the extent that it is based on: (1) the alleged failure to disclose to the FDA the results of two studies (referred to by the State as "RIS-113" and "ERI"); and (2) the supposed "off-label promotion" of Risperdal or other violations of federal law or regulations. *See, e.g.*, Trial Tr. vol. III, 633:16-634:2, Mar. 9, 2011 (Dr. Wirshing testifying that results of "RIS-113" should have been disclosed to the FDA); Trial Tr. vol. V, 1074:21-1075:12, Mar. 11, 2011 (Dr. Plunkett testifying that results of "RIS-113" and "ERI" should have been disclosed to the FDA); Trial Tr. vol. IV, 861:5-22, Mar. 10, 2011 (Dr. Plunkett reviewing an internal Janssen document and agreeing with State's counsel that it appears as if Janssen was engaging in "off-label promotion"). The first simply is a "fraud on the FDA claim," which is impliedly preempted. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001). The second is expressly preempted by the Food, Drug, and Cosmetic Act as an impermissible attempt to pursue a private cause of action for alleged violations of that Act. 21 U.S.C. § 337(a); *Buckman*, 531 U.S. at 349 n.4 (explaining that Food, Drug, and Cosmetic Act "leaves no doubt that it is the Federal Government that is "authorized to file suit for noncompliance" with FDA regulations (quoting 21 U.S.C. § 337(a)).

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The South Carolina Supreme Court recently held that: "When a federal statute contains an express provision regarding preemption, the preemption inquiry must focus on the plain wording of that provision, which generally contains the most reliable evidence as to whether Congress intended to preempt state law." *City of Cayce v. Norfolk S. Ry. Co.*, __ S.E.2d __, No. 26925, 2011 WL 382553, at *3 (S.C. Feb. 7, 2011). Given the express preemption set forth in 21 U.S.C. § 337(a), the State cannot base any part of its SCUTPA claim on violations of federal law or regulations. The State's attempt to do exactly that is preempted by federal law.

## IV. The State's SCUTPA Claim Should Not Be Submitted To The Jury Because The Evidence In The Record Does Not Show Janssen's November 2003 Mailing Had An Impact On The Marketplace.

Under South Carolina law, in order to show that Janssen's November 2003 mailing violated SCUTPA, the State must prove that the mailing had an impact on the South Carolina marketplace. *See deBondt*, 342 S.C. at 269, 536 S.E.2d at 407 ("Whether an act or practice is unfair or deceptive within the meaning of the [SC]UTPA depends upon the surrounding facts and the impact of the transaction on the marketplace."). Under the plain language of the *deBondt* decision, this requires *facts* showing the impact. *See id.*, 536 S.E.2d at 407.

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*The only evidence in this case regarding the impact – or lack thereof – the* November 2003 mailing had on the South Carolina marketplace is evidence presented by Defendants through the testimony of Dr. Bank and Dr. Ratliff. Dr. Bank testified that as *each atypical antipsychotic was introduced into the marketplace, he observed the diabetes-*related effects associated with that particular medicine within the first year or two of prescribing the medicine. Trial Tr. vol. IX, 2112:12-23, Mar. 17, 2011. He also testified that by 2002, other physicians who prescribed atypical antipsychotics also had observed diabetes-related side effects, including weight gain, in their patients. *Id.* at 2118:11-18, 2119:4-6. Dr. Bank further testified that the only thing "new" in the Consensus Statement, which was published in February 2004, "was that the American Diabetes Association and the American Psychiatric Association had concurred that this [observing an association between atypical antipsychotics and diabetes] was the experience of a community of physicians that are represented by this document." *Id.* at 2125:2-7, 2125:16-23. Dr. Ratliff testified that the Consensus Statement was consistent with her observations and with what she had discussed with her colleagues. *Id.* at 2161:21-2163:13. Equally significant, the parties stipulated that there was no change in Risperdal's market share for the South

Carolina Medicaid or State Health Plan programs when the November 2003 mailing was sent *or* when Janssen sent a follow-up letter in July 2004. *See* Ex. D, D7337.

Because there is no evidence that the November 2003 mailing had any impact whatsoever on the South Carolina marketplace, the mailing did not violate SCUTPA. The State's SCUTPA claim as to the November 2003 mailing should not be submitted to the jury.

## V. There Is No Evidence In The Record Sufficient To Send To The Jury The Question Whether Johnson & Johnson Violated SCUTPA.

When ruling on Defendants' Motion for a Direct Verdict regarding Johnson & Johnson, the Court stated:

> Finally, as to the inclusion of Johnson & Johnson in the case, I've reviewed the cases in South Carolina that have to do with alter ego corporations. I'm also not unmindful that many of the exhibits that have been presented during this trial were on Johnson & Johnson letterhead or signed by officials of the Johnson & Johnson corporation. Many of the representations were made with approval by people who are high in the Johnson & Johnson chain of command. And I find there is sufficient evidence for them to remain in the case.

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Trial Tr. vol. VIII, 1805:22-1806:07, Mar. 16, 2011. There are documents in the record that appear on the letterhead of Johnson & Johnson Pharmaceutical Research & Development, L.L.C ("J&JPRD"), signed by employees of J&JPRD. *See, e.g.*, Ex. E, D6211 (Apr. 18, 2002 Letter from S. Merchant to R. Katz); Ex. F, D3140 (Sept. 24, 2003 Letter from E. Brann to R. Katz); Ex. G, P430 (Nov. 26, 2003 Letter from S. Merchant to R. Katz); Ex. H, P436 (Apr. 28, 2004 Letter from D. Ohye to T. Abrams); Ex. I, D919 (Mar. 29, 2004 Letter from S. Merchant to R. Katz); Ex. J, D7334 (Aug. 27, 2004 Letter from S. Merchant to R. Katz). But there are no documents in the record on Johnson & Johnson letterhead and no letters signed by officials acting for Johnson & Johnson. J&JPRD is not the same as Johnson & Johnson; it has a separate corporate identity, as indicated by the different name

and the "L.L.C.," and as explained by Michael Chester. *See* Trial Tr. vol. VIII 1931:2-8, Mar. 16, 2011 (testimony of Mr. Chester explaining that J&JPRD is a "subsidiary" of Johnson & Johnson). *Moreover, the State has not presented any evidence that an official of Johnson* & Johnson approved any of the statements at issue in this case.

Three slide presentations with a Johnson & Johnson logo on the first slide also appear in the record, but they do not establish the essential elements of the State's SCUTPA claim; indeed, they do not even relate to the State's claim. One document is the Johnson & Johnson Credo. *See* Ex. K, P1035. The other two documents contain information presented at meetings of the Integrated Development Committee ("IDC"). *See* Ex. L, P435; Ex. M, P2587. The IDC is a committee comprised of senior scientists employed by J&JPRD and other Johnson & Johnson subsidiaries. *See* Trial Tr. vol. VII, 1644:10-19, Mar. 15, 2011 (testimony of Dr. Mahmoud); Trial Tr. vol. VIII, 1838:3-6, Mar. 16, 2011 (testimony of Dr. Caers).

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These documents do not allow veil piercing by way of the alter ego theory. And they certainly are not sufficient to establish direct liability on the part of Johnson & Johnson as they are not evidence of any misstatements, misrepresentations, or any action by Johnson & Johnson.

Notably, when the Court ruled on the admissibility of these internal documents, it allowed them to be admitted only as to the question of "willfulness":

> THE COURT: *And the parameters are going to be limited to* willfulness?
>
> MR. COGGINS: *Yes, sir.*
>
> THE COURT: Won't be any, as you said, cards, promotional materials, things of that nature. *I'm not going to allow it, but I* will allow it on the issue of willfulness in terms of internal documents that you referenced.

Trial Tr. vol. I, 86:23-87:5, Mar. 7, 2011. These documents could be considered *only* as to the question of willfulness *only if and only after* the jury determines that Johnson & Johnson's conduct violated SCUTPA. *See* slip op. at 4 (Feb. 25, 2011) ("The question to be decided in this case under S.C. Code § 39-5-110(a) is whether or not unfair methods of competition and unfair or deceptive acts have occurred in the conduct of the Defendants trade or commerce as is defined in S.C. Code § 39-5-20. Should that question be answered in the affirmative, the next inquiry will be whether or not those illegal acts or practices have been employed "willfully.").

Accordingly, a verdict should be directed in favor of Johnson & Johnson and against the State on the State's SCUTPA claim.

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## VI. CONCLUSION

For the foregoing reasons, Defendants respectfully request that this Court enter an Order granting a directed verdict in favor of Defendants and against Plaintiff on its sole remaining claim.

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March 21, 2011.

# EXHIBIT A

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**DEFENDANTS' MOTION FOR A DIRECTED VERDICT** |

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TO: JOHN B. WHITE, JOHN S. SIMMONS, AND FLETCHER V. TRAMMELL
ATTORNEYS FOR PLAINTIFF

Pursuant to Rule 50(a) of the South Carolina Rules of Civil Procedure, Defendants Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby move this Court for a directed verdict as to the claim of Plaintiff, the State of South Carolina (the "State"), under the South Carolina Unfair Trade Practices Act ("SCUTPA"). The State's SCUTPA claim is based on: (1) a November 10, 2003 mailing from Janssen to South Carolina physicians (the "November 2003 mailing"); and (2) the distribution of the U.S. Food and Drug Administration ("FDA")-approved package insert for Risperdal® ("Risperdal package insert").

Despite years of litigation and sweeping allegations of misconduct directed at Janssen, the State's claim lacks both evidence and legal support. A directed verdict is appropriate for a number of independent reasons.

First, the State's SCUTPA claim based on the November 2003 mailing fails in its entirety because it is expressly preempted by federal law. As this Court and many others

have previously recognized, the U.S. Food, Drug, and Cosmetic Act (the "FDCA" or the "Act") does not permit private causes of action based on violations of the Act. Indeed, federal law provides that *only* the federal government may enforce the FDCA. 21 U.S.C. § 337(a). Nevertheless, the State's evidence that the November 2003 mailing was "deceptive," including the testimony of its expert witnesses, is based only on the FDA's characterization of the November 2003 mailing as "false and misleading in violation of Sections 502(a) and 201(n) of the [FDCA]." As counsel for the State noted, this question is one "for the FDA to decide." Trial Tr. vol. V, 1183:3-9, Mar. 11, 2011.

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**Second**, the State's SCUTPA claim based on the FDA-approved Risperdal package insert fails in its entirety because it is barred by SCUTPA's regulated activity exemption. S.C. Code Ann. § 39-5-4(a). The testimony of the State's experts, that the Risperdal package insert was "inadequate" at the time of product launch, places the Risperdal package insert claim squarely within the regulated activity exemption as enunciated by this Court. Not only federal regulations but also common sense dictate that a pharmaceutical manufacturer cannot have a duty to update the package insert on the very first day it is issued, when the FDA approved every single word of the initial label, which was required to be used "verbatim."

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**Third**, the State's deceptive trade practice claim cannot be submitted to the jury because:

(1) the November 2003 mailing and the Risperdal package insert do not contain any actionable representations – opinions accompanied by all the support for them are not actionable;

(2) the State has no evidence – factual, expert, or otherwise – that: (a) Janssen did not have a reasonable basis for the opinions set forth in either the November 2003 mailing or the Risperdal package insert; or (b) either the November 2003 mailing or the Risperdal package insert had a tendency to deceive or was likely to deceive the relevant audience, South Carolina physicians; and

(3) the State has no evidence – factual, expert, or otherwise – that either the November 2003 mailing or the Risperdal package insert was material to South Carolina physicians' decisions to prescribe Risperdal for their patients.

**Fourth**, the State's belated claim that the November 2003 mailing and the Risperdal package insert constitute "unfair" trade practices also cannot be submitted to the jury because:

(1) the State has no evidence – factual, expert, or otherwise – that satisfies the essential elements of a claim for an unfair trade practice; and

(2) alleged violations of public policy alone are not a basis for a finding that an act or practice is "unfair."

**Fifth**, the State's SCUTPA claim, whether based on a deceptive trade practice or an unfair practice fails because the State did not introduce sufficient evidence to satisfy the element that the alleged unfair or deceptive trade practice adversely affected the public interest.

**Sixth**, the State's claim of unfair and/or deceptive trade practices also fails because the State has not introduced sufficient evidence for the jury to find willful conduct – as "willfulness" is defined by South Carolina law.

**Seventh**, the State's claim is barred by SCUTPA's three year statute of limitations.

**Finally**, there are no facts of record that would support any claim or effort to disregard the separate corporate existence of defendant Johnson & Johnson, a separate legal entity that functions solely as a holding company. Accordingly, a judgment must be entered in favor of Johnson & Johnson and against the State on the State's SCUTPA claim.

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WHEREFORE, for the reasons stated herein and in the accompanying memorandum of law, the Court should grant Defendants' Motion in its entirety.

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' MOTION FOR A DIRECTED VERDICT** |

Defendants, Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") and Johnson & Johnson (erroneously named as Johnson & Johnson, Inc.), by and through the undersigned counsel, hereby submit this Memorandum of Law in support of their Motion for a Directed Verdict.

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## I. INTRODUCTION

Plaintiff, the State of South Carolina (the "State"), has chosen to pursue a single claim against Defendants – a claim under the South Carolina Unfair Trade Practises Act ("SCUTPA"). As its sole remaining claim, the State asserts that Defendants engaged in certain allegedly unfair or deceptive trade practices: (1) the dissemination of a November 10, 2003 mailing by Janssen to South Carolina physicians (the "November 2003 mailing") and (2) the distribution of a package insert, or product label, for Risperdal® (the "Risperdal package insert" or the "package insert"), which was approved repeatedly by the U.S. Food and Drug Administration ("FDA") over a fifteen-year period.

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The State does not challenge either the November 2003 mailing or the Risperdal package insert in its entirety. Rather, the State only asserts that: (1) three sentences of the

cover letter to the November 2003 mailing are purportedly "deceptive" or "unfair"; and (2) several sentences of the multi-page FDA-approved Risperdal package insert are also purportedly "deceptive" or "unfair," and then only as to certain limited potential risks as to Risperdal.

After four years of litigation, however, the State has offered *no* material facts in support of its SCUTPA claim. Instead, the State has only offered as "evidence" the personal opinions of two experts. Neither South Carolina law nor applicable federal decisions (applicable to the determination of the State's claim by the express terms of SCUTPA) allow such speculative evidence to be submitted to a jury in support of a claim for either a deceptive or an unfair trade practice. Defendants' motion for a directed verdict should be granted because the factual and legal grounds upon which the State's SCUTPA claim fails are not only numerous but also insurmountable.

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## II. THE STATE'S "EVIDENCE"

### A. As To The November 2003 Mailing.

In its case in chief, the State's only "evidence" that the November 2003 mailing was "unfair" or "deceptive" in violation of SCUTPA was: (1) the opinions of its experts, Laura M. Plunkett, Ph.D. (a toxicologist and pharmacologist, not a physician or an epidemiologist) and William C. Wirshing, M.D. (a psychiatrist); and (2) an April 2004 "warning letter" from the Director of the Division of Drug Marketing, Advertising, and Communications ("DDMAC") of the FDA.

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### B. As To The Risperdal Package Insert.

The State's "evidence" that the Risperdal package insert was "unfair" or "deceptive" again consisted only of the testimony of experts. One of the State's experts, Dr. Wirshing, testified that the label from 1994 to 2004 did not adequately disclose the risk of diabetes; the label from 1997 to 2006 did not adequately disclose the risk of death in the elderly; and

the label from 1994 to 2007 did not adequately disclose the risk of hyperprolactinemia. Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011. The State's other expert, Dr. Plunkett, testified that from 1994 to 2007 the label did not adequately warn of the dangers of hyperprolactinemia and from 1994 to 2004 the label did not adequately warn of the risk of diabetes. Trial Tr. vol. IV, 935:3-936:22, Mar. 10, 2011.

## III. DIRECTED VERDICT STANDARD

"In deciding whether to grant or deny a directed verdict motion, the court is concerned only with the existence or nonexistence of evidence." *Ecclesiates Prod. Ministries v. Outparcel Assocs., Inc.*, 374 S.C. 483, 491, 649 S.E.2d 494, 498 (Ct. App. 2007) (citation omitted). Further, although "[t]he issue must be submitted to the jury whenever there is material evidence tending to establish the issue in the mind of a reasonable juror," *id.* at 490, 656 S.E.2d at 407 (internal quotations and citations omitted), it is clear that "this rule does not authorize submission of speculative, theoretical, and hypothetical views to the jury," *Parrish v. Allison*, 376 S.C. 308, 319-20, 656 S.E.2d 382, 388 (Ct. App. 2007). Thus, "[a] directed verdict should be granted where the evidence raises no issue for the jury as to the defendant's liability." *Guffey v. Columbia/Colleton Reg'l Hosp., Inc.*, 364 S.C. 158, 163, 612 S.E.2d 695, 697 (2005). In addition, a directed verdict also is proper "where there is no evidence on any one element of the alleged cause of action." *Id.*

## IV. ARGUMENT

### A. The State's SCUTPA Claim Based On The November 2003 Mailing Is Preempted By Federal Law.

As the State presented its case, the SCUTPA claim as to the November 2003 mailing is based entirely on Janssen's alleged violations of federal law. Time and again, the State introduced or based its expert witnesses' testimony on the 2004 warning letter sent by

the FDA and merely had its experts agree with the statements in the letter. *See, e.g.*, Trial Tr. vol. V, 1058:1-1059:15, Mar. 11, 2011 (Plunkett's opinion that the November 2003 mailing was false and misleading is "based upon the FDA standard"). In fact, the State presented testimony from a Janssen sales representative seemingly to prove the point that "it's for [the FDA] to decide." *Id.* at 1183:3-9 (testimony of Alderman).

This Court, like many others, previously acknowledged that preemption would clearly apply to a claim like this, based on an alleged violation of federal law. *See State ex rel. McMaster v. Eli Lilly & Co.*, No. 2007-CP-42-1855, slip op. at 23, 2009 WL 6058384 (S.C. Ct. Com. Pl. Sept. 22, 2009) (Couch, J.) ("*Lilly*") (recognizing that "to the extent that the Plaintiff in this case might be seeking to bring a private cause of action based on the [Food, Drug, and Cosmetic Act (the 'FDCA' or the 'Act')] the motion [for summary judgment] would be granted"); *see also Weston v. Kim's Dollar Store*, 385 S.C. 520, 537, 684 S.E.2d 768, 778 (Ct. App. 2009) (holding that the circuit court correctly applied the doctrine of federal preemption in determining that state law claims "dependent on warning, labeling, design, marketing, misbranding, or other similar claims" are preempted by federal law "because a jury's acceptance of the disputed claims could result in different or additional requirements from the federal requirements").

Indeed, federal law provides that *only* the federal government may enforce federal drug labeling law and expressly prohibits attempts to use state law to enforce federal drug labeling law. The FDCA provides that any "proceedings for the enforcement, or to restrain violations, of this chapter [of the FDCA] shall be by and in the name of the United States." 21 U.S.C. § 337(a). There can be no uncertainty as to the primacy of the FDA because, as the United States Supreme Court has explained, Section 337(a) "leaves no doubt that" the federal government has the exclusive authority to "file suit for noncompliance" with FDA

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regulations. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4 (2001); *accord Lilly*, No. 2007-CP-42-1855, slip op. at 23, 2009 WL 6058384 (Couch, J.).

The State's entire claim as to the November 2003 mailing is inextricably intertwined with the April 2004 DDMAC warning letter, the centerpiece of the State's claim. But that warning letter speaks only of purported violations of the FDCA. Thus, the State's claim is that the November 2003 mailing was "deceptive" because it was, in DDMAC's view, "false or misleading in violation of Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act." Trial Ex. P232. The State, then, is improperly attempting to impose liability based on alleged violations of the FDCA. *Id.*

This is particularly inappropriate in the present case because DDMAC investigated all aspects of the November 2003 mailing and took no further steps after Janssen issued its July 2004 letter. Trial Tr. vol. IV, 838:13-23, Mar. 10, 2011. That is, DDMAC made a conscious decision not to pursue any of the panoply of remedies available to it. See *generally* FDA Regulatory Procedures Manual § 4-1-1 ("The Warning Letter was developed to correct violations of the statutes or regulations. Also available to the agency are enforcement strategies which are based on the particular set of circumstances at hand and may include sequential or concurrent FDA enforcement actions such as recall, seizure, injunction, administrative detention, civil money penalties and/or prosecution to achieve correction."). *See also* Trial Tr. vol. III, 838:13-23, Mar. 10, 2011 (If Janssen had not complied, the FDA could have pursued administrative enforcement actions).[1]

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[1] The State's claim also is preempted to the extent that it is based on: (1) the alleged failure to disclose to the FDA the results of two studies (referred to by the State as "RIS-113" and "ERI"); and (2) the supposed "off-label promotion" of Risperdal. *See, e.g.*, Trial Tr. vol. III, 633:16-634:2, Mar. 9, 2011 (Wirshing testifying that results of "RIS-113" should have been disclosed to the FDA); Trial Tr. vol. V, 1074:21-1075:12, Mar. 11, 2011 (Plunkett testifying that results of "RIS-113" and "ERI" should have been disclosed to the FDA); Trial Tr. vol. IV,

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Thus, Defendants are entitled to a directed verdict as to the State's claim based on the November 2003 mailing because such a claim is preempted by federal law.

**B. <u>The State's SCUTPA Claim Based On The FDA-Approved Risperdal Package Insert Fails Because The Evidence Presented Does Not Support An "Ability to Update" Exception To The Regulated Activity Exemption.</u>**

This Court declined, at the summary judgment stage, to apply the regulated activity exemption provided under S.C. Code Ann. § 39-5-40 as a bar to the State's claim based on the FDA-approved Risperdal package insert. The Court explained:

> This Court has previously noted that drug manufacturers have a continuing duty to update its labels so as to include new more stringent warnings concerning the use and efficacy of it drugs and the warning associated therewith. *See* 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C). It is clear to this Court that the FDA does not allow or permit deceptive activities in the marketing and labeling of drugs, and further, it requires that drug manufactures are required to up-date their warnings based on available information.

Slip op. at 7-8 (Feb. 25, 2011).

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861:5-22, Mar. 10, 2011 (Plunkett agreeing with State's counsel upon review of internal Janssen document that it appears as if Janssen was engaging in "off-label promotion"). The first simply is a "fraud on the FDA claim," which is barred by *Buckman* and this Court's decision in *Lilly*. *See Buckman*, 531 U.S. at 348; *Lilly*, slip op. at 23, 2009 WL 6058384; *see also* Trial Tr. vol. I, 56:10-12, 58:5, Mar. 7, 2011. The second is expressly preempted by the FDCA as an impermissible attempt to pursue a private cause of action for alleged violations of the FDCA. Trial Tr. vol. IV, 757:24-25, 758:1-25, 1101:14-17, 1102:1-25, 1103:1-10, Mar. 11, 2011 (Plunkett agreeing with State's counsel that "off label" promotion is against "FDA rules," which "have the force of law"; FDA supposedly "caught" Janssen engaging in off-label promotion (in 1999), which is "against the law"). The off-label promotion claim should also be barred by the representation of the State's counsel, on the first day of trial, that "we're not making a claim based on any of that," i.e., alleged off-label promotion; there would only be "some evidence" of the delivery of package inserts to physicians. Trial Tr. vol. I, 134:6-14, Mar. 7, 2011; *see also Id.* at 77:22-24 (State's counsel: "We'll never come to the Court and say, on November 5th, 1999, ten sales reps said this, which we think violates the statute.").

In support of its decision denying summary judgment on the regulated activity exemption, this Court cited 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C). Under this regulation, known as a changes being effected ("CBE") regulation, a pharmaceutical manufacturer is *not* required – or even permitted – to update a package insert based simply on "available information." Rather, a pharmaceutical manufacturer may *only* update a package insert when it has (i) "newly acquired information" that (ii) constitutes "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter." *Id.*

Under 21 C.F.R. § 201.57(c)(6)(i), "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitively established." In its 2008 revisions to the CBE regulation, the FDA made abundantly clear that use of a CBE submission is appropriate "only to reflect newly acquired information . . . [and then] only if there is sufficient evidence of a causal association with the drug, biologic, or medical device." 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008). The FDA's revision was "intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, *and to prevent overwarning*, which may deter appropriate use of medical products, or overshadow more important warnings." *Id.* at 49605-06 (emphasis added); *see also id.* at 49603 (CBE regulation was meant to "codify the agency's longstanding view concerning when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change.").

The FDA also made clear that what constitutes "newly acquired information" sufficient for application of the CBE regulations is very limited:

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> The definition of "newly acquired information" has been revised to clarify that data, whether derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) needs to be of a "different type or greater severity or frequency than previously included in submissions to FDA".

*Id.* at 49604.

Thus, to show that Janssen had an obligation at some point in time after approval of the initial package insert by the FDA to update its package insert under the CBE regulation, the State was required to provide specific evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" between Risperdal and the risks of hyperglycemia, diabetes, weight gain, hyperprolactinemia, and alpha toxicity. Neither of the State's experts could identify with any specificity exactly what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence of a causal association," or exactly "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). Dr. Wirshing actually testified that at the time of the FDA-mandated class label change, the evidence did not support a conclusion of a "causal" connection between Risperdal and diabetes. Trial vol. III, 496:25-497:10, Mar. 9, 2011 (evidence was "not conclusive" and it was not causal). Dr. Plunkett conceded she was not retained to form a failure to warn opinion related to the Risperdal label. Trial Tr. vol. IV, 932:9-933:21, Mar. 10, 2011.

Both of the State's experts also testified that the Risperdal package insert was "inadequate" at the time of product launch. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). As a matter of law, logic, and common sense, a pharmaceutical manufacturer

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cannot have a duty to update the package insert on the very first day it is issued, when the FDA had just approved every word of the initial label, which was required to be used "verbatim" by Janssen. Trial Ex. P571 (Initial approval letter). The State's expert testimony thus falls far short of establishing any obligation by Janssen to update its package insert as to the risks of diabetes, hyperprolactinemia, and alpha toxicity.

The State attempted to satisfy its burden by repeatedly offering "evidence" as to Janssen's "awareness" of the risks of hyperglycemia, diabetes, weight gain, and hyperprolactinemia. *See, e.g.*, Trial Tr. vol. III, 623-15-626:13, Mar. 9, 2011 (testimony of Wirshing). As the FDA regulations, and the FDA itself make clear, general awareness and knowledge of risks of the use of a prescription medicine are insufficient to require a manufacturer to update its package insert – and will not support the use of the CBE procedures. *See* 21 C.F.R. 314.70(c)(6)(iii)(A),(C); *id.* § 201.57(c)(6)(i); 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008).

Finally, neither of the State's experts provided any testimony as to exactly "what" would cure the alleged inadequacy of the Risperdal package insert. *See, e.g.*, Trial Tr. vol. V, 994:17-24, Mar. 11, 2011 (Plunkett testifying that she has not re-written the label as to the risk of hyperprolactinemia). This lack of clarity is another reason the Court should not allow a jury to decide the State's package insert claim. *Schering-Plough Healthcare Prods. Inc. v. Schwarz Pharma, Inc.*, 586 F. 3d 500, 508 (7th Cir. 2009) ("But Schering has been coy about what it thinks the disclaimer should say, and its coyness makes us doubt that this is a matter that can be resolved intelligently without a decision by the FDA.").

Although the Court permitted the State's "package insert" claim to proceed beyond summary judgment, the State's evidence at trial confirms that: (1) at all times, the Risperdal package insert was approved and permitted by the FDA; (2) the FDA has never determined that the Risperdal package insert was not properly updated by Janssen; (3) the FDA has

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never determined that the Risperdal package insert was false or misleading; (4) the Risperdal package insert was updated and revised multiple times by Janssen with the approval and permission of the FDA; and (5) the State did not present sufficient evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" as to any of the risks which the State alleged were inadequately disclosed. Rather, the State continues to maintain that the Risperdal package insert was "inadequate" from Day One of the sale of Risperdal, a position unsupported by logic, fact, or the law. As the State has not introduced any evidence that Janssen was required to – or permitted to – update its label with a CBE submission, this Court's prior holding and SCUTPA's regulated activity exemption bar the State's package insert claim.

C. **The State Has Failed To Introduce Sufficient Proof Of Each Of The Elements Of Both Its Deceptive Trade Practice Claim And Its Unfair Trade Practice Claim.**

The express terms of SCUTPA require South Carolina courts to be guided by decisions and interpretations of the Federal Trade Commission ("FTC"), including, obviously, policy pronouncements of the FTC itself. *Plowman v. Bagnal*, 316 S.C. 283, 287, 450 S.E.2d 36, 38 (1994) ("In section 39 5 20(b), the Legislature specifically instructs state courts to be guided by the decisions of the Federal Trade Commission (FTC) and the Federal Courts construing the Federal Trade Commission Act, 15 U.S.C. [§] 45(a)(1), interpreting section 39-5-20(a)[.]"). This direction is significant because, as outlined below, these sources not only establish the necessary elements of the State's claim of an unfair or deceptive practice or act but also establish the insufficiency of the evidence offered by the State.

Stated another way, these standards set forth the applicable evidentiary burden for the State. And it is a burden that cannot be satisfied with opinion testimony alone as to whether a particular act or practice is "unfair" or "deceptive"; instead, the State is required to



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present *facts* supporting each of the elements of its SCUTPA claim. As the State's evidence fails to establish the essential elements of either a deceptive trade practice claim or an unfair trade practice claim, judgment in favor of Defendants is mandated. *Guffey*, 364 S.C. at 163, 612 S.E.2d at 697 (directed verdict is proper "where there is no evidence on any one element of the alleged cause of action").

### 1. The State Lacks Sufficient Evidence As To The Essential Elements Of Its Deceptive Trade Practices Claim.

Well-settled law provides that to establish liability for a deceptive trade practice, "the FTC must establish that (1) there was a representation; (2) the representation was likely to mislead customers acting reasonably under the circumstances; and (3) the representation was material." *FTC v. Tashman*, 318 F.3d 1273, 1277 (11th Cir. 2003) (citations omitted). The State equally, therefore, is required to establish these elements.

#### a. Lack Of An Actionable Representation.

The November 2003 mailing expressed Janssen's opinion as to the conclusions that could be drawn from a certain "body of evidence from published peer-reviewed epidemiology research." *See* Trial Ex. P1736 (November 10, 2003 mailing). Equally significant, the November 2003 mailing also cited to each of the published epidemiological peer-reviewed studies, thereby fully disclosing the entire scientific basis for the opinion. *Id.* Because Janssen's statement of its opinion was accompanied by a disclosure of the sources upon which the opinion was based – allowing any reader of the November 2003 mailing to draw his own conclusions about the scientific evidence – the mailing cannot be considered deceptive. *See Bruette v. Stokes, Kia, Isuzu, Subaru, Inc.*, No. 2001-CP-10-1800, slip op. at 9, 2002 WL 34128304 (S.C. Ct. Com. Pl. Nov. 6, 2002) ("When the alleged unfair trade practice 'is a misrepresentation, the claimant is not entitled to recover if he had an equal and ample opportunity to ascertain the truth but failed to exercise proper diligence

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to do so.'" (citation omitted)); *see also Pizza Hut, Inc. v. Papa John's Int'l, Inc.*, 227 F.3d 489, 496 (5th Cir. 2000) (holding, under analogous Lanham Act, 15 U.S.C.A. § 1125(a): "Bald assertions of superiority or general statements of opinion cannot form the basis of Lanham Act liability." Rather the statements at issue must be a 'specific and measurable claim, capable of being proved false or of being reasonably interpreted as a statement of objective fact.'" (citations omitted)); *Cytyc Corp. v. Neuromedical Sys., Inc.*, 12 F. Supp. 2d 296, 300 (S.D.N.Y. 1998) ("In the actual statement, contained in a press release, Cytyc identified the specific screening site, and the numbers of positive cases diagnosed with the pap smear and with ThinPrep. The inclusion of such specific evidence means that this statement could not be found to be misleading."). This is especially true where the opinions relate to scientific and medical research. *See, e.g., McDonagh v. Bergan*, No. 03 C 146, 2003 WL 21798735, at *3 (N.D. Ill. July 25, 2003) ("disagreements of this type among medical professionals should be settled by discussion and research in the medical community, not by the courts").

The statements in the Risperdal package insert, like the statements in the November 2003 letter, reflect judgments, by Janssen and/or the FDA, about the meaning and significance of the scientific evidence. As to the package insert, neither of the State's experts even attempted to argue that the statements about diabetes, hyperprolactinemia, etc. were based on anything other than extensive medical research and information as to the use of Risperdal for over a decade, although they took issue with the significance of some of that research and with decisions about the wording of certain parts of the package insert and the prominence of the "risk" information in it. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). And this is dispositive of the State's deceptive trade practice claim.

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The present case illustrates precisely the logical problem and, equally important, the constitutional problem, with the entirety of the State's SCUTPA claim – the State improperly seeks to punish reasonable expressions of scientific opinions by Janssen. To proceed on that claim, the State erroneously believes that the jury may choose among the different experts' positions in the scientific debate and then have the Court punish Janssen for having a different – yet scientifically supported – view. Nothing under applicable law supports this conclusion or result. Thus, the complete absence of a provably false factual representation that could "deceive" the persons to whom it was made precludes the State's deceptive trade practice claim in the first instance.

b. **Absence Of Evidence That The November 2003 Mailing Or The Risperdal Package Insert Had A "Tendency To Deceive" Or Was "Likely To Deceive" South Carolina Physicians.**

Under South Carolina law, the test for SCUTPA liability is whether the challenged statement or act "has a tendency to deceive." *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (Ct. App. 2000). Whether an act has a "tendency to deceive" or is "likely to deceive" "depends upon the surrounding facts and the impact of the transaction on the marketplace." *Id.* As directed by the express terms of SCUTPA, this Court must look to the FTC's Policy Statement on Deception, which similarly provides that the knowledge and sophistication of the relevant audience is to be considered when determining whether a company's trade practice is deceptive or misleading. See 2 Fed. Trade Comm'n App. D-2 (2009). Pursuant to the Policy Statement, "practice or representation directed to a well-educated group, such as a prescription drug advertisement to doctors, would be judged in light of the knowledge and sophistication of that group." *Id.* (emphasis added). The relevant audience, or "marketplace," for the State's SCUTPA claim necessarily is South Carolina physicians because: (1) Risperdal can only be obtained by

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prescription; (2) the November 2003 mailing was sent to physicians; and (3) the package insert is written for physicians.

As part of its proof, therefore, the State was required to present evidence that the November 2003 mailing and the Risperdal package insert actually had a "tendency to deceive" or were "likely to deceive" South Carolina physicians. *See TC X, Inc. v. Commw. Land Title Ins. Co.*, 928 F. Supp. 618, 625 (D.S.C. 1995), *aff'd without op.*, 86 F.3d 1152 (4th Cir. 1996) (granting summary judgment for the defendant on a SCUTPA claim, stating that "[t]here is no evidence that Commonwealth deceived TC X or anyone else regarding its interpretation of the policy").

The State's claim fails because the State did not to prove that either the November 2003 mailing or the Risperdal package insert had a tendency to deceive or were likely to deceive. The State's experts took the position that the November 2003 mailing was somehow inherently "deceptive" and that the Risperdal package insert was "inadequate" as to certain risks. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). But they provided no testimony whatsoever about the knowledge and sophistication of South Carolina physicians, and no testimony as to whether the November 2003 mailing or the Risperdal package insert, with their statements as to the scientific evidence, actually deceived or were "likely to deceive" those physicians. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Wirshing). Without supporting facts, the speculation of experts as to whether a statement is actually "deceptive" is insufficient to satisfy the State's evidentiary burden.

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c. **Lack Of Evidence Of Materiality.**

A material claim is one that is "likely to affect" a party's "conduct or decision with regard to a product or service." FTC Policy Statement on Deception at 2. As the State has

introduced no evidence that either the November 2003 mailing or the Risperdal package insert was material to a single prescribing decision by a South Carolina physician, its deceptive trade practice claim fails for this reason as well.

### 2. The State Also Lacks Sufficient Facts As To Its Unfair Trade Practices Claim.[2]

The State's alternative claim that the November 2003 mailing and the Risperdal package insert are "unfair" acts or practices also cannot be submitted to the jury. "Unfair" acts or practices cannot be "inferred." *Wingard v. Exxon Co., U.S.A.*, 819 F. Supp. 497, 506 (D.S.C. 1992) ("Additionally, an unfair or deceptive trade practice cannot be inferred from the conduct of Exxon. Generally, an unfair trade practice involves a misrepresentation made to a consumer. In this case there is no element of misrepresentation." (citations omitted). Further, "[t]he SCUTPA does not prohibit all business activities that someone may consider 'unfair', however." *Miller v. W.H. Bristow, Inc.*, 739 F. Supp. 1044, 1055 (D.S.C.1990). Thus, the State is required to prove the essential elements of an unfair trade practice, which can easily be determined by reference to both the Federal Trade Commission Act as well another FTC long-standing Policy Statement. *See* 15 U.S.C.A. § 45(n) (FTC Act); FTC Policy Statement on Unfairness (1980).

#### a. Lack Of Evidence Of The Essential Elements Of An Unfair Trade Practices.

In construing SCUTPA, the South Carolina Supreme Court has found decisions from Tennessee courts persuasive authority. *See, e.g., Ward v. Dick Dyer Assocs., Inc.*, 304

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[2] Defendants previously filed a motion to limit, among other things, the State's claim to "deceptive" trade practices, consistent with the State's numerous discovery responses to that effect. As the Court has not ruled explicitly on that aspect of the motion to limit, Defendants address here the insufficiency of the State's evidence as to its purported "unfair" trade practices claim.

S.C. 152, 156, 403 S.E.2d 310, 312 (citing *Skinner v. Steele*, 730 S.W.2d 335 (Tenn. App. 1987)). In defining what constitutes an unfair trade practice, Tennessee courts have adopted the elements set forth in 15 U.S.C. § 45(n) (part of the Federal Trade Commission Act). *Tucker v. Sierra Builders*, 180 S.W.3d 109 (Tenn. App. 2005). As held by the court in *Tucker*:

> In the 1994 legislation reauthorizing the Federal Trade Commission, Congress undertook to codify the Commission's policy statement on unfairness by stating that an act or practice should not be deemed unfair "unless the act or practice causes or is likely to cause substantial injury to consumers which is not reasonably avoidable by consumers themselves and not outweighed by countervailing benefits to consumers or to competition." 15 U.S.C.A. § 45(n). Following the mandate of Tenn. Code Ann. § 47-18-115, we will use this description of unfairness to guide our interpretation of Tenn. Code Ann. § 47-18-104(a).

*Id.* at 116-117. As further explained by the court:

> To be considered "substantial," consumer injury must be more than trivial or speculative. Substantial injury usually involves monetary injury or unwarranted health and safety risks. Consumer injury will be considered substantial if a relatively small harm is inflicted on a large number of consumers or if a greater harm is inflicted on a relatively small number of consumers. Even if an act or practice causes or is likely to cause substantial injury, it will not be considered unfair unless the injury is not reasonably avoidable by consumers themselves. Consumers cannot reasonably avoid injury when a merchant's sales practices unreasonably create or take advantage of an obstacle to the free exercise of consumer decision-making. Practices that unreasonably interfere with consumer decision-making include (1) withholding important information from consumers, (2) overt coercion, or (3) exercising undue influence over a highly susceptible class of consumers.

*Id.* at 117 (citations omitted).

The State's evidence for its unfair trade practice claim falls far short of meeting any of these essential elements. First, any alleged "substantial" injury to consumers from either the November 2003 mailing or the Risperdal package insert is nothing more than

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speculation. Second, any alleged "substantial" injury is more than outweighed by the undisputed benefits to South Carolina residents from the availability and use of Risperdal. The State's expert, Dr. Wirshing, in particular testified in great detail as to the substantial medical benefits of Risperdal. Trial Tr. vol. III, 561:7-568:2, 624:7-14, Mar. 9, 2011. Finally, the State introduced no evidence whatsoever from which a jury could conclude that any aspect of the November 2003 mailing or the Risperdal package insert "unreasonably interfered" with either a consumer's or a physician's decision to choose Risperdal.

**b. <u>Alleged Violations Of Public Policy Alone Are Not A Basis Upon Which The Jury Can Make A Finding That An Act Or Practice Is "Unfair."</u>**

Ever since they were first advanced, only a few weeks ago, the State's "public policy" arguments have been unclear – shifting depending on the particular issue raised. *See, e.g.*, Pl.'s Opp'n to Defs.' Mot. In Limine To Preclude Irrelevant And Unfairly Prejudicial Evidence at 18 ("the State is entitled to introduce evidence of loss and harm sustained by the South Carolina Medicaid program to show that Defendants' labeling of Risperdal prescriptions paid or reimbursed by the State violated S.C. Code § 39-5-20(a) because it was unethical, immoral, and offensive to South Carolina's public policy of not defrauding public agencies that protect the health and welfare of its citizens."); Pl.'s Opp'n To Defs. Mot. For Summ. J. As To Pl.'s Unfair Trade Practices Claim Based On The November 2003 Mailing at 21 ("In its April 2004 Warning Letter to Janssen, the FDA recognized the significant and detrimental impact of the November 2003 "Dear Doctor" letter on the South Carolina public: 'The healthcare community relies on [Dear Doctor] letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers is *a serious public health issue.*'").

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Regardless of the State's public policy argument *du jour*, the State has nothing but speculative public policy concerns as the basis of its unfairness claim. The FTC Act, as well as the FTC's "unfairness" policy statement unequivocally confirm, however, that a violation of public policy alone is not a basis upon which the jury can find that the November 2003 mailing or the Risperdal package insert was an unfair trade practice. 15 U.S.C.A. § 45(n); FTC Policy Statement on Unfairness (1980). Similarly, a violation of public policy cannot be the primary basis upon which the jury can find that the November 2003 mailing was an unfair trade practice. 15 U.S.C.A. § 45(n). Because, after all the State's evidence is in, the State has nothing more than vague, conclusory assertions of a violation of an unspecified "public policy," the State's unfair trade practice claim may not be submitted to the jury.

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**D. Absence Of Sufficient Evidence To Establish That The Alleged Unfair Or Deceptive Trade Practices Adversely Affected The Public Interest.**

The State is required to show that the challenged practice has the potential for repetition. Slip op. at 4 (Feb. 25, 2011). The potential for repetition may be proven by showing: (1) the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) the defendant's procedures created a potential for repetition of the unfair and deceptive acts. *See, e.g., Singleton v. Stokes Motors, Inc.*, 358 S.C. 369, 595 S.E.2d 461 (2004).

**1. The November 2003 Mailing.**

As to the November 2003 mailing, the State did not introduce any evidence that any similar kind of action occurred in the past. Nor did the State introduce any evidence that any procedure of Defendants created a potential for repetition. Indeed, the State introduced no evidence that any prior or subsequent letter to physicians ever has been challenged by anyone, including the FDA. In over a decade of communications with physicians as to the

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risks of Risperdal, the single piece of correspondence challenged by the State is insufficient to establish that the November 2003 mailing "has the potential for repetition."

The January 5, 1999 DDMAC letter, which raised a concern, in the view of a DDMAC reviewer, about "a campaign that markets Risperdal for geriatric patients," Trial Ex. P200, is not sufficient evidence to satisfy SCUTPA's "capable of repetition" element under the decision of *Burbach v. Investors Management Corp.*, 326 S.C. 492, 484 S.E.2d 119 (Ct. App. 1997). Under *Burbach*, the January 5, 1999 DDMAC letter is insufficient – and inadmissible – evidence to satisfy the "capable of repetition" element because: (1) it was issued over five years before the 2004 warning letter; (2) there is no similarity whatsoever between the two letters; the 1999 letter concerned certain marketing materials in connection with geriatric patients and the 2004 warning letter concerned a mailing to healthcare professionals as to changes to the Risperdal package insert as to the risks of diabetes, hyperglycemia, and weight gain; and (3) in over sixteen years, these are the only two isolated instances where the FDA ever raised any concern as to Janssen's activities in relation to Risperdal. *Id.* at 498 n.3, 484 S.E.2d at 122 n.3.

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2. **The Risperdal Package Insert.**

The State's Risperdal package insert claim suffers from the same lack of evidence. The evidence shows that, for more than sixteen years, the agency charged with determining the sufficiency and accuracy of the label, the FDA, never took any issue with the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. The State also could not identify a single Janssen "procedure" that purportedly would result in an unfair or deceptive Risperdal package insert in the future.

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The mere fact that the challenged act or practice remains in effect, i.e., the Risperdal package insert remains in use, is insufficient to establish the essential element that the challenged practice be capable of repetition. *See Jefferies v. Phillips*, 316 S.C. 523, 529,

451 S.E.2d 21, 23-24 (Ct. App. 1994) ("In the course of human endeavor, every action has some potential for repetition. The mere proof that the actor is still alive and engaged in the same business is not sufficient to establish this element."); *see also Wilson Group, Inc. v. Quorum Health Res., Inc.*, 880 F. Supp. 416, 428 (D.S.C. 1995) ("There is no evidence in this case of other similar acts and, therefore, no basis to conclude that Quorum's alleged acts have the potential for repetition." (footnote omitted)).

In the absence of a showing that the challenged conduct has the potential for repetition, to establish a SCUTPA violation, the alleged unfair act or deceptive practice must affect the public interest. That is, the State also "must establish, *by specific facts*, that members of the public were adversely affected by the defendants'" alleged unfair trade practice. *Bessinger v. Food Lion Inc.*, 305 F. Supp. 574, 584 (D.S.C. 2003), *aff'd*, 116 F. App'x 636 (4th Cir. 2004) (emphasis added). But the mere invocation of such words as "public interest," "public policy," and "public health issue" by the State's experts, without specific facts supporting such conclusory statements, is insufficient. *Orangeburg Pecan Co. v. Farmers Inv. Co.*, 869 F. Supp. 2d 359, 362 (D.S.C. 1994) ("Plaintiff here has done little more than chant phrases like 'public interest' and 'public impact' without producing a shred of evidence that such alleged wrongdoing is capable of repetition, or was, in fact, repeated."); *see, e.g.*, Trial Tr. vol. IV, 760:7-9, Mar. 10, 2011 (Plunkett merely agreeing with State's counsel that DDMAC's 2004 letter says November mailing "creates a serious public health issue").

A SCUTPA claim cannot be speculative. Yet, the State presented no factual evidence that either the November 2003 mailing or the Risperdal package insert had an *actual* adverse affect on the public or on physicians. *See* Trial Tr. vol. V, 993:16-994:8, 995:10-17, 999:3-8, 1024:21-1025:10 (Plunkett testifying that she had no contact with any South Carolina physicians regarding the Risperdal label or any of the matters that are the

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subject of the lawsuit; no specific knowledge of any South Carolina resident experiencing hyperprolactinemia or diabetes after receiving Risperdal). At most, one of the State's experts testified that the November 2003 mailing it "potentially" was a serious public health issue. Trial Tr. vol. III, 473:17-20, Mar. 9, 2011 (testimony of Wirshing). As such, the failure of the State to establish the required SCUTPA element of an adverse impact on the public also precludes the submission of the State's case to the jury. *See, e.g., Omni Outdoor Adver. Inc. v Columbia Outdoor. Adver. Inc.*, 974 F.2d 502, 507 (4th Cir. 1992) ("Omni suggests that the practice of double billing inflates costs to the advertisers and hence to consumers. Omni, however, cites no evidence in the record to support this proposition. It offers no basis other than sheer speculation to conclude that the total advertising costs of the affected companies rose as a result of the alleged COA practices. South Carolina courts have consistently rejected speculative claims of adverse public impact and required evidentiary proof of such effects.") (citations omitted).

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**E. The State Has Failed To Introduce Sufficient Facts For The Jury To Find Willful Conduct.**

The State also lacks sufficient evidence as to the essential element of a "willful" violation of SCUTPA. Under SCUTPA, a violation is willful only "when the party committing the violation knew or should have known that his conduct was a violation of [the South Carolina Unfair Trade Practices Act]." S.C. Code Ann. § 39-5-140(d). As held by South Carolina courts, conduct is willful for purposes of a SCUTPA violation only "[i]f in the exercise of due diligence, a person of ordinary prudence engaged in trade or commerce could have ascertained that his conduct violates the Act." *State ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 290 S.C. 124, 128, 348 S.E.2d 381, 384 (Ct. App. 1986) ("*Nest Egg*").

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According to the State, to satisfy this requirement, "it is merely necessary to show that Defendants knew or should have known that the labeling was unfair or deceptive." *See*

Pl.'s Opp'n to Defs.' Mot. For Summ. J. As To Pl.'s Unfair Trade Practices Claim Based On The FDA-Approved Risperdal Package Insert at 18. But the limited South Carolina decisions interpreting this element of SCUTPA have interpreted the element of a willful violation far more narrowly – a violation is willful only where the defendant's conduct violated a specific South Carolina statute that expressly prohibits the precise practice that the Attorney General alleges is a violation of SCUTPA. *See Nest Egg*, 290 S.C. at 124, 348 S.E.2d at 381 (willful conduct was a pyramid scheme expressly proscribed by S.C. Code Ann. § 39-5-30). *See generally Gentry v. Yonce*, 337 S.C. 1, 12, 522 S.E.2d 137, 143 (1999) ("Advertising a jackpot over the statutory $125 limit [set forth in S.C. Code 12-21-2791] is offensive and has a tendency to deceive a person into thinking that a jackpot over $125 is legal."). Even more significant, the South Carolina Supreme Court has made clear that a defendant's conduct is not willful if the conduct challenged as unfair or deceptive is not prohibited and there is evidence that the conduct challenged as unfair or deceptive is a common practice in the defendants' trade or business. *Haley Nursery Co., Inc. v. Forrest*, 298 S.C. 520, 525, 381 S.E.2d 906, 908 (1989) ("[Defendant's] conduct is not prohibited and there is evidence it is in accord with the common practice of the trade. Applying the statutory definition, we hold the record supports the trial judge's finding the violation was not willful.").

The State presented no evidence that the Risperdal package insert was ever "prohibited" by the FDA or anyone else. The State's expert, in fact, acknowledged the contrary; the FDA has never taken any action as to the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. Further, not only is the use of a package insert in accord with the "common practice of the trade," but it is required for prescription medicines such as Risperdal. *See* 21 U.S.C.A. § 355 (b)(1)(F) (new drug application shall include "specimens of the labeling proposed to be used for such drug"). Accordingly, the State has not

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introduced any evidence from which a jury could find that Defendants committed a willful violation of SCUTPA in connection with the Risperdal package insert.

As to the November 2003 mailing, the State failed to introduce any evidence that Janssen knew or should have known that the statements in the mailing were false. States with statutes similar to SCUTPA that also impose a "willfulness" requirement have held that, at a minimum, a plaintiff must establish that a defendant knew or should have known that the representations challenged as deceptive were false. *See, e.g., Adamson v. Worldcom Commc'ns, Inc.*, 78 P.3d 577, 583 (Or. App. 2003) (for unlawful trade practices claim, for a willful violation, "it suffices that the defendant knew of the falsity of a representation, without knowing that the representation violated the law"); *State ex rel. Corbin v. United Energy Corp. of Am.*, 725 P.2d 752, 758-59 (Ariz. App. 1986) ("The evidence presented [as to willfulness] was sufficient for the jury to have concluded that appellants knew or should have known that the performance representations were false.").

Neither of the State's experts testified that the materials cited by Janssen in the November 2003 mailing did not support the statements made by Janssen. The testimony in fact was to the contrary. *See* Trial Tr. vol. III, 457:20-458:4, 613:15-614:4, Mar. 9, 2011 (Wirshing admitting that it was fair to say that the primary conclusion from the eight articles cited in the mailing were supportive "to a degree" of the middle paragraph of the November 2003 mailing; six of the eight articles support the statement that Risperdal has a lower diabetes risk than Zyprexa; and, while the word "infrequently" may not be the best word used in the November 2003 mailing to describe the occurrence rate for hyperglycemia, expert admitted that "it wasn't really common at any rate"). As such, any conduct as to the November 2003 mailing also was not "willful." Thus, the State also failed to introduce sufficient evidence for the jury to find that Defendants committed a willful violation of

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SCUTPA in connection with either the Risperdal package insert or the November 2003 mailing.

F. The State's Entire SCUTPA Claim Is Barred By The Statute Of Limitations.

A SCUTPA claim must be filed no more than three years after discovery of the unlawful conduct. S.C. Code Ann. § 39-5-150. Any alleged "deception" as to the November 2003 mailing would have been apparent to any reader of the November 10 "Dear Healthcare Provider" letter, as the letter states *both* (1) Janssen's opinion as to the conclusions "suggest[ed]" by a certain "body of evidence from published peer-reviewed epidemiology research," *and* (2) the identification of – and citations to – that published peer-reviewed epidemiology research." *See* Trial Ex. P1736 (November 2003 mailing). Certainly, any of the physicians and other prescribers to whom the letter was addressed – and the State – had the ability to review the publicly available published studies to which Janssen pointed them and to "discover" any alleged deception in the opinion Janssen offered about them.[3] As such, the limitations period began to run at the time of

[3] In its February 25, 2011 Opinion, the Court stated that "the essential question before this Court is when the State Attorney General's Office would have become aware of 'unfair or deceptive acts or practices' in the Defendant's marketing and labeling actions relative to the sale of Risperdal." Slip op. at 6 (Feb. 25, 2011). The only South Carolina court to address the issue, however, held that the State is subject to the same principles governing the application of the statute of limitations as anyone else. *Willcox v. Stroup*, 358 B.R. 824 (D.S.C.), *aff'd*, 467 F.3d 409 (4th Cir. 2006). Similarly, another state court interpreting its consumer protection statute found that an attorney general is not entitled to preferential treatment in connection with stale claims. *See State of Delaware ex rel. Brady v. Pettinaro Enters.*, 870 A.2d 513, 532 (Del. Ch. 2005) ("Given the public policy underlying statutes of limitation in general – to compel timely pursuit of claims and to avoid the adjudication of stale claims – and these apt criminal law analogies, in particular – I cannot accept the State's strange argument that the [statute's] limitation period did not start to run until the Attorney General received complaints from consumers. To do so would be to condone torpor on the part of consumers, as well as the State itself."); *id.* at 533 ("I realize, of course, that as a practical matter, state agencies may be reliant on citizen complaints to trigger their investigations as to even blatantly unlawful conduct. But that reality does not allow the

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dissemination of the November 2003 mailing. *See Prestwick Golf Club, Inc. v. Prestwick Ltd. P'ship*, 331 S.C. 385, 393, 503 S.E.2d 184, 188 (Ct. App. 1998) (limitations period began to run on SCUTPA claim when defendant "announced its intention"); *see also Gibson v. Bank of Am., N.A.*, 383 S.C. 399, 407-08, 680 S.E.2d 778, 782-83 (Ct. App. 2009) (limitations period began to run at time of receipt of bank statements showing withdrawals that were the subject of claim). As the State did not file its original Complaint until April 23, 2007, the SCUTPA claim based on the November 2003 mailing is time-barred.

The State's package insert claim also is time-barred. According to the State's experts, the Risperdal package insert was "inadequate" from day one in 1994. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Wirshing). Also according to the State's experts, the inadequacy of the Risperdal package insert as to the precise risks which the State alleges were inadequately disclosed could be predicted and were *known* based on: (1) the chemical compound of Risperdal itself; and (2) instances of weight gain, hyperglycemia, and hyperprolactinemia that were seen in the *pre-marketing clinical studies* of Risperdal. Trial Tr. vol. IV, 687:22-687:25, 691:16-23, 689:19-690:6, Mar. 10, 2011 (testimony of Plunkett); Trial Tr. vol. III, 475:24-477:23, 528:14-25 (Wirshing testifying that weight gain warning should have been made earlier based on pre-marketing clinical trials; risk of alpha toxicity "inherent in the molecule"; risk was known "[i]n the 80s"). The statute of limitations, therefore, began to run on the State's package insert claim at the time of the initial Risperdal package insert in 1994. *Prestwick Golf Club, Inc.*, 331 S.C. at 393, 503 S.E.2d at 188; *see also Gibson*, 383

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BERKELEY COUNTY

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(...continued)

State the luxury to recline in a leather chair, believing that the statute of limitations will only run once some aggrieved citizen gets around to making a complaint." (footnote omitted)).

S.C. at 407-08, 680 S.E.2d at 782-83.[4] As the alleged deceptive conduct occurred more than three years prior to the initiation of this action, the State's entire package insert claim is time-barred.

### G. The State Has Failed To Introduce Sufficient Evidence For The Jury To Determine That Johnson & Johnson Is Liable For The Purported Violations Of SCUTPA.

Defendant Johnson & Johnson is named as, and is in fact, a separate corporate entity. *See* Second Am. Compl. Caption & ¶ 23. Johnson & Johnson is a holding company; it owns operating companies. Thus, the State has no evidence that Johnson & Johnson did anything that could give rise to liability. To impose liability on Johnson & Johnson for the acts of its subsidiary, defendant Janssen, the State would have to pierce the corporate veil. Application of the doctrine of piercing the corporate veil, however, is "not to be applied without substantial reflection" because "[i]f any general rule can be laid down, it is that a corporation will be looked upon as a legal entity until sufficient reason to the contrary appears." *Sturkie v. Sifly*, 280 S.C. 453, 457, 313 S.E.2d 316, 318 (Ct. App. 1984) (citation omitted).

A plaintiff who seeks to avoid the protections generally afforded corporations must satisfy a two-prong test. First, a number of eight factors must weigh in favor of piercing the veil; they are: (1) whether the subordinate corporation was grossly undercapitalized;

[4] South Carolina courts consistently have rejected any argument that a statute of limitations is tolled based on alleged continuing conduct by a defendant. *See Epstein v. Brown*, 363 S.C. 372, 610 S.E.2d 816 (2005) (rejecting "continuous representation" argument to toll statute of limitations); *Harrison v. Bevilacqua*, 354 S.C. 129, 580 S.E.2d 109 (2003) (rejecting "continuous treatment" rule to toll statute of limitations); *see also Maher*, 331 S.C. 371, 384, 500 S.E.2d 204, 211 (Ct. App. 1998) ("The objective test in South Carolina's discovery rule is sufficient to allow plaintiffs the opportunity to discover and act upon the original breach, without need for application of the 'continuing wrong' doctrine in this situation.").

(2) whether the parent corporation observed corporate formalities; (3) whether the subordinate corporation paid dividends; (4) whether the subordinate corporation was insolvent at the time; (5) whether the parent corporation siphoned the funds of the subordinate corporation; (6) whether the subordinate corporation had non-functioning officers or directors; (7) whether the subordinate corporation maintained corporate records; and (8) whether the subordinate corporation was a facade for the operations of the parent. *Dumas v. InfoSafe Corp.*, 320 S.C. 188, 192, 463 S.E.2d 641, 643-44 (Ct. App. 1995) (citations omitted).

Second, the plaintiff must prove that "an element of injustice or fundamental unfairness [will be done] if the acts of the corporation be not regarded as the acts of the individuals [or parent]." *Id.*, 463 S.E.2d at 644 (internal quotations and citation omitted). "To prove fundamental unfairness, the plaintiff must establish that (1) the defendant was aware of the plaintiff's claim against the corporation, and (2) thereafter, the defendant acted in a self-serving manner with regard to the property of the corporation and in disregard of the plaintiff's claim in the property." *Id.* (citation omitted).

Here, the State has not attempted to introduce evidence that would satisfy even one of the initial eight factors that must be considered. In addition, the State did not introduce any evidence that an injustice or fundamental unfairness would be worked if Johnson & Johnson were not held liable for the purported violations of SCUTPA by Janssen – the sole defendant against whom the State has even attempted to introduce any "evidence."

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## V. CONCLUSION

For the foregoing reasons, Defendants respectfully request that this Court enter an Order granting a directed verdict in favor of Defendants and against Plaintiff on its sole remaining claim.

RICHARDSON PLOWDEN & ROBINSON, PA
1900 Barnwell Street (29201)
Post Office Drawer 7788
Columbia, South Carolina 29202
(803) 771-4400

By: _____
Steven J. Pugh
Steven W. Hamm

-and-

Thomas F. Campion (admitted *pro hac vice*)
DRINKER BIDDLE & REATH LLP
500 Campus Drive
Florham Park, NJ 07932-1047
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Edward M. Posner (admitted *pro hac vice*)
Kenneth A. Murphy (admitted *pro hac vice*)
One Logan Square, Suite 2000
Philadelphia, PA 19103-6996
(215) 988-2700

ATTORNEYS FOR DEFENDANTS

March 14, 2011.

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# EXHIBIT B

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|---|---|
| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**DEFENDANTS' REPLY IN SUPPORT OF MOTION FOR A DIRECTED VERDICT** |

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Contrary to the State's suggestion, *State ex rel. Daniel v. Broad River Power Co.*, 157 S.C. 1, 153 S.E. 537 (1929) ("*Broad River*"), does not support the proposition that this Court can ignore the factors set forth in *Dumas v. InfoSafe Corp.*, 320 S.C. 188, 192, 463 S.E.2d 641, 643-44 (Ct. App. 1995) (citation omitted). The *Broad River* court, in fact, specifically weighed a number of these same factors, reasoning:

> [W]hen the facts show not only stock ownership, common officers and the like, but that the subsidiary company was a mere agency or department of the holding company, or that it was an instrumentality to subserve some special purpose of the holding company, particularly where the public interests are involved, the Court will deal with the substance of the transaction as if separate corporate entities did not exist.

*Broad River*, 157 S.C. at 26, 153 S.E. at 545. The State did not introduce in its case in chief any evidence that Johnson & Johnson and Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen") have common officers, that Janssen is a mere agency or department of Johnson & Johnson, that Janssen exists to subserve some special purpose of Johnson & Johnson, or any of the other relevant factors.

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And, even if the involvement of the public interest was the sole factor to be considered, the conduct challenged by the State here is not at all the type of public interest the *Broad River* court considered. There, the court was asked to issue "a writ of mandamus requiring and compelling [corporations] to resume and continue the operation of the electric street railway system in the city of Columbia and other places near said city." *Broad River*, 157 S.C. at 15, 64, 153 S.E. at 541, 559 ("In this connection attention is called to the fact that the corporation before the court is not an 'ordinary private money-making corporation,' but is a corporation of a public service character.").

Finally, the State's alter ego-veil piercing theory also fails. Even if the standard for alter ego liability is as the State suggests, the State utterly failed to introduce any evidence that Johnson & Johnson "exercises control over the subsidiary [Janssen] to the extent that the subsidiary [Janssen] manifests no separate corporate interests and functions solely to achieve the purpose of the parent corporation [Johnson & Johnson], and the retention of separate corporate personalities would promote fraud, wrong, or injustice, or would contravene public policy." Pl.'s Response in Opp'n to Defs.' Mot. for a Directed Verdict at 30 (citation omitted).

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WHEREFORE, for the reasons stated herein and in Defendants' Motion for a Directed Verdict and accompanying memorandum of law, the Court should grant Defendants' Motion in its entirety.

RICHARDSON PLOWDEN & ROBINSON, PA
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By: _____
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-and-

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ATTORNEYS FOR DEFENDANTS

March 15, 2011.

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# EXHIBIT C

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# facsimile
## TRANSMITTAL

[redacted]

| | |
|---|---|
| To: | Megan Zoschg, Pharm.D. |
| Sponsor: | Johnson & Johnson Pharmaceutical Research and Development, L.L.C. |
| Fax #: | (609) 730-3091 |
| Re: | Hyperglycemia and Diabetes letter dated 9/11/03 |
| Date: | September 12, 2003 |
| Pages: | 4 (including cover letter) |

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify me by telephone and return it to me at the address below by mail. Thank you.

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From the desk of
Robbin Nightswander, R.Ph., M.S.
Supervisory Regulatory Health Project Manager
Division of Neuropharmacological Drug Products
HFD-120
Food and Drug Administration
Rockville, Maryland 20857

301-594-5531
Fax: 301-594-2858

Exhibit
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-272
NDA 20-588
NDA 21-444

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Claude McGowan, Ph.D.
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to your new drug application (NDA) for Risperdal (risperidone) Tablets and Oral Solution and Risperdal M-TAB (risperidone) Orally Disintegrating Tablets.

After reviewing the available data pertaining to the use of atypical antipsychotic medications and diabetes mellitus adverse events, we have concluded that the product labeling for all atypical antipsychotics should be updated to include information about these events.

While we acknowledge that the relationship between atypical antipsychotic use and diabetes mellitus adverse events has not been completely described, we believe the safe use of Risperdal can be enhanced by informing prescribers and patients about these events. Increased attention to the signs and symptoms of diabetes mellitus may lead to earlier detection and appropriate treatment, and thus reduce the risk for the most serious outcomes.

We request that the following changes in the labeling be made so as to furnish adequate information for the safe and effective use of the drug:

**WARNINGS**
**Hyperglycemia and Diabetes Mellitus**
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including Risperdal. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. The available data are insufficient to provide reliable estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.

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Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Although we believe that the labeling changes accurately reflect the currently available information about antipsychotic use and diabetes mellitus, we acknowledge that additional labeling changes may be required as new information becomes available. Areas that require additional research include, but are not limited to, identification of subpopulations at greatest risk for diabetes mellitus adverse events, exploration of the relative risk for diabetes mellitus adverse events among the different antipsychotics, and evaluation of potential mechanisms of action.

Please submit twenty copies of final printed labeling, ten of which are individually mounted on heavyweight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected." Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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# EXHIBIT D

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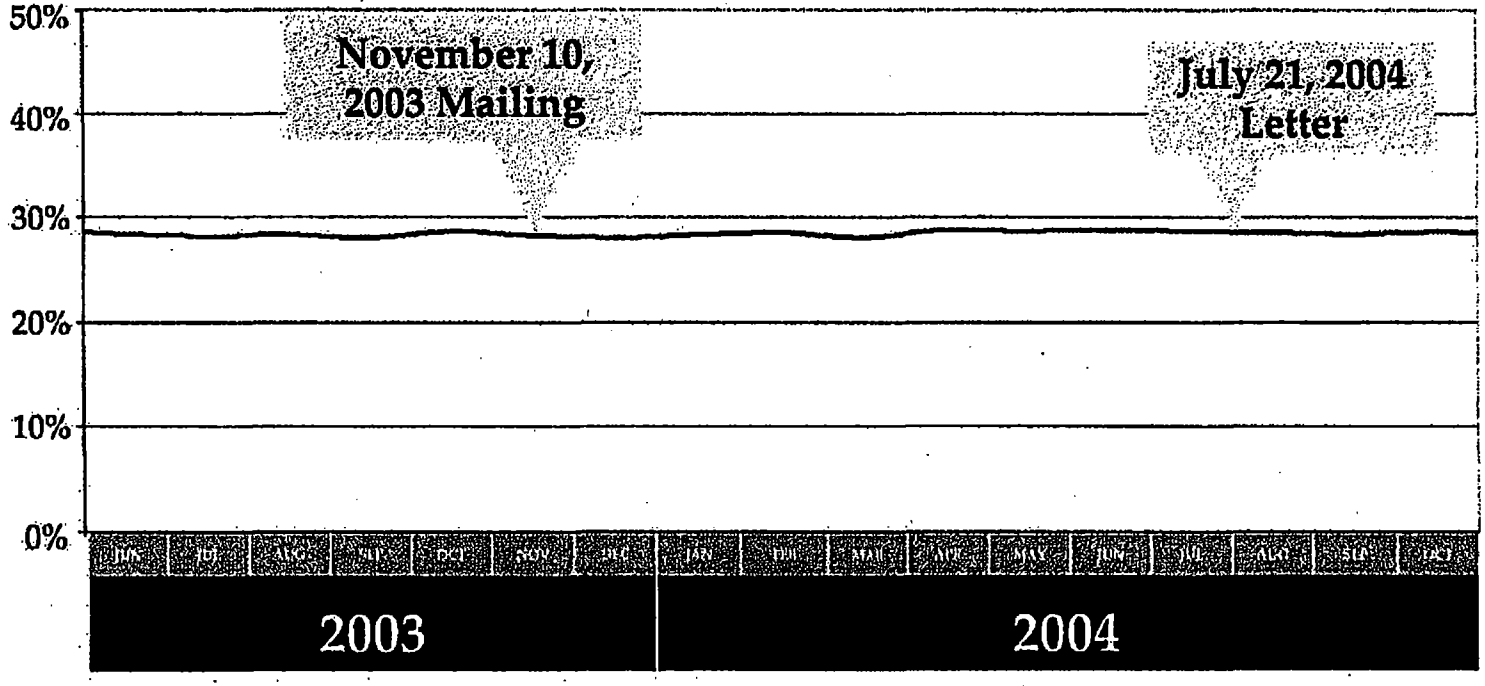
# Risperdal Prescriptions: No Change

South Carolina Medicaid & SHP Claims Data, Jun. 2003 – Oct. 2004




Source: South Carolina Medicaid and State Health Plan Claims Databases.



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# EXHIBIT E

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**Johnson & Johnson Pharmaceutical Research & Development, L.L.C.**
1125 TRENTON-HARBOURTON ROAD, TITUSVILLE, NEW JERSEY 08560-0200

18 APR 2002

Russell Katz, MD, Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
U.S. Food and Drug Administration
**Attn: Document Control Room 10B-40**
1451 Rockville Pike
Rockville, MD 20852

Subject: **NDA 20-272/SLR-024**
Cross reference: NDA 20-588/SLR-015
RISPERDAL® (risperidone) Tablets and Oral Solution
**Amendment to Pending CBE Labeling Supplement – Postintroduction *Reports* Section**

Dear Dr. Katz:

On behalf of Janssen Pharmaceutica Products, L.P., please refer to our New Drug Application, NDA 20-272, for Risperdal (risperidone) Tablets. In accordance with 21 CFR 314.70(c)(2), Johnson & Johnson Pharmaceutical Research & Development, L.L.C. is submitting an amendment to supplement SLR-024 to provide the supporting documentation not included with the original supplement. The supplement is for the addition of the term "hyperglycemia" to the **ADVERSE REACTIONS: Postintroduction *Reports*** section of the package insert for Risperdal (risperidone) tablets and oral solution. Immediately following this letter is Form 356h, a copy of the original supplement cover letter, table of contents, marked and clean copies of the package insert, and two supporting safety reports.

For your convenience, this amendment is being supplied with a CD-ROM as a review aid. This CD-ROM has been virus scanned using McAfee VirusScan (virus Definition 4.0.4064/Scan Engine E 4.0.25) and is virus free.

Please contact me at (609) 730-2712 if you have any questions regarding this submission.

Sincerely,

Susan J. Merchant
Manager, Regulatory Affairs

cc: S. Hardeman (DNDP RMO)

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# EXHIBIT F

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Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

EDMS-PSDB-2987877

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

24 SEP 2003

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I
U.S. Food and Drug Administration
Attn: Document Control Room
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-272
RISPERDAL® (risperidone) Tablets
Cross-reference NDAs 20-588, 21-444
Response to Request for Label Revision

Dear Dr. Katz,

Please refer to your letter of September 16, 2003 with a request for a change in RISPERDAL labeling to include a Warning for "Hyperglycemia and Diabetes Mellitus".

Unfortunately, prior to receipt of your letter, we did not have the opportunity to provide you the new data we have been gathering on this subject since agreement with you on diabetes-related labeling in your letter of November 19, 2002, nor did we have an opportunity to review the data on which your request was based.

The proposed class labeling is not consistent with our interpretation of the data regarding RISPERDAL. We would like the opportunity to share our data and interpretations to ensure accurate labeling. We would appreciate your review of the summary contained in this letter, and would like to request a teleconference with you on Friday, September 26, 2003. The objective of the teleconference will be to reach consensus that updated data on RISPERDAL should be reviewed before a final decision is reached on the appropriate labeling for RISPERDAL.

The proposed class Warning titled "Hyperglycemia and Diabetes" refers to both hyperglycemia/diabetes and to more serious and life-threatening adverse events (diabetic ketoacidosis, hyperosmolar coma, and death). Two key points make the proposed class warning not applicable to RISPERDAL.

1) A substantial body of epidemiologic evidence argues against an association between RISPERDAL and a risk of diabetes that is greater than can be attributed to conventional antipsychotics, or even in some studies to untreated patients. Additionally, there is little evidence that serious and life-threatening events (diabetic ketoacidosis, hyperosmolar coma, and death) occur with a greater

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incidence among patients treated with RISPERDAL than in a comparable background population. These data suggest that it may not be appropriate to group RISPERDAL with other atypical antipsychotics (e.g., olanzapine, clozapine) for which such risks have been consistently documented.

2) There are clinically significant differences in diabetes risk among the atypical antipsychotics. RISPERDAL is associated with a lower epidemiologic risk than some other atypical antipsychotics. This difference among drugs is further supported by evidence from mechanistic studies, and argues against grouping all atypical antipsychotic agents.

In support of these points, we would like to discuss the following evidence with the Division:

- Epidemiology studies - including new data from our studies, and an overview of all 8 published studies on this topic,
- Mechanistic studies - including new data concerning glucoregulatory physiology and differential mechanism of action, and
- Clinical studies - including our risperidone clinical trials database, which includes over 12,000 RISPERDAL-treated patients, an increase of approximately 50% since submission of clinical data on August 10, 2000 in response to FDA's request for information on the effect of risperidone on glucose metabolism.

**Epidemiology.**

*Epidemiologic Evidence Regarding Serious and Life-threatening Events;*

In a recent Medicaid claims database analysis of >100,000 persons, olanzapine was associated with a 60% increased risk (OR=1.6) of diabetic ketoacidosis (DKA) as compared to risperidone. The study found duration of exposure was correlated with difference in risk (higher risk of DKA with increasing duration of exposure to olanzapine compared to risperidone). Further, in 38,552 patients exposed to risperidone or olanzapine for at least 180 days, olanzapine demonstrated a 250% increased risk (OR=3.5) of DKA as compared to risperidone[1].

An analysis of MedWatch data through first quarter 2002 utilizing an empirical Bayesian geometric mean (ratio of the observed count to the expected count for a given drug event combination) examined the relationship of six antipsychotics (risperidone, olanzapine, quetiapine, clozapine, ziprasidone, haloperidol) to specific diabetes-related MedDRA terms. Very little data were available for quetiapine and ziprasidone due to the significantly lower usage of these drugs during this time period. Of the remaining four agents, when examining 'diabetes mellitus, insulin dependent' or 'diabetes mellitus, non-insulin dependent' as terms, the largest effect was seen with clozapine, second largest with olanzapine and the least with risperidone. When examining 'diabetic ketoacidosis' as a term, the largest effect was again seen with olanzapine, second largest with clozapine and the least effect with risperidone. In both of these comparisons, risperidone did not score worse than haloperidol. (Lincoln Technologies, Inc., Wellesley Hills, MA,

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www.lincolntechnologies.com. February 17, 2003. Source: SRS and AERS data through 1Q02)

*Epidemiology Summary*

We are aware of 19 different epidemiological studies in the public domain evaluating the association between antipsychotics and development of diabetes. Of these studies, 8 have been published in peer-reviewed journals (all 8 are reviewed in Table 1).

The weight of evidence from the available epidemiology research suggests that RISPERDAL is not associated with increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics. This evidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other atypical antipsychotics (e.g, olanzapine, clozapine).

***Studies of Glucoregulatory Physiology / Mechanism of Action***

Evidence from controlled studies specifically aimed at evaluation of glucose metabolism suggests some atypical antipsychotics (e.g., olanzapine, clozapine) have significantly more risk in impairing glucose regulation than risperidone. A modified oral glucose tolerance test (OGTT) performed in a cross-sectional sample of 48 schizophrenic patients demonstrated greater risk of significant glucose elevations in olanzapine- and clozapine-treated patients than in risperidone-treated patients.[10] Three 'clamp' studies (hyperglycemic and hyperinsulinemic clamps in humans and a comprehensive metabolic study in an animal model) have also been conducted. These studies are summarized below:

a. Two clamp studies in healthy volunteers treated with olanzapine, risperidone or placebo were not highly informative; each study measured either insulin secretion or insulin sensitivity, but not both.[11, 12] Both glucose and insulin exert similar actions to increase glucose uptake into tissues (e.g., muscle and fat) and to suppress glucose production by liver. It is therefore necessary to measure both insulin secretion and insulin sensitivity in the same subject in order to properly assess potential drug effects.

b. A dog model was intensively studied by Ader et al., including both a euglycemic clamp to assess insulin sensitivity and a full stepwise hyperglycemic clamp for insulin secretion.[13] Adiposity was assessed by MRI. Olanzapine was found to cause significant increases in adiposity, hepatic insulin resistance, and beta-cell dysfunction (a potential mechanism for drug-induced DKA)[14]. Risperidone-treated dogs were comparable to placebo in all these parameters. This study elucidates at least one plausible mechanism for olanzapine-induced glucose metabolism dysregulation which is not shared by risperidone.



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The weight of evidence from the available physiological data supports differences in the risk of glucose dysregulation among atypical antipsychotics, particularly between risperidone, a benzisoxazole, and the chemically distinct dibenzodiazepines (e.g., olanzapine, clozapine). There is little evidence to support a common glucoregulatory effect among these structurally diverse chemical classes.

**RISPERDAL Clinical Trials**

Completed clinical trials of RISPERDAL through December 1, 2002 were examined for incidence of glucose related adverse events and random glucose levels when available (see Table 2).

Data from clinical trials indicate that the risk for glucose related adverse events with RISPERDAL is comparable to placebo or the conventional antipsychotic haloperidol.

**Weight of Evidence**

In view of the data summarized above, the proposed class labeling concerning hyperglycemia and diabetes does not accurately reflect the current evidence related to RISPERDAL. There is limited evidence for increased risk associated with RISPERDAL compared to conventional antipsychotics or untreated patients, and there is a particular lack of evidence suggesting an increased risk of serious and life-threatening events, such as diabetic ketoacidosis. Furthermore, a substantial body of epidemiologic evidence supports a differential effect among atypical antipsychotics. Data concerning physiologic mechanisms of action also suggest that risk for both diabetes and ketoacidosis is not a class effect.

We request that other submissions concerning RISPERDAL be concluded without being linked to the review that is needed to address the proposed diabetes class warning.

I will contact Mr. Steve Hardeman to confirm an appropriate time to contact you on September 26, 2003, or as soon thereafter as possible.

Thank you for your review of this brief summary. If you have any questions, please contact me at 609-730-3486.

Sincerely yours,

Edward G. Brann
Director, Regulatory Affairs

Cc: S. Hardeman

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**Table 1. All Published Epidemiological Studies of Antipsychotics and Diabetes**

| Reference | Conclusions | Primary Results | Risk[a] (95%CI) | Population |
|---|---|---|---|---|
| American Journal of Psychiatry – April 2002, Sernyak et al.[2] | "... the prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine, and quetiapine, but not risperidone." | RIS = CONV<br>OLZ > CONV<br>QUE > CONV<br>CLZ > CONV | 1.1 (0.98-1.1)<br>1.1 (1.04-1.2)*<br>1.3 (1.1-1.6)*<br>1.3 (1.1-1.5)* | 38,632 schizophrenia patients from the VA (1999) |
| British Medical Journal – August 2002, Koro et al.[3] | "The risk [for diabetes] was significantly increased with the newer antipsychotic olanzapine but not with the other newer antipsychotic, risperidone." | RIS = Untreated<br>OLZ > Untreated<br>RIS = CONV<br>OLZ > CONV | 2.2 (0.9-5.2)<br>5.8 (2.0-16.7)*<br>1.6 (0.7-3.8)<br>4.2 (1.5-12.2)* | 19,637 schizophrenia patients from the U.K. GPRD (1987-2000) |
| The Journal of Clinical Psychiatry – October 2002, Gianfrancesco et al.[4] | "In contrast to these agents [olanzapine and clozapine], risperidone was not associated with an increased risk of type 2 diabetes." | RIS = Untreated<br>OLZ > Untreated<br>CLZ > Untreated<br>OLZ > RIS<br>CONV = RIS | 0.9 (0.4-2.1)<br>3.1 (1.6-5.9)*<br>7.4 (1.6-34.8)*<br>3.5*<br>2.4 | 7,395 psychosis patients from 2 insurance claims databases (1/1996-12/1997) |
| The Journal of Clinical Psychiatry – December 2002, Caro et al.[5] | "Compared with risperidone, olanzapine was associated with an increased risk of developing diabetes." | OLZ > RIS | 1.2 (1.00-1.4)* | 33,946 patients from a Quebec health claims database (1/1997-12/1999) |
| Journal of Clinical Epidemiology - 2003, Buse et al.[6] | "An increased risk of developing diabetes compared with the AdvancePCS general patient population was observed during treatment with conventional or atypical antipsychotics." | RIS > Untreated<br>OLZ > Untreated<br>QUE > Untreated<br>CLZ > Untreated<br>RIS > HAL<br>OLZ = HAL<br>QUE < HAL<br>CLZ = HAL | 3.4 (3.1-3.8)*<br>3.0 (2.6-3.5)*<br>1.7 (1.2-2.4)*<br>3.3 (1.4-8.0)*<br>1.2 (1.01-1.5)*<br>1.1 (0.9-1.4)<br>0.7 (0.5-0.97)*<br>1.3 (0.6-2.9) | 58,751 patients from the AdvancePCS prescription-claims database (12/1998-2/2000) |
| Clinical Therapeutics – April 2003, Gianfrancesco et al.[7] | "In contrast to olanzapine,..., risperidone... was not associated with an increased risk for development of type 2 diabetes..." | RIS = Untreated<br>OLZ > Untreated<br>OLZ > RIS<br>CONV = RIS | 1.0 (0.4-3.0)<br>4.3 (2.1-8.8)*<br>4.2*<br>1.9 | 5,236 patients with mood disorders from 2 insurance claims databases (1/1996-12/1997) |
| Journal of Clinical Psychopharm. – August 2003, Gianfrancesco et al.[8] | "...quetiapine and risperidone patients had estimated odds of ... diabetes that were lower than those of patients untreated with antipsychotics (not statistically significant) ...olanzapine had odds that were significantly greater than those of patients untreated..." | RIS = Untreated<br>OLZ > Untreated<br>QUE = Untreated<br>CONV = Untreated | 0.7 (0.3-1.4)<br>1.4 (1.0-2.0)*<br>1.0 (0.4-2.3)<br>1.0 (0.7-1.6) | 16,878 patients with psychosis from 2 insurance claims databases (4/1997-10/2000) |
| Pharmacother – August 2003, Fuller et al.[9] | "Olanzapine was associated with a ... increased risk of development of diabetes compared with risperidone in a VA population..." | OLZ > RIS<br>FLU = RIS<br>HAL = RIS | 1.4 (1.1-1.8)*<br>1.1 (0.7-1.8)<br>0.9 (0.7-1.2) | 5,837 patients from a Veterans Affairs (VA) database (1/1997-12/2000) |

[a] Comparative risk was evaluated utilizing odds ratio, relative risk and hazard ratio assessments in different studies.
* Indicates results are statistically significant (p<0.05). Legend: RIS = risperidone, OLZ = olanzapine, QUE = quetiapine, CLZ = clozapine, HAL = haloperidol, FLU = fluphenazine, CONV = conventional antipsychotics



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**Table 2. Glucose Related Adverse Events and Random Glucose Levels**

| | Placebo | Risperidone | Haloperidol | Olanzapine | Other Neuroleptics |
|---|---|---|---|---|---|
| *Any Glucose Related Adverse Events*[a] | | | | | |
| | N=1439 | N=7326 | N=712 | N=536 | N=293 |
| Short-Term Trials[b] | 12 (0.83%) | 55 (0.75%) | 2 (0.28%) | 5 (0.93%) | 1 (0.34%) |
| | — | N=4741 | N=579 | — | N=234 |
| Long-Term Trials[c] | — | 46 (0.97%) | 9 (1.55%) | — | 0 |
| Elevated Glucose Levels (Short term) | | | | | |
| | N=803 | N=3042 | — | — | N=606 |
| Suggestive of "diabetes"[d] | 9 (1.12%) | 26 (0.85%) | — | — | 4 (0.66%) |
| Suggestive of "impaired glucose tolerance"[e] | 68 (8.47%) | 174 (5.72%) | — | — | 25 (4.13%) |

a = List of glucose-related adverse events: metabolic acidosis, decreased blood sugar, increased blood sugar, diabetic coma, hyperosmolar, diabetes mellitus, diabetes mellitus aggravated, diabetes mellitus deteriorated, new onset diabetes mellitus, diabetes mellitus precipitated, diabetes mellitus reactivated, diabetic ketoacidosis, abnormal glucose tolerance, glucose tolerance decreased, abnormal glucose tolerance test, glycosuria, hyperglycemia, hypoglycemia, hypoglycemic reaction, ketoacidosis, and ketonuria

b = short-term trials – duration <3months
c = long-term trials – duration up to 2 years
d = random glucose levels of ≥11.1 mmol/L
e = random glucose levels of ≥7.8 and <11.1mmol/L

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**References:**


1. Ramaswamy K, Nasrallah, H, and Kozma C. The relationship between duration of exposure and development of DKA in patients in treated with risperidone or olanzapine. [Poster] 42nd Annual Meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 2003
2. Sernyak M, Leslie D, Alarcon R et al. Association of diabetes mellitus with use of atypical neuroleptics in the treatment of schizophrenia. Am J Psychiatry 2002;159:561-566
3. Koro C, Fedder D, L'Italien G et al. Assessment of independent effect of olanzapine and risperidone on risk of diabetes among patients with schizophrenia: population based nested case-control study. BMJ 2002;325:243-248.
4. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of risperidone, olanzapine, clozapine, and conventional antipsychotics on type 2 diabetes: findings from a large health plan database. J Clin Psychiatry 2002;63:920-930
5. Caro J, Ward A, Levinton C et al. The risk of diabetes during olanzapine use compared with risperidone use: a retrospective database analysis. J Clin Psychiatry 2002;63:1135-1139
6. Buse J, Cavazonni P, Hornbuckle K et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiology 2003;56:164-170
7. Gianfrancesco F, Grogg A, Mahmoud R et al. Differential effects of antipsychotic agents on the risk of development of type 2 diabetes mellitus in patients with mood disorders. Clin Therapeutics 2003;25(4):1150-1171
8. Gianfrancesco F, White R, Wang R et al. Antipsychotic-induced type 2 diabetes: evidence from a large health plan database. J Clin Psychopharmacol 2003;23(4):328-335
9. Fuller M, Shermock M, Secic M et al. Comparative study of the development of diabetes mellitus in patients taking risperidone and olanzapine. Pharmacotherapy 2003;23(8):103.7-1043
10. Newcomer, J et al. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch Gen Psychiatry. 2002 (Apr.); 59 (4): 337-45.
11. Sowell, M. et al. Hyperglycemic clamp assessment of insulin secretory responses in normal subjects treated with olanzapine, risperidone and placebo. J Clin Endo and Met. 2002; 87 (6); 2918-2923.
12. Beasley, C. et al. Prospective evaluation of insulin sensitivity by the hyperinsulinemic, euglycemic clamp in healthy volunteers treated with olanzapine, risperidone or placebo. Poster presented at the 41st American College of Neuropsychopharmacology annual meeting, December 8-12, 2002; San Juan, Puerto Rico.
13. Ader, M. et. al. Differential metabolic effects between atypical anti-psychotics in normal dogs, Poster presented at American Diabetic Association annual meeting, June 13-17, 2003; New Orleans.
14. Ader, M. et al. Marked increase in adiposity during olanzapine vs risperidone treatment: results of a placebo-controlled study in normal dogs. Poster presented at ECNP annual meeting, September 20-24, 2003; Prague, Czech Republic.




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Proposed J&J Participants

| | |
|---|---|
| Primary Participants | |
| Ivo Caers, PhD | RISPERDAL Team Leader |
| Fred Grossman, DO | Sr. Dir. Drug Development, Psychiatry Franchise Medical Leader |
| Ramy Mahmoud, MD, MPH | Vice President CNS Medical Affairs |
| Amy Grogg, Pharm.D. | Group Director, Outcomes Research |
| Sagar Adusumali, Ph.D. | Director, Global Regulatory Affairs |
| | |
| J&JPRD Management | |
| Garry Neil, MD | Sr. Vice President Drug Development |
| Jack Grebb, MD | Sr. Vice President Drug Development, CNS Therapeutic Area |
| Scott Reines, MD, PhD | Vice President Drug Development, Pain and Pediatric Therapeutic Area |

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, Parts 314 & 601)*

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

## APPLICANT INFORMATION

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Janssen Pharmaceutica Products, L.P. | 24 SEP 2003 |
| **TELEPHONE NO.** *(Include Area Code)* | **FACSIMILE** *(FAX)* **Number** *(Include Area Code)* |
| 609-730-3486 | 609-730-3091 |
| **APPLICANT ADDRESS** *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200<br><br>On behalf of Janssen Pharmaceutica Products, L.P. 1125 Trenton-Harbourton Road Titusville, New Jersey 08560-0200 | **AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE |

## PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(if previously issued)* NDA 20-272

| ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* | PROPRIETARY NAME *(trade name)* IF ANY |
|---|---|
| risperidone | RISPERDAL® |

| CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* | CODE NAME *(if any)* |
|---|---|
| 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9,-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one | R064766 |

| DOSAGE FORM: | STRENGTHS: | ROUTE OF ADMINISTRATION: |
|---|---|---|
| Tablet | 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg | Oral |

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Schizophrenia

## APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Request for teleconference - RE: Diabetes Class Labeling

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
NDAs 20-588 and 21-444

FORM FDA 356h (9/02) PAGE 1 OF 2

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| This application contains the following items: *(Check all that apply)* | |
|---|---|
| ☐ | 1. Index |
| ☐ | 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling |
| ☐ | 3. Summary (21 CFR 314.50 (c)) |
| ☐ | 4. Chemistry section |
| ☐ | A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2) |
| ☐ | B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request) |
| ☐ | C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2) |
| ☐ | 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2) |
| ☐ | 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2) |
| ☐ | 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4)) |
| ☐ | 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2) |
| ☐ | 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2) |
| ☐ | 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2) |
| ☐ | 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2) |
| ☐ | 12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2) |
| ☐ | 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c)) |
| ☐ | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A)) |
| ☐ | 15. Establishment description (21 CFR Part 600, if applicable) |
| ☐ | 16. Debarment certification (FD&C Act 306 (k)(1)) |
| ☐ | 17. Field copy certification (21 CFR 314.50 (l)(3)) |
| ☐ | 18. User Fee Cover Sheet (Form FDA 3397) |
| ☐ | 19. Financial Information (21 CFR Part 54) |
| ☒ | 20. OTHER *(Specify)* Request for teleconference |

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

*If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.*

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

| SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | TYPED NAME AND TITLE | DATE |
|---|---|---|
| | Edward G. Brana<br>Director, Regulatory Affairs | 24 SEP 2003 |

| ADDRESS *(Street, City, State, and ZIP Code)* | Telephone Number |
|---|---|
| 1125 Trenton-Harbourton Road<br>Titusville, New Jersey 08560-0200 | (609)-730-3436 |

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

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Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

26 NOV 2003

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I
U.S. Food and Drug Administration
Attn: Document Control Room
1451 Rockville Pike
Rockville, MD 20857

Re: NDA 20-272/S-035
RISPERDAL® (risperidone) Tablets
Cross-reference NDAs 20-588, 21-444, 21-346
Response to Approval Letter

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Dear Dr. Katz,

Please refer to your letter of November 21, 2003 which approved our "Changes Being Effected" supplemental new drug application (S-035) submitted November 6, 2003 to incorporate the hyperglycemia text from the RISPERDAL CONSTA labeling (NDA 21-346) into the oral RISPERDAL labeling under WARNINGS. Your letter requested that we issue a "Dear Healthcare Professional" letter to communicate that new information.

We recognize and agree with your desire to communicate this safety information to physicians. Therefore, Janssen has already voluntarily mailed a medical communication concerning the new "Hyperglycemia and Diabetes Mellitus" labeling to more than 600,000 physicians and healthcare providers. Enclosed please find a copy of the letter. In addition, through their sales representatives, Janssen has individually informed over 70,000 physicians of this label change for RISPERDAL. A complete copy of the package insert, including the new Warning, was provided as part of both communications to physicians. The letter has also been posted on Janssen's website.

Feedback from physicians during this communication process is that the medical community already knows of the reports of hyperglycemia and diabetes with the atypical antipsychotics. Substantial press coverage of the issue has occurred in major media. We are also aware of efforts by Eli Lilly & Co. to communicate this new safety information concerning the atypical antipsychotic class of drugs to physicians.

We request that you review the proactive efforts already undertaken by Janssen to inform and educate the medical community, consider the overall level of information already provided to the public and physicians concerning the issue, and concur that no additional communication on this topic is necessary.

PRD-1C

Exhibit
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08.20.09



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Plaintiff Ex. 430
R. 8945

If you have any questions, please contact me at 609-730-2712.

Sincerely yours,

Susan Merchant
Manager, Regulatory Affairs

Enclosure: Janssen Medical Communication, Nov. 2003

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# EXHIBIT H

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PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

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**TRANSMITTED VIA FACSIMILE AND FEDEX**

April 28, 2004

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising and Communications
HFD-42, Rm. 8B-45
5600 Fishers Lane
Rockville, MD 20857

**RE: NDA 20-272 and 20-588**
**RISPERDAL ® (risperidone) Tablets and Oral Solution**
**MACMIS # 12195**

*Dear Mr. Abrams:*

On behalf of Janssen Pharmaceutica Products L.P. (Janssen), please refer to our approved New Drug Applications, NDA 20-272 and 20-588 for RISPERDAL® (risperidone) Tablets and Oral Solution, and MACMIS # 12195. Reference is also made to the Division of Drug Marketing, Advertising & Communication 's (DDMAC) correspondence to Janssen dated April 19, 2004, sent in response to a "Dear Healthcare Provider Letter (DHCP)" disseminated by Janssen on November 10, 2003. We have carefully reviewed your letter of April 19, 2004, and provide our response below.

Janssen and Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) share FDA's interest in accurate and timely communication of labeling changes to the healthcare community. Janssen and J&JPRD received the Division of Neuropharmacological Drug Products' (DNDP) letter of September 11, 2003 to all manufacturers of atypical antipsychotics requesting that labeling for all atypical antipsychotics, including RISPERDAL, be updated to include information about diabetes mellitus adverse events. Within three days, Janssen and J&JPRD contacted DNDP to request an opportunity to discuss the proposed class labeling.

On November 6, 2003, after several correspondences between J&JPRD and DNDP regarding the proposed class labeling, which led to agreement on modified class labeling, J&JPRD submitted a "Special Supplement – Changes Being Effected" ("Special Supplement") to provide for changes in the WARNINGS section of the RISPERDAL® labeling. Immediately thereafter, with the goal of informing health care professionals in a timely manner regarding these labeling changes, Janssen voluntarily issued, to healthcare providers, the November 10, 2003 DHCP communication.

On November 21, 2003, DNDP approved our Special Supplement and at that time requested that Janssen issue a "Dear Health Care Professional" letter regarding the addition of language relative to hyperglycemia and diabetes mellitus to the WARNING section of the prescribing information for RISPERDAL®. On November 26, 2003, J&JPRD informed DNDP that a medical communication with this purpose was previously sent on November 10 and provided a copy of the letter to DNDP at that time.

Exhibit
Caers - 47
08.20.09

PRD-18

NDA #20-272, 20-588
MACMIS # 12195

Regarding your assertions of omission of material information and minimization of risks/misleading comparative claims, it is important to note that the November 10, 2003 communication contained a copy of the complete prescribing information for RISPERDAL containing the updated, FDA approved, WARNING language on hyperglycemia related events, with a prominent reference to the full prescribing information in the body of the DHCP letter.

Based upon Janssen's comprehensive review of the data pertaining to risperidone[1], we have a differing view of the data on Risperdal and diabetes mellitus. However, we acknowledge the Agency's position.

Notwithstanding our differing views, in order to address your concerns, we agree to do the following. With your agreement, we will send the attached proposed DHCP letter (Attachment A) pursuant to 21 CFR 200.5 (c)(1) to the same audience that received the November 10, 2003 communication. Please be aware that the November 10, 2003 letter is no longer being disseminated. In addition, we are providing as attachment B, pursuant to your request, a list of current RISPERDAL promotional materials containing same or similar claims to those addressed in your April 19, 2004 letter, all of which are discontinued.

With regard to submission pursuant to post marketing requirements, we considered the November 10, 2003, letter a medical communication informing healthcare providers of an important change to labeling, and therefore did not consider it subject to 21 CFR 314.81(b)(3)(i). However, we acknowledge your position and will modify future submissions accordingly.

We trust that this letter adequately responds to your April 19 letter and we look forward to resolving this matter in a timely fashion. Should you have any questions, please contact James Burrus at 609-730-3617.

Sincerely,

Donna Ohye

Donna Ohye
Senior Director, Advertising and Promotion
Global Regulatory Affairs and Quality Assurance
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Attachments

[1] Including the eight published studies cited in the November 10 DHCP letter and other epidemiology, physiology, clinical trial and pharmacovigilance data (data submitted to DNDP 3/29/04)

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NDA #20-272, 20-588
MACMIS # 12195

Attachment A

[insert date]

*Dear Health Care Provider,*

*Janssen Pharmaceutica Products* L.P., *makers of RISPERDAL®(risperidone), distributed a "Dear* Healthcare Provider" letter dated November 10, 2003, notifying you that the product labeling for RISPERDAL had been updated to include a WARNING regarding hyperglycemia and diabetes mellitus. FDA has informed us of their view that this letter was misleading, in part due to omission in the letter of certain information, and the inclusion of certain other information. FDA has requested us to further clarify the new WARNING information, which is provided below:

Hyperglycemia and Diabetes Mellitus

"Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes *mellitus in the general population. Given these confounders, the relationship between* atypical antipsychotic use and hyperglycemia-related adverse events is not completely *understood. However, epidemiological studies suggest an increased risk of treatment* emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available."

"Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. *In some cases, hyperglycemia has resolved when the atypical antipsychotic was* discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug."

If you have any questions regarding this important safety information, please contact Janssen Medical Affairs at 1-800-JANSSEN. Please refer to the full prescribing information for RISPERDAL included with this letter. As always, we request that serious adverse events be reported to Janssen at 1-800-JANSSEN or to the FDA MedWatch program by phone (1-800-FDA-1088), by fax (1-800-FDA-0178), or by email (www.fda.gov/medwatch).

Sincerely,

Ramy A. Mahmoud, MD, MPH
Vice President, CNS
Janssen Medical Affairs, LLC

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SPARTANBURG COUNTY
2011 MAR 21 AM 10:50
M. HOPE BLACKLEY

NDA #20-272, 20-588
MACMIS # 12195

Attachment B

The following promotional items have been discontinued in accordance with the requested action.

Bipolar Mania Promotion aides:

- 01-RS-1374-PCP/CNS, 01-RS-1404, 01-RS-1377, 01-RS-1440,

Managed Care Promotional aide template: (Note: These are identical excluding the managed care plan name)

- 01-RS-MAN- (338, 349, 229, 252, 272, 278, 279, & 281)

Reprint Carriers & Reprint & Speaker Slide Kit:

- 01-RS-1433, 01-RS-1200R1, 01-RS-146101-RS-1126, 01-RS-1385

Exhibit Panels

- 01-RS-1290E, 01-RS-1299A

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# EXHIBIT I

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Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

29 MAR 2004

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation 1
U.S. Food and Drug Administration
**Attn: Document Control Room 10B-40**
1451 Rockville Pike
Rockville, MD 20857

**Subject:** **NDA 20-272**
Cross reference: NDA 20-588, 21-444, and 21-346
**RISPERDAL® (risperidone) Tablets**
**General Correspondence – Hyperglycemia/Diabetes Data For RISPERDAL®**

Dear Dr. Katz,

On behalf of Janssen Pharmaceutica, L.P., please refer to the joint consensus development conference of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity held November 19-21, 2003 and the resulting Consensus publication (Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes, Diabetes Care, Volume 27, 2, February 2004, pages 596-601).

At that meeting, Dr. Judy Racoosin, presenting the FDA position, indicated that the FDA is willing to review additional data and reconsider its position if supported by the data. We believe that we have substantial new information concerning the risk of diabetes and related serious adverse events with RISPERDAL® treatment, and would like to share that information. We believe this new data is necessary for a thorough evaluation by the FDA of all the available risperidone data and for an accurate assessment of risk for diabetes and related adverse events among approved antipsychotics.

In response to the November expression of FDA's willingness to consider data on this issue, Johnson and Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) has reviewed all of the available risperidone data and is providing an information package that includes the following:

- A summary of epidemiology data from our studies, including new data, and an overview of all 10 published studies on the topic, in addition to a summary of all non-published results presented at scientific congresses (e.g., both V.A. studies reported in the press in August 2003);

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PRD-1C

- A review of studies of related physiology and differential mechanism of action, including new data;
- An update to previously submitted clinical data from the J&JPRD clinical trial database, which now includes over 12,000 Risperdal-treated subjects; and
- An update to the RISPERDAL® pharmacovigilance database.

Taken together, these data demonstrate the following:

- Epidemiology evidence does not support an increased risk of diabetes with risperidone treatment. In particular, serious or life-threatening events (e.g. diabetic ketoacidosis) are not more common than with haloperidol. The weight of epidemiologic evidence suggests that diabetes among risperidone-treated patients is not more common than in untreated patients with psychotic disorders or in patients treated with conventional antipsychotics and is less common than in patients treated with olanzapine or clozapine;
- Understanding the critical caveat that trials conducted for primarily psychiatric research purposes lack sensitivity to detect glucoregulatory disturbances and may therefore be relatively uninformative. Nevertheless, in the clinical database for risperidone, disturbances of glucose metabolism are not very common and, in general, the risk with risperidone is similar to that with placebo;
- Pharmacovigilance data from the Johnson & Johnson pharmacovigilance database demonstrate no emerging risk for diabetes or related events; and
- Based on the available preclinical and clinical data, risperidone does not affect insulin secretion or Beta-cell function. This reflects a differential effect of risperidone among tested atypical antipsychotics.

We request that FDA consider this comprehensive review of the available data pertaining to risperidone. This dataset is more robust in supporting relative safety with regard to glucose-related adverse events than data available for any of the more recently introduced antipsychotics, which lack comparable patient exposure. Based on this or other data, should the FDA reconsider the broad application of an identical "class label" on this issue to all drugs in this "class," we respectfully request an opportunity to meet with the Agency to help assure that accurate label language reflecting the most current evidence is applied to risperidone.

As documented and approved in a series of electronic mail communications with Kenneth Edmunds, Jr. of the FDA, a variation of the bookmarking requirements under *FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999* for this submission was requested. Per Mr. Edmund's approval, this submission is bookmarked as follows:

- The document table of contents is hyperlinked to the sections and attachments in the volumes.

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- The text within the primary report is hyperlinked to appropriate key references, tables, etc.

This submission is presented electronically and is designed to meet electronic archival requirements as outlined within the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999* with the exceptions noted above. Submission files are presented in Adobe Acrobat Portable Document Format (PDF) on one CD-ROM and totals approximately 25 MB. McAfee VirusScan v4.5.1 SP1 as used to ensure a virus free submission.

Please call me at 609-730-2712 if you have further questions.

Yours sincerely,

Susan Merchant

Susan Merchant
Associate Director, Regulatory Affairs
Global Marketed Products

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Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

EDMS-PSDB-3725373:2.0 VD

1125 Trenton-Harbourton Road
P.O. Box 200, Titusville, NJ 08560

27 AUG 2004

Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Office of Drug Evaluation I
U.S. Food and Drug Administration
**Attn: Document Control Room 10B-40**
1451 Rockville Pike
Rockville, MD 20857

**NDA 20-272**
**RISPERDAL® (risperidone) Tablets**

**Cross reference to:**
NDA 20-588, NDA 21-444, and NDA 21-346

**General Correspondence**
Response To Request For Information – Dyslipidemia and Metabolic Syndrome

Dear Dr. Katz,

On behalf of Janssen Pharmaceutica, L.P., please refer to NDA 20-272 for RISPERDAL® (risperidone) Tablets, the Division's letter dated 8 April 2004, and e-mail communications between J&JPRD and the Division from 17 May to 2 June 2004. The Division's letter requested sponsors of atypical antipsychotic drugs to investigate the potential influence of these drugs on lipid metabolism and metabolic syndrome. Specifically, your letter requested a review and evaluation of our clinical trial databases and postmarketing adverse event surveillance system, as well as a comprehensive literature review, to identify and describe reports of abnormal blood levels of triglycerides or cholesterol, or cases of metabolic syndrome reported with the use of risperidone. The review was to include both analyses of adverse events related to dyslipidemias and/or the metabolic syndrome and analyses of pertinent laboratory data (total cholesterol, LDL, HDL, and triglycerides).

Johnson and Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) has completed a review of all available risperidone data and is providing the enclosed summary document and attachments with our findings. The summary report reviews data from our clinical trial database of Phase 2-4 studies in over 12,000 subjects, Janssen Medical Affairs studies which specifically collected data to assess metabolic syndrome, interim data from an investigator-initiated study which also assessed metabolic syndrome, an analysis of relevant data from the postmarketing adverse event surveillance database, and a comprehensive literature review of dyslipidemias and abnormal blood levels with the use of risperidone.

This submission is presented electronically and is designed to meet electronic archival requirements as outlined within the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs, January 1999.* Submission files are presented in Adobe Acrobat Portable Document Format (PDF) on one CD-ROM and totals approximately 16 MB. McAfee VirusScan v7.1.0 was used to ensure a virus free submission.

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Please contact me at 609-730-2712 if you have further questions.

Yours sincerely,

Susan Merchant

Susan Merchant
Associate Director, Regulatory Affairs
Global Marketed Products

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# EXHIBIT K

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Johnson & Johnson

# CREDO

Survey 2004

## Manager's Communications to Employees

## Let Your Voice Be Heard

JJRE 06622373
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Plaintiff Exh. 1035

# Our Credo
# From Understanding to Believing

We believe our first responsibility is to the doctors, nurses and patients,
to mothers and fathers and all others who use our products and services.
In meeting their needs everything we do must be of high quality.
We must constantly strive to reduce our costs in order to maintain reasonable prices.
Customers' orders must be serviced promptly and accurately.
Our suppliers and distributors must have an opportunity to make a fair profit.

We are responsible to our employees, the men and women who work with us throughout the world.
Everyone must be considered as an individual. We must respect their dignity and recognize their merit.
They must have a sense of security in their jobs. Compensation must be fair and adequate,
and working conditions clean, orderly and safe.We must be mindful of ways to help our employees fulfill
their family responsibilities. Employees must feel free to make suggestions and complaints.There must be equal opportunity
for employment, development and advancement for those qualified.We must provide competent management, and their
actions must be just and ethical.

We are responsible to the communities in which we live and work and to the world community as well.
We must be good citizens - support good works and charities and bear our fair share of taxes.
We must encourage civic improvements and better health and education.We must maintain in good order
the property we are privileged to use, protecting the environment and natural resources.

Our final responsibility is to our stockholders. Business must make a sound profit.
We must experiment with new ideas. Research must be carried on, innovative programs developed and mistakes paid for.
New equipment must be purchased, new facilities provided and new products launched.
Reserves must be created to provide for adverse times. When we operate according to these principles,
the stockholders should realize a fair return.

M. HOPE BLACKLEY

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Credo Survey Information Session

SPARTANBURG

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Plaintiff Exh. 1035

R. 8961

JJRE 06622374
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# Our Credo : why & what ?

- **Written by Robert Wood Johnson in 1943**
- **Today more relevant than ever because**
  **It shows us the social responsibility of each Johnson & Johnson company and employee :**
  1. **The customers**
  2. **The employees**
  3. **The community**
  4. **The shareholders**
- **"Our Credo" is NOT a code of conduct, it is the HEART of the company**

M. HOPE BLACKLEY
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Plaintiff Exh. 1035

R. 8962

JJRE 06622375
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# Our Credo : why & what ?

**"Our Credo sets us apart from other companies, and enables us to grow and succeed, as we chart our course toward the future."**

***Harlan Weisman, President J&JPRD***

M. HOPE BLACKLEY
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Plaintiff Exh. 1035

R. 8963

JJRE 06622376
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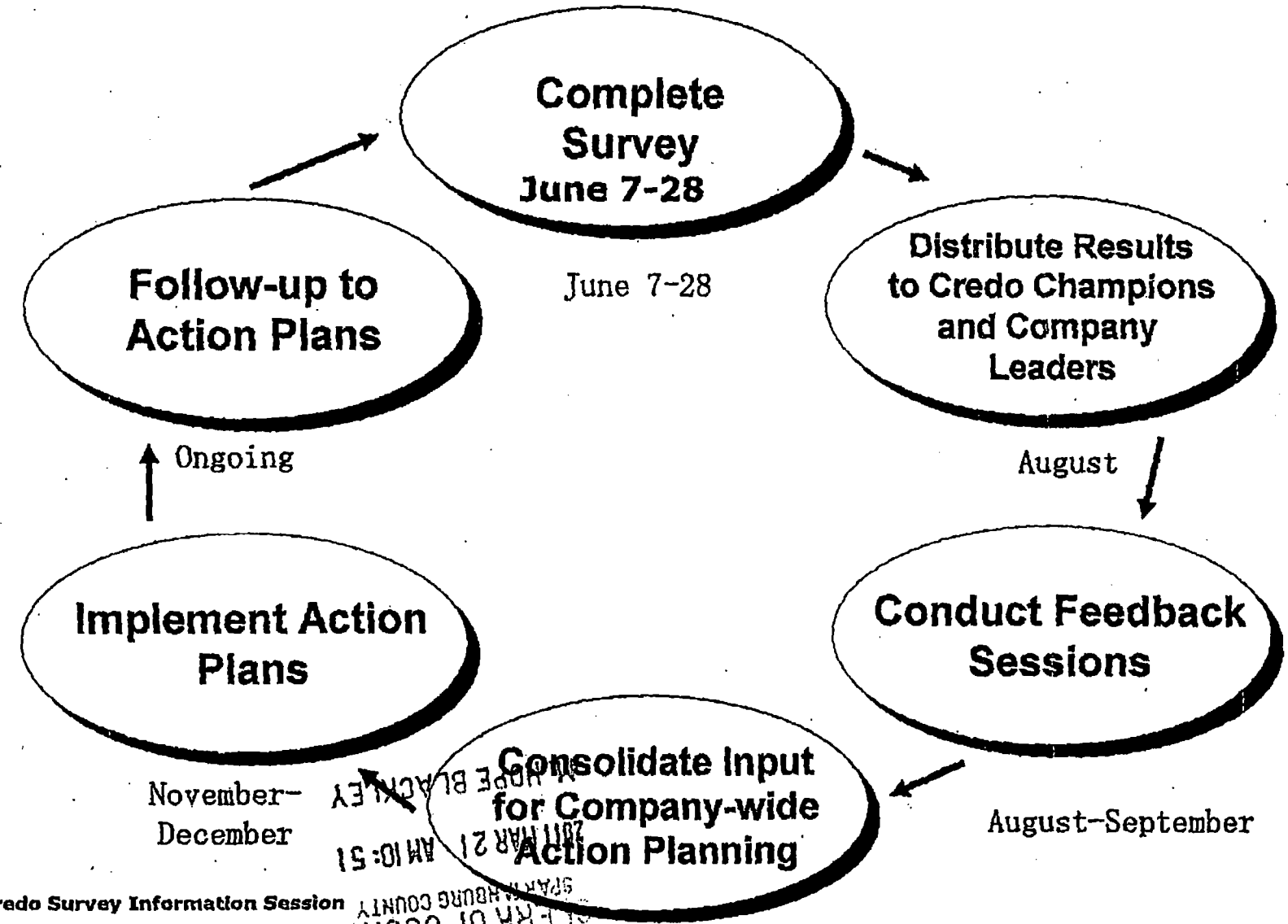
# Credo Survey Process Overview




Credo Survey Information Session

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R. 8964

# Credo Survey: 4 basic objectives

- To keep a finger on the pulse of the company
  - How are the Credo values adhered to?
  - Are the changes we apply in our environment consistent with the idea behind the Credo values?
- To observe trends in opinions
- To provide specific feedback to management
- To develop appropriate action plans to increase organizational effectiveness

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R. 8965

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# Guarantee of Anonymity

- **Information compiled by external organization**
  - 3rd Party—Genesee Survey Services
- **No reports for groups**
  - **Smaller than 7**
  - **Less than 30 responses for a site**

***"Let your voice be heard"***

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Plaintiff Exh. 1035

R. 8966

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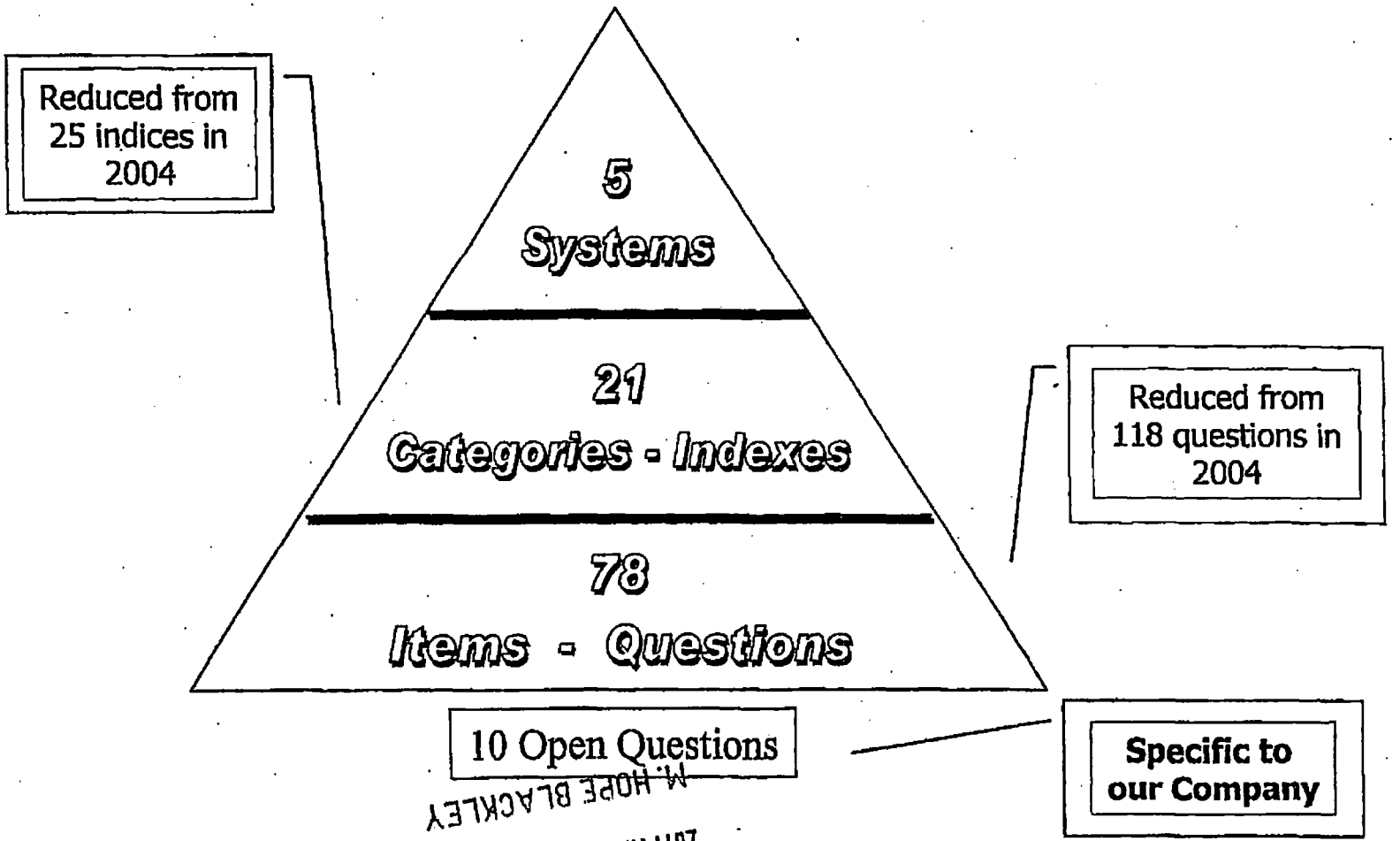
# 2004 Survey Structure

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R. 8967

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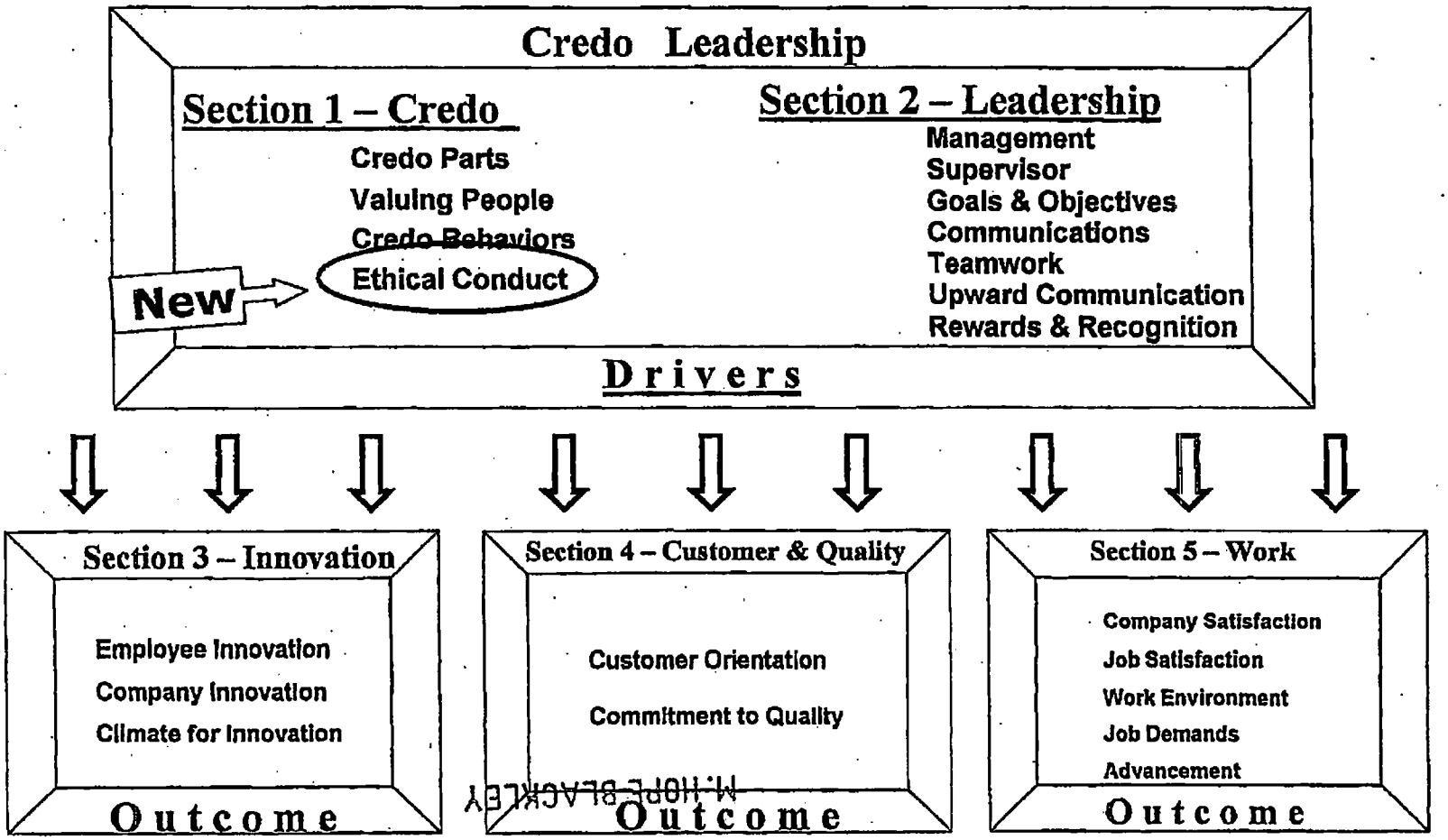
# Credo Survey Structure

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R. 8968

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# What is ethical conduct ?

- Living the Credo = being ethical, putting honor and integrity first.
- Ethics is about principles that prescribe what is morally right, good and proper.
- What happens if we do not behave ethically ?
  - We may loose our customer's or employee's trust
  - Employees are demotivated and may leave the organization
  - The environment may turn against us
  - High costs and high risks

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# Our Credo
# A guide in ethical decision making

| clearly good | "gray zone" | clearly wrong |
|---|---|---|

- We all need to make decisions.
- Many decisions are situated in a "gray" zone between clearly good and clearly wrong.
- The Credo is a guide in right decision making, daily and in a crisis.

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# Guiding Questions in Ethical Decision Making

- Would the reputation of my company be damaged if this decision reached the front page of the newspapers?
- Would I advice my child/family member to do the same thing if he/she were confronted with this dilemma?
- Would I personally feel good if I were treated in this way?
- Is this what my "gut feeling", my intuition tells me to do?
- Would the Legal Department agree with my decision?

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R. 8971

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# Ethical Conduct in Practice

- **Patients and customers**
  - Safe and high quality products at reasonable prices
  - Trust
  - Correct information
- **Employees**
  - Respect their dignity
  - Fair treatment
  - Safe, clean and orderly conditions
  - Equal opportunity
- **Community**
  - Legal
  - Sustainable
  - Good citizens
- **Stakeholders**
  - Sound profit
  - Good return



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R. 8972

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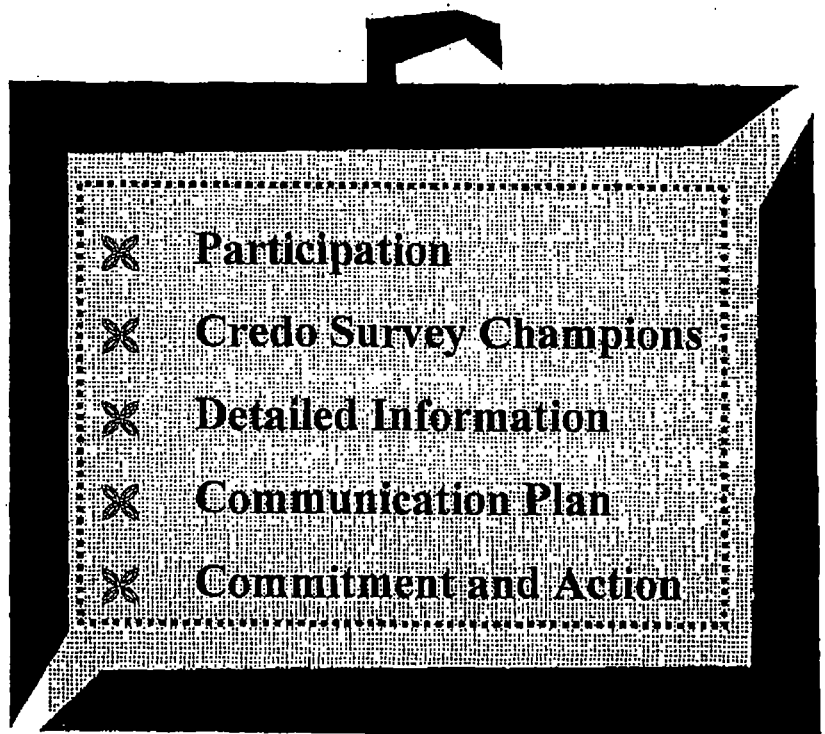
# Critical Success Factors

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R. 8973

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# Your role (1)

- Let your voice be heard and fill out the survey.
- Tell - anonymously - whether the content of "Our Credo" is effectively applied and lived up to in our company.
- Some tips when filling out the questionnaire:
  - Let your answers be led by your own opinion and not the opinion of the group.
  - Base your opinion on what you experienced over a longer period, rather than on a one time or recent event.
  - If you do not have an opinion with regard to a specific question, then do not answer that question.

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R. 8974

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# Your role (2)

- **Some definitions of terms used in the questionnaire:**
  - **Company: J&JPRD specific, not the J&J Corporation.**
  - **Management: those above your immediate supervisor/manager-all the way to the top of J&JPRD.**
  - **Supervisor or Immediate Supervisor: the person to whom you report directly.**

- **Participate actively in future group discussions:**
  - **Express your opinions and feelings.**
  - **Help looking for solutions.**
  - **Support the implementation and follow-up of the action plans.**

- **Live the CREDO daily**

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R. 8975

JJRE 06622388
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JJRE 06622389
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R. 8976

Dank U

Merci

THANK YOU!

Gracias Danke

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Plaintiff Exh. 1035

# EXHIBIT L

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JJREv 04247347
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# RISPERDAL® and US Diabetes Label Text

## IDC decision required:

Permission for meeting with the FDA on the current Risperdal diabetes labeling to :

- ensure accurate label text that is aligned with full set of Risperdal data
- prevent potential disadvantage vs. future labels of newer atypicals which may have a similar low risk for diabetes as risperidone.

R. 8978

- Ivo Caers, Risperdal Team Leader
- Sagar Adusumalli, Risperdal Regulatory Leader
- Mariëlle Eerdekens, Risperdal Clinical Leader
- Ramy Mahmoud, Janssen US CNS Medical Affairs

Exhibit
Caers - 46
08.20.09

**IDC Meeting**

**January 13, 2004**

Johnson & Johnson



Plaintiff Ex. 435

# Risperdal and US Diabetes Label Text

## Agenda

Regulatory background and history

Status of atypical antipsychotics diabetes label

Risperdal data - epidemiology
- physiology
- clinical trials
- pharmacovigilance

Recommendation, potential risks and benefits

Potential outcomes

Proposed action plan

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R. 8979

JJREv 04247348
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# Risperdal and US Diabetes Label Text

**Regulatory Background and History**

| | |
|---|---|
| 2002 Apr | Submission of revised US label including hyperglycemia to A.E. Post-introduction reports |
| 2002 Nov 19 | FDA approval of April 2002 label revision |
| 2003 Sept 12 | FDA sends proposed label for oral Risperdal class warning on diabetes and hyperglycemia |
| 2003 Sept 17 | Eli Lilly publicly announces FDA request for diabetes class warning and its inclusion in US Zyprexa label |
| 2003 Oct 27 | Compromise with FDA on Risperdal diabetes class warning text leading to approval of Risperdal Consta |
| 2003 Nov 19 | J. Racoosin (FDA) expressed willingness to review additional data and reconsider its position (ADA/APA consensus meeting) |
| 2003 Dec 3 | Inclusion of Risperdal class warning text in oral label with approval in bipolar mania |
| 2003 Dec 29 | Symbyax (olanzapine + fluoxetine, Lilly) approval with diabetes class warning identical to the one agreed upon for Risperdal |

R. 6980

JJREv 04247349
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# Risperdal and US Diabetes Label Text

JJRErev 04247350
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R. 8981

## FDA position

- Primary source is a recent epidemiological study in VA population showing an increased risk for diabetes with 3 studied atypical antipsychotics (Zyprexa, Risperdal, Seroquel), assumed to be consistent with existing literature.
- Severe cases of hyperglycemia and associated symptoms incl. fatalities have been reported on all 3 of these compounds.
  Reported on all "studied" atypical antipsychotics => class effect.
  However, some (newcomers) in class may lack data.
- Prescribers need guidance on how to handle / prevent risk => need for monitoring guidelines.

M. HOPE BLACKLEY
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# FDA Proposed Hyperglycemia Labeling and agreed upon text for Risperdal (Consta) (Modifications in Underline/Strikethrough)

JJREev 04247351
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R. 8982

**WARNINGS**

**Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics ~~studied~~. Precise risk estimates for hyperglycemia-related adverse events in patients with atypical antipsychotics are not available. ~~The available data are insufficient to provide reliable risk estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.~~

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment ~~baseline~~ and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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# Status of Atypical Antipsychotics Label in the US

## FDA Hyperglycemia/Diabetes Class WARNING label: 9/11/03

**ZYPREXA / SYMBYAX** (olanzapine-fluoxetine combination)

- Accepted the FDA proposed class WARNING
- Implemented in September 2003
- Lilly informed physicians on October 6, 2003
- October 2003 "Risperdal revision" of class warning included in newly approved Symbyax label December 2003

**RISPERDAL**

- Accepted a revision of the FDA proposed class WARNING label
- Implemented in October 2003
- JPI informed physicians on November 10, 2003

**SEROQUEL / GEODON / ABILIFY**

- Not accepted yet, announced they will discuss with FDA
- Negotiations likely ongoing

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R. 8983

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# Atypical Antipsychotics and Diabetes; Commercial Overview

- Lilly's misleading promotion in 2002 continued despite complaints to Lilly and FDA
- Janssen disseminates diabetes reprints to HPC since March 2003
- Intense media coverage of diabetes issue (Aug-Oct '03)
- No Lilly issued DDL
- Janssen: HCP communication 11/10/2003
- FDA request for DDL on 11/21/2003 (J&JPRD response 11/26/03)
- Sales impact minimal to date due to Risperdal viewed as positively differentiated from Zyprexa
- Significant risk of being associated with Zyprexa if other atypicals receive differentiated label (precaution)

R. 8984

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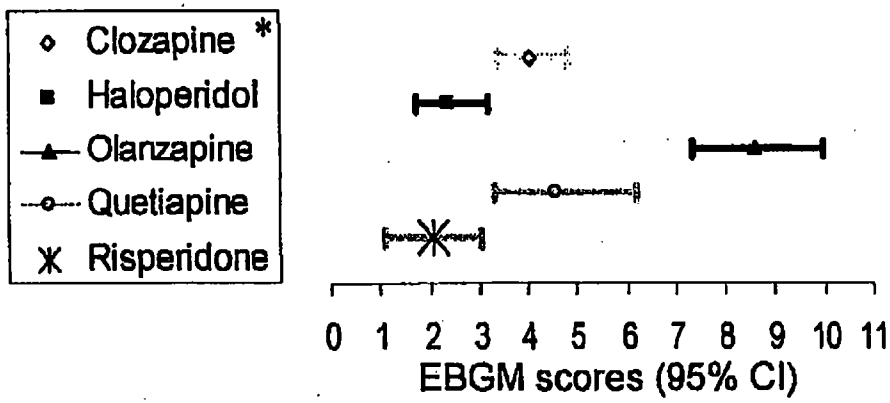
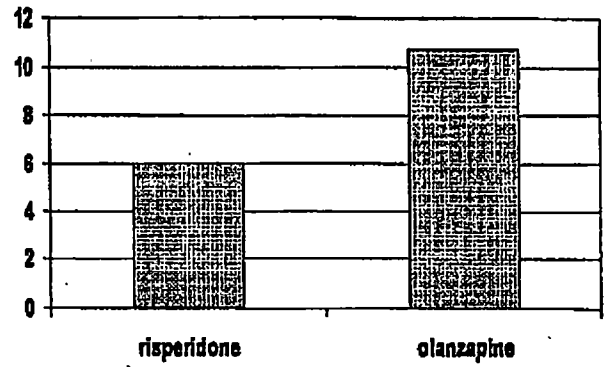
# Epidemiology Evidence: Risk of Diabetes Events with Atypical Antipsychotics

Comparative Rates of Life-Threatening Events from MedWatch Data Analysis




Incidence of DKA per 10,000 patients




Relative Risk 1.6 (p<0.05)

- **In all 4 studies compared to untreated patients, risperidone demonstrated no difference in risk for diabetes**
  - **Olanzapine risk higher in all four studies (43-480%)**
- **In 10 of 13 studies, risperidone demonstrated equal or less risk for diabetes compared to conventional antipsychotics**
- **In 8 of 11 studies, risperidone demonstrated significantly lower risk of diabetes compared to olanzapine (risk 20-319% higher)**

* *Launches: H 1969, Cloz 1991, Ris 1994, Ola 1996, Quet 1997*



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# Physiology evidence; Insulin Sensitivity and ß-cell Function

| | Effect on Insulin Sensitivity | | Effect on β-cell Function | |
|---|---|---|---|---|
| | Risperidone | Other Drugs | Risperidone | Other Drugs |
| **Hyperglycemic Clamp** (Sowell) | ? | ? | NO | ↑ INSULIN (OLZ) |
| **Euglycemic Clamp** (Beasley) | NO | NO | N/A | N/A |
| **Hyperglycemic/ Euglycemic Clamp in dogs** (Bergman and Ader) | NO | ↓ HEPATIC SI (OLZ) | NO | ↓ B-CELL FUNCTION (OLZ) |
| **FSIVGTT** (Cagliero and Henderson) | NO | ↓ SI (OLZ and CLO) | NO | NO |



R. 8986

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# Data from Clinical Trials

- 12,000 patients treated for up to 3 months
- 7,500 patients treated for > 6 months

| glucose related AE's | | children | adults | elderly | Total |
|---|---|---|---|---|---|
| short term | risperidone (n=8458) | 0.00 %* | 0.52 % | 2.17 % | 0.72 % |
| | placebo (n=1825) | 0.00 %* | 0.43 % | 1.70 % | 0.88 % |
| | olanzapine (n=536) | - | 0.87 % | 1.28 %* | 0.93 % |
| | haloperidol (n=920) | - | 0.25 % | 0.85 %* | 0.33 % |
| long term | risperidone (n=6590) | 0.13 % | 1.51 % | 2.66 % | 1.49 % |
| | olanzapine (n=300) | - | 1.66 % | - | 1.66 % |
| | haloperidol (n=579) | - | 1.55 % | - | 1.55 % |

** denominator < n=200*

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# Data from Risperdal Pharmacovigilance

- Total estimated patient exposure: 17,200,000 patients
- 375 reports of glucose related AE's, 12 patients died (diabetic ketoacedosis: 34 reports, diabetic coma: 10 reports)
- In 4 cases deterioration of glucose control in known stabilized diabetic patients was reported to be temporarily related to Risperdal initiation.
  In 1 case, a possible positive rechallenge occurred.

R. 8988

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# Summary of evidence re. Risperdal and risk for diabetes

- Epidemiology evidence does not support increased risk of diabetes with risperidone
  - Serious life-threatening events (e.g. DKA) not more common than with Haldol
  - Weight of evidence; diabetes is not more common than in untreated or conventional antipsychotic treated patients and less common than with olanzapine and clozapine
- The clinical database suggests that disturbances of glucose metabolism are not very common and not different between risperidone and placebo
- The PV database does not suggest an increased risk for diabetes or related events
- Risperidone does not effect insulin secretion or β-cell function.

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R. 8989

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# Summary of Evidence => appropriate Label Text

**Recommendation:**

**Precaution covering;**

- Hyperglycemia and exacerbation of diabetes have been reported
- No established causal relationship
- Monitoring may be desirable in line with good clinical practice

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R. 8990
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JJREev 04247360
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# Risperdal and US Diabetes Label Text

## Potential benefits and risks of re-opening negotiations with FDA;

### *Risks*

- Relationship with FDA
  => loss of confidence by FDA in J&JPRD commitment and its credibility
- => impact on future CNS projects / approvals

### *Benefits*

- Earlier insight in FDA preparedness for label compromises
  => potential to mitigate our risk for competitive disadvantage
- Differentiated label vs. Zyprexa confirming present perception in the market and clinical impressions
- Differentiated US label will support maintaining current differentiation ex-US labels

R. 8991

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# Potential outcomes

## Background:

- FDA expressed willingness to review additional data and reconsider its position (J. Racoosin, ADA/APA consensus meeting, Nov 2003)
- Our perceived "weight of evidence" demonstrating low diabetes risk with risperidal may be interpreted differently by the FDA.

| Outcomes | Probablitity |
|---|---|
| Avoid having a worse label than future labels of other "low risk" atypical antipsychotics | Moderate |
| Precaution text rather than warning | Low |

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R. 8992
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# Proposed Action Plan

- Subject to January 13 IDC endorsement;
  - Meeting with FDA to discuss significant differentiation in label

- Timing;
  - Request for meeting; Jan 2004
  - If FDA grants a meeting, briefing document to FDA mid February 2004
  - FDA Meeting: 2nd half March 2004

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R. 8993
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# RISPERDAL® and US Diabetes Label Text

## IDC decision required:

Permission for meeting with the FDA on the current Risperdal diabetes labeling to :

- ensure accurate label text that is aligned with full set of Risperdal data
- prevent potential disadvantage vs. future labels of newer atypicals which may have a similar low risk for diabetes as risperidone.

- Ivo Caers, Risperdal Team Leader
- Sagar Adusumalli, Risperdal Regulatory Leader
- Mariëlle Eerdekens, Risperdal Clinical Leader
- Ramy Mahmoud, Janssen US CNS Medical Affairs

**IDC Meeting**

**January 13, 2004**

Johnson & Johnson



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## Risperdal and US Diabetes Label Text

### Agenda

Regulatory background and history

Status of atypical antipsychotics diabetes label

*Risperdal data* - *epidemiology*
- physiology
- clinical trials
- pharmacovigilance

Recommendation, potential risks and benefits

Potential outcomes

Proposed action plan



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## Risperdal and US Diabetes Label Text

**Regulatory Background and History**

| | |
|---|---|
| 2002 Apr | Submission of revised US label including hyperglycemia to A.E. Post-introduction reports |
| 2002 Nov 19 | FDA approval of April 2002 label revision |
| 2003 Sept 12 | FDA sends proposed label for oral Risperdal class warning on diabetes and hyperglycemia |
| 2003 Sept 17 | Eli Lilly publicly announces FDA request for diabetes class warning and its inclusion in US Zyprexa label |
| 2003 Oct 27 | Compromise with FDA on Risperdal diabetes class warning text leading to approval of Risperdal Consta |
| 2003 Nov 19 | J. Racoosin (FDA) expressed willingness to review additional data and reconsider its position (ADA/APA consensus meeting) |
| 2003 Dec 3 | Inclusion of Risperdal class warning text in oral label with approval in bipolar mania |
| 2003 Dec 29 | Symbyax (olanzapine + fluoxetine, Lilly) approval with diabetes class warning identical to the one agreed upon for Risperdal |



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## Risperdal and US Diabetes Label Text

**FDA position**

- Primary source is a recent epidemiological study in VA population showing an increased risk for diabetes with 3 studied atypical antipsychotics (Zyprexa, Risperdal, Seroquel), assumed to be consistent with existing literature.
- Severe cases of hyperglycemia and associated symptoms incl. fatalities have been reported on all 3 of these compounds.
  Reported on all "studied" atypical antipsychotics => class effect.
  However, some (newcomers) in class may lack data.
- Prescribers need guidance on how to handle / prevent risk => need for monitoring guidelines.



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R. 8997

## FDA Proposed Hyperglycemia Labeling and agreed upon text for Risperdal (Consta) (Modifications in Underline/Strikethrough)

**WARNINGS**

**Hyperglycemia and Diabetes Mellitus**

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including RISPERDAL®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics studied. Precise risk estimates for hyperglycemia-related adverse events in patients with atypical antipsychotics are not available. ~~The available data are insufficient to provide reliable risk estimates of differences in hyperglycemia-related adverse event risk among the marketed atypical antipsychotics.~~

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.



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R. 8998

## Status of Atypical Antipsychotics Label in the US

**FDA Hyperglycemia/Diabetes Class WARNING label: 9/11/03**

**ZYPREXA / SYMBYAX** (olanzapine-fluoxetine combination)
- Accepted the FDA proposed class WARNING
- Implemented in September 2003
- Lilly informed physicians on October 6, 2003
- October 2003 "Risperdal revision" of class warning included in newly approved Symbyax label December 2003

**RISPERDAL**
- Accepted a revision of the FDA proposed class WARNING label
- Implemented in October 2003
- JPI informed physicians on November 10, 2003

**SEROQUEL / GEODON / ABILIFY**
- Not accepted yet, announced they will discuss with FDA
- Negotiations likely ongoing



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R. 8999

## Atypical Antipsychotics and Diabetes; Commercial Overview

- Lilly's misleading promotion in 2002 continued despite complaints to *Lilly and FDA*
- Janssen disseminates diabetes reprints to HPC since March 2003
- *Intense media coverage of diabetes issue (Aug-Oct '03)*
- No Lilly issued DDL
- *Janssen: HCP communication 11/10/2003*
- FDA request for DDL on 11/21/2003 (J&JPRD response 11/26/03)
- Sales impact minimal to date due to Risperdal viewed as positively differentiated from Zyprexa
- Significant risk of being associated with Zyprexa if other atypicals receive differentiated label (precaution)



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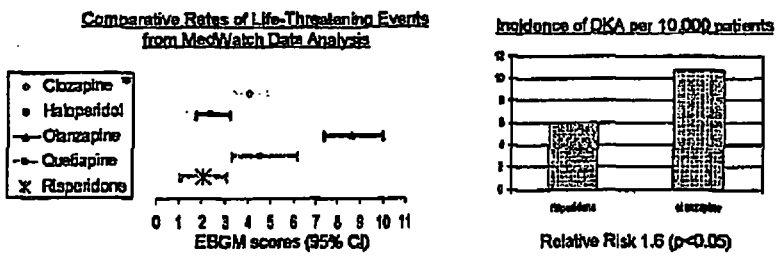
Rev 9000

## Epidemiology Evidence: Risk of Diabetes Events with Atypical Antipsychotics




- In all 4 studies compared to untreated patients, risperidone demonstrated no difference in risk for diabetes
  - Olanzapine risk higher in all four studies (43-480%)
- In 10 of 13 studies, risperidone demonstrated equal or less risk for diabetes compared to conventional antipsychotics
- In 8 of 11 studies, risperidone demonstrated significantly lower risk of diabetes compared to olanzapine (risk 20-319% higher)

*Launchax H 1969, Cloz 1991, Ris 1994, Ola 1996, Quet 1997

Risperdal Hyperglycemia/Diabetes Labeling Johnson & Johnson Confidential IDC, January 13, 2004 8

In a study utilizing data from the FDA MedWatch database, we examined the strength of the association between antipsychotic usage and reports of life-threatening diabetes-related events. Life-threatening events were defined as DKA and diabetic coma. An empirical bayesian geometric mean or EBGM score was calculated for 5 different antipsychotics. An EBGM score is the ratio of observed to expected number of events for a given medication. For example, a drug with a score of 4 would have 4 times the number of events observed as compared to the number which could be expected during the same time period. In understanding the results of this study, let's use haloperidol patients as the reference group because it's use has not been linked to an increased rate of incident diabetes. Patients receiving clozapine, olanzapine and quetiapine have a significantly higher rate of life-threatening events, 4 to 8 times the expected rate, as compared to those receiving haloperidol, while risperidone patients were no different than haloperidol patients.

In order to better evaluate the risk of DKA among atypical antipsychotic users, an epidemiological study of a very large database was conducted. In a study of over 100,000 of patients from the California Medicaid database, risperidone patients demonstrated an incident rate of DKA of 6 per 10,000 while olanzapine patients had a rate of over 10 per 10,000. In logistic analyses, this resulted in a 60% increased relative risk for DKA with olanzapine use.

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Based on pharmacovigilance and epidemiological evidence, serious and life-threatening events like DKA have not been associated with risperidone unlike some other antipsychotics.

Differences exist in the excess risk of diabetes among atypical antipsychotics. Four studies evaluated the risk as compared to an untreated similar patient population and all four found that the risk among risperidone patients was no different than an



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R. 9001

## Physiology evidence; Insulin Sensitivity and ß-cell Function

| | Effect on Insulin Sensitivity | | Effect on β-cell Function | |
|---|---|---|---|---|
| | Risperidone | Other Drugs | Risperidone | Other Drugs |
| Hyperglycemic Clamp (Sowell) | ? | ? | NO | ↑ INSULIN (OLZ) |
| Euglycemic Clamp (Beasley) | NO | NO | N/A | N/A |
| Hyperglycemic/ Euglycemic Clamp in dogs (Bergman and Ader) | NO | ↓ HEPATIC SI (OLZ) | NO | ↓ B-CELL FUNCTION (OLZ) |
| FSIVGTT (Cagliero and Henderson) | NO | ↓ SI (OLZ and CLO) | NO | NO |



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R. 9002

## Data from Clinical Trials

- 12,000 patients treated for up to 3 months
- 7,500 patients treated for > 6 months

| glucose related AE's | | children | adults | elderly | Total |
|---|---|---|---|---|---|
| short term | risperidone (n=8458) | 0.00 %* | 0.52 % | 2.17 % | 0.72 % |
| | placebo (n=1825) | 0.00 %* | 0.43 % | 1.70 % | 0.88 % |
| | olanzapine (n=536) | - | 0.87 % | 1.28 %* | 0.93 % |
| | haloperidol (n=920) | - | 0.25 % | 0.85 %* | 0.33 % |
| long term | risperidone (n=6590) | 0.13 % | 1.51 % | 2.66 % | 1.49 % |
| | olanzapine (n=300) | - | 1.66 % | - | 1.66 % |
| | haloperidol (n=579) | - | 1.55 % | - | 1.55 % |

** denominator < n=200*



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R. 9003

## Data from Risperdal Pharmacovigilance

- *Total estimated patient exposure: 17,200,000 patients*
- 375 reports of glucose related AE's, 12 patients died (diabetic ketoacedosis: 34 reports, diabetic coma: 10 reports)
- In 4 cases deterioration of glucose control in known stabilized diabetic patients was reported to be temporarily related to *Risperdal initiation.*
  In 1 case, a possible positive rechallenge occurred.



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## Summary of evidence re. Risperdal and risk for diabetes

- Epidemiology evidence does not support increased risk of diabetes with risperidone
  - Serious life-threatening events (e.g. DKA) not more common than with Haldol
  - Weight of evidence; diabetes is not more common than in untreated or conventional antipsychotic treated patients and less common than with olanzapine and clozapine
- The clinical database suggests that disturbances of glucose metabolism are not very common and not different between risperidone and placebo
- The PV database does not suggest an increased risk for diabetes or related events
- Risperidone does not effect insulin secretion or β-cell function.



The purpose of this presentation today is to provide evidence that there is little or no risk of diabetes with risperidone treatment. At the end of this presentation, I would like to be able to conclude that:

Epidemiolgy evidence does not support risk of diabetes with risperidone.

Risperidone does not effect insulin secretion or β-cell function.

And finally serious and life-threatening events (like DKA) have not been associated with risperidone use.

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## Summary of Evidence => appropriate Label Text

**Recommendation:**

**Precaution covering;**

- Hyperglycemia and exacerbation of diabetes have been reported
- No established causal relationship
- Monitoring may be desirable in line with good clinical practice



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# Risperdal and US Diabetes Label Text

**Potential benefits and risks of re-opening negotiations with FDA:**

| *Risks* | *Benefits* |
|---|---|
| • Relationship with FDA => loss of confidence by FDA in J&JPRD commitment and its credibility<br>• => impact on future CNS projects / approvals | • Earlier insight in FDA preparedness for label compromises => potential to mitigate our risk for competitive disadvantage<br>• Differentiated label vs. Zyprexa confirming present perception in the market and clinical impressions<br>• Differentiated US label will support maintaining current differentiation ex-US labels |



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R. 9007

## Potential outcomes

**Background:**

- FDA expressed willingness to review additional data and *reconsider its position (J. Racoosin, ADA/APA consensus meeting,* Nov 2003)
- Our perceived "weight of evidence" demonstrating low diabetes risk with risperidal may be interpreted differently by the FDA.

| Outcomes | Probablitity |
|---|---|
| Avoid having a worse label than future labels of other "low risk" atypical antipsychotics | Moderate |
| Precaution text rather than warning | Low |



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R. 9008

## Proposed Action Plan

- Subject to January 13 IDC endorsement;
  - Meeting with FDA to discuss significant differentiation in label
- Timing;
  - Request for meeting; Jan 2004
  - If FDA grants a meeting, briefing document to FDA mid February 2004
  - FDA Meeting: 2nd half March 2004



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# EXHIBIT M

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JJRE 14243093

R. 9011

# RISPERDAL and Pituitary Tumors

## IDC Decision required:
## Approval of Action plan/Recommendation for Further Investigation

Ivo Caers (CDTL)
Vivek Kusumakar (Clinical Leader)
Gahan Pandina (Med. Aff.)
Leo Russo (BRM, epidemiology)
Danielle Coppola (BRM, Physician)

**IDC Meeting**
**July 20, 2006**

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Plaintiff Ex. 2587

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JJRE 14243094

# Agenda

- History of Key Decisions
- Update to IDC
  - CCDS change October 2005
  - Szarfman et al. (FDA) publication
  - FDAs plan to study Risperdal and pituitary adenomas
- Research Questions
- Study proposals
- Approach towards FDA
- Team recommendations

R. 9012

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# History of Key Decisions

| Date | Decision Forum | Decision | Synopsis of Contract |
|---|---|---|---|
| Aug. 16, 05 | IDC | Endorsement of Team position re. Risperdal/ pituitary adenoma | - Team to develop label proposal.<br>- Develop PRL strategy [redacted] |
| Jan. 26, 06 | IDC | Endorsement of PRL Strategic Scientific Plan | - No credible Pit. Adenoma study design selected.<br>- Evaluate<br>  - scanning bias study<br>  - prospective cross-sectional case controlled study. |

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# Update to IDC

- Incorporation of "Benign Pituitary Adenomas" in CCDS October 14, 2006.
- Szarfman et al. (Office of Pharmacoepidemiology + Statistical Sciences, FDA) publication on "Atypical Antipsychotics and Pituitary Tumors. Pharmacotherapy 2006; 26 (6): 748-58.
- June 12, 2006 Pink Sheet; "FDA's division of Psychiatry Products and Office of Surveillance & Epidemiology are planning a study to determine if risperidone has an increased risk of pituitary adenoma vs. other antipsychotics".

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JJRE 14243096

# Regulatory Status on Risperdal and Pituitary Adenomas

USA: CBE October 2005; Postintroduction Reports
"Adverse Events reported since market introduction which were Temporally (but not necessarily causally) related to RISPERDAL therapy include ....., benign pituitary adenomas, ..."

CCDS: October 14, 2005; Section 4.8 (Undesirable Effects)
"Benign pituitary adenomas have been reported very rarely in risperidone users during postmarketing surveillance. No causal association could be detected".

No formal feedback to these submissions yet from any RAs.

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JJRE 14243097

# BRM Analysis (July 2005); Conclusions

- 160 case reports pituitary adenoma, enlargement, or other abnormalities found in SCEPTRE database.
- As of 30 April 2005, > 22M patient-years exposure to risperidone
- Thus, reporting frequency = < 1/10,000 (very rare, vs. background 1 in 5)
- Multiple confounders, including concomitant or past medications known to elevate PRL, increased pituitary volume in patients with psychiatric illness, high background incidence, and detection bias
- No evidence of causal association with pituitary tumors
- No evidence of increased morbidity (mass effects) or mortality in patients with pre-existing lesions

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JJRE 14243099

# BRM analysis; Putting the Signal into Context

1. Hyperprolactinemia is an ADR for antipsychotics
2. Risperidone elevates PRL more often than other atypical antipsychotics (89% of patients in one study)[1]
3. DDx for hyperprolactinemia includes pituitary adenoma; thus standard practice guidelines recommend MRI[2]
4. Three subsequent potential biases:
   - Screening bias: Clinicians are more likely to order MRIs for patients taking risperidone than other antipsychotics
   - Detection bias: Radiologists reading MRIs in pts with Dx of hyperprolactinemia are more likely to read as pituitary adenoma than other causes of sellar masses, incl. physiologic enlargement
   - Reporting bias: Pituitary tumors are more likely to be reported in patients on risperidone
5. Higher sensitivity but lower specificity with improved MRI techniques
6. Further confounded by high background rate of pituitary tumors and pituitary enlargement more common in drug naïve mentally ill

[1]Melkersson K.J Clin Psychiatry 2005; 66(6);761-767

[2]Harrisons Principles of Internal Medicine, 17th Ed. Accessed at: http://www.accessmedicine.com/content.aspx?aid=97187.



R. 9017

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JJRE 14243100

# OR

# Slides 6 + 7 as Back-up

# and slide 9 instead

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R. 9018

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JJRE 14243101

# PRL and Pituitary Adenomas

- HyperPRL does not cause pituitary adenomas
- Pituitary adenomas present in 10-25% of healthy normal individuals
- Risperidone & pituitary adenomas: no detectable causal link
- Risperidone treated subjects investigated more often for pituitary adenomas because of PRL related adverse events
- Disproportionate reports of pituitary adenomas with risperidone treatment: detection and reporting biases

R. 9019

M. HOPE BLACKLEY
2011 MAR 21 AM 10:53
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# Szarfman et al. study

- Design:
  Retrospective pharmacovigilance analysis of disproportionality of reporting of pituitary tumors (PT) with 7 widely used antipsychotic drugs (AERS database).
- Main Findings:
  - Risperdal PT adjusted reporting ratio of 18.7 (90% CI 14.9-23.3) > all others.
  - Clinical complications in 14/54 Risperdal cases. Appr. half reported as benign.
  - Women > men (85% of women reports were RISPERDAL cases), 3 cases in adolescents.
  - PT/MMRx; ziprasidone (1.66) and RISPERDAL (0.53) > others (0.03-0.11)
- Conclusions:
  - Treatment with patent $D_2$-receptor antagonists may be associated with pituitary tumors.
  - Consistent with animal (mice) studies.
  - High reporting ratio cannot prove causality.

Letter to editors (Coppola & Schmider) submitted: "Pitfalls of Data Missing".



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R. 9020

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JJRE 14243102

# Research Questions

A. Are users of Risperdal more likely to undergo radiological examinations as compared to patients receiving other antipsychotics?

B. Is the rate of pituitary tumors greater among Risperdal than other antipsychotic users?

- A confounding factor in retrospective studies is the hyper PRL inspired over-diagnosis of pituitary micro-adenomas vs. glandular enlargement (hyperglasia/hypertrophy).

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R. 9021

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JJRE 14243104

- HECON Ass. Inc.; Retrospective (July 1, 1999 – June 30, 2005) ~~analysis.~~

  A: Relative frequencies of radiological examinations in various drug cohorts (≥60 days Rx, monotherapy/combination ± Risperdal).

  B: - Diagnosis of pituitary tumors is assessed amongst different antipsychotics.

  - Treatment of newly diagnosed pituitary tumors in different antipsychotic cohorts.

- J & J Outcomes Research: Retrospective PharMetrics database analysis.

  A: - Relative frequencies of radiological examinations.

  B: - Rate of pituitary tumors in those who receive radiological examination.

  - Control for potential detection bias.

R. 9022

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JJRE 14243105

# Placeholder Leo Russo

R. 9023

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# Placeholder Approach vs FDA

R. 9024

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# Team Recommendations

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R. 9025

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JJRE 14243108

# RISPERDAL and Pituitary Tumors

## BACK-UPS

R. 9026

**IDC Meeting**
**July 20, 2006**

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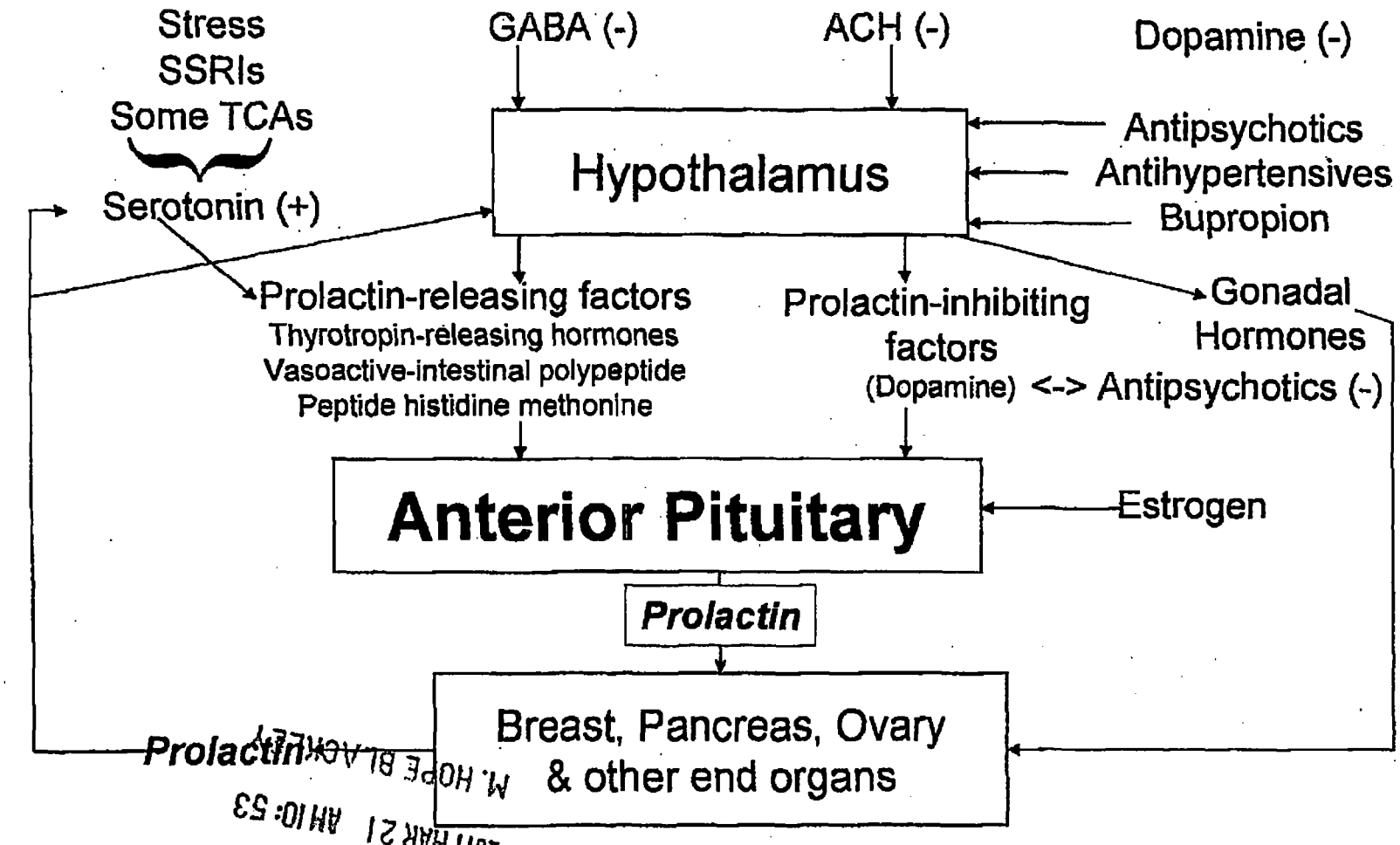
SPARTANBURG COUNTY

Johnson & Johnson

# PRL Regulatory Mechanisms




Halbreich U, et al. Psychoneuroendocrinology 2003;28:53-67.



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JJRE 14243109
R. 9027

# Pituitary Tumors: Options (1)

| Studies Considered | Recommendation |
|---|---|
| • *Confirm scanning bias with RIS vs. Other atypicals*<br>– Replicate BRM report finding | **EVALUATE:** limited value beyond BRM report |
| • *Prospective MRI study (baseline/follow-up)*<br>Required n ? Power calculation?<br>- follow-up time unknown | **NO**; Not feasible |
| • *Retrospective analysis of existing databases*<br>– Similar bias as for spontaneous reporting<br>– Counting surgical interventions only to select for pituitary tumors is biased by multiple treatment options, variable decision trees towards surgery | **NO**; Bias<br>False positive |
| • *Autopsy study; antipsychotics treated patients vs. controls*<br>– Credible sample size not achievable, multiple antipsychotic drug treatment histories<br>– Elderly, Ris most common AP | **NO**; Not feasible |



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R. 9028

# Pituitary Tumors: Options (2)

## Studies Considered, cont'd

- *Cross-sectional case controlled study*
  - MRI scan in patients ≥ 6 months (TBD) on Risperdal vs.on low hyper-PRL antipsychotics.
    - Factors to control for: TBD
    - Central blinded reading of MRI scans required
    - Age 20-50: point prevalence of ± 3.5% -> 700-1000/group = 1400-2000 patients required to detect a doubling of risk
    - Costs; approximate (to be confirmed)
      - –up to 2000 MRI scans = $ 3 MM
      - –up to 8000 patients to be screened = $ 1.6 MM
      - –Organizational costs = $ 1 MM

## Recommendation

**EVALUATE;** Despite difficulty in controlling for previous treatment

Minimal bias identified if:

- random selection
- central, blind MRI Dx
- high cost
- timeline > 2yrs



R. 9029

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JJRE 14243111

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | ) | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC. f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | ) | Civil Action No. 2007-CP-42-1438<br><br>**DEFENDANT ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC.'S MOTION FOR JUDGMENT NOTWITHSTANDING THE VERDICT OR, IN THE ALTERNATIVE FOR A NEW TRIAL** |

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SPARTANBURG COUNTY
2017 APR -1 PM 4:40
HOPE BLACKLEY

TO: JOHN B. WHITE, JOHN S. SIMMONS, AND FLETCHER V. TRAMMELL
ATTORNEYS FOR PLAINTIFF

Pursuant to Rules 50(b) and 59(a) of the South Carolina Rules of Civil Procedure, Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen"), by and through the undersigned counsel, hereby moves this Court for a judgment notwithstanding the jury's verdict or, in the alternative, for a new trial.

Plaintiff, the State of South Carolina (the "State"), asserted one claim against Janssen pursuant to the South Carolina Unfair Trade Practices Act ("SCUTPA") based on: (1) the supposedly "deceptive" nature of one paragraph of a November 10, 2003 mailing from Janssen to South Carolina physicians (the "November 2003 mailing"); and (2) the purported "inadequacy" of the U.S. Food and Drug Administration ("FDA")-approved package insert for Risperdal® ("Risperdal package insert"). Nevertheless, the focus of the case the State presented at trial was on alleged nondisclosures to the FDA, off-label promotion, and correspondence from the FDA characterizing certain conduct as "false" or

"misleading." The State's case turned out to be one about "breaking FDA rules," rather than about "deceptive" statements and "inadequate" package inserts.

For a number of reasons, judgment in favor of Janssen notwithstanding the jury's verdict is appropriate. But, at a minimum, Janssen is entitled to a new trial.

**First**, the State's claim based on the FDA-approved Risperdal package insert is barred by several legal doctrines. Specifically:

(1) the State's "package insert" claim is barred by SCUTPA's regulated activity exemption, S.C. Code Ann. § 39-5-40(a). Every version of the Risperdal package insert, from product launch to the present, was permitted by the FDA. Faced with that dispositive fact, the State argued that Janssen could have added "warnings" to the package insert, using the FDA's changes being effected ("CBE") procedures. Even if the ability to update a package insert might be an "exception" to the regulated activity exemption, the State failed to present any testimony that Janssen should – or even could – have taken advantage of the CBE regulation to update the Risperdal label;

(2) the State's evidence that the FDA-approved Risperdal package insert constitutes an unfair or deceptive trade practice amounted to nothing more than an attempt by the South Carolina Attorney General to enforce the U.S. Food, Drug, and Cosmetic Act (the "FDCA" or the "Act"), barred by principles of primary jurisdiction, *see, e.g., Smith v. S.C. Ret. Sys.*, 336 S.C. 505, 527, 520 S.E.2d 339, 351 (Ct. App. 1999); *Isgett v. Atl. Coast Line R. Co.*, 223 S.C. 56, 64, 74 S.E.2d 220, 223 (1953); and

(3) the FDA-approved Risperdal package insert cannot, as a matter of law, be considered "unfair" or "deceptive" to consumers because it is not written for consumers, *see Brooks v. Medtronic, Inc.*, 750 F.2d 1227, 1231 (4th Cir. 1984).

**Second**, the State's entire SCUTPA claim is preempted by federal law. As this Court and many others have previously recognized, the FDCA does not permit private causes of action based on violations of the Act. *See, e.g.*, 21 U.S.C. § 337(a). Nevertheless, the State's proof with respect to the November 2003 mailing, including the testimony of its expert witnesses, rests on the FDA's characterization of the November 2003 mailing as "false or misleading in violation of Sections 502(a) and 201(n) of the [FDCA]." Trial Ex. P232. As counsel for the State aptly noted, this question is one "for [the FDA] to

decide." Trial Tr. vol. V, 1183:3-9, Mar. 11, 2011.[1] The "mailing" claim is expressly preempted. The "package insert" claim also fails in its entirety because the State's claim simply is that the label was – and perhaps is – "inadequate." But that claim is barred by federal "conflict" preemption.

**Third**, the State was required to prove certain additional elements because its SCUTPA claim sought to punish Janssen's speech. Specifically, the State was required to introduce (i) evidence that the statements it sought to punish could be proven true or false and (ii) clear and convincing evidence that the statements were made with actual malice.

**Fourth**, the State's belated claim that the November 2003 mailing and the Risperdal package insert constitute "unfair" trade practices fails because:

(1) the use of an FDA-approved package insert cannot be an "unfair" trade practice;

(2) the State has no evidence – factual, expert, or otherwise – that satisfies the essential elements of a claim for an unfair trade practice; and

(3) alleged violations of public policy alone are not a basis for a finding that an act or practice is "unfair."

**Fifth**, the State's deceptive trade practice claim fails because:

(1) the November 2003 mailing and the Risperdal package insert do not contain any actionable representations – opinions accompanied by all the support for them are not actionable;

(2) the State has no evidence – factual, expert, or otherwise – that: (i) Janssen did not have a reasonable basis for the opinions set forth in either the November 2003 mailing or the Risperdal package insert; or (ii) either the November 2003 mailing or the Risperdal package insert had a tendency to

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[1] Citations to "Trial Tr." in this Motion and the supporting memorandum of law refer to the unofficial daily transcript the parties received during the trial, a true and correct copy of which is attached to this Motion and the accompanying memorandum of law as Exhibit A. Janssen will, at the Court's request, supply references to the official transcript when it becomes available.

deceive or was likely to deceive the relevant audience, South Carolina physicians; and

(3) the State has no evidence – factual, expert, or otherwise – that either the November 2003 mailing or the challenged statements in the Risperdal package insert were material to South Carolina physicians' decisions to prescribe Risperdal for their patients.

**Sixth**, the State's SCUTPA claim, whether based on an "unfair" or "deceptive" trade practice, fails because the State did not introduce sufficient evidence for the jury to find that the alleged unfair or deceptive trade practice adversely affected the public interest.

**Seventh**, the State's claim of unfair and/or deceptive trade practices also fails because the State did not introduce sufficient evidence for the jury to find willful conduct – as "willfulness" is defined by South Carolina law.

**Eighth**, the State's entire claim is barred by SCUTPA's three-year statute of limitations.

**Ninth**, this Court's evidentiary rulings tainted the jury's verdict against Janssen in this matter. In particular, the Court erred in:

(1) failing to limit the State's SCUTPA claim to the conduct the State consistently identified in discovery as the basis of its SCUTPA violation: Janssen's purportedly "deceptive" conduct in the dissemination of the November 2003 mailing and the FDA-approved Risperdal package insert;

(2) admitting various categories of evidence, including but not limited to, documents and testimony related to (i) informal, advisory letters from the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC"); (ii) the number of Risperdal prescriptions filled in South Carolina; (iii) Defendants' profits, sales, revenues, and business plans; (iv) e-mails sent by Scott Reines, the former vice president of one of Janssen's sister companies, who did not participate in any aspect of the November 2003 mailing; (v) alleged off-label and otherwise improper and deceptive promotional and marketing activities; and (vi) purported nondisclosures to the FDA;

(3) excluding relevant evidence, including documents and testimony that would have shown that: (i) the FDA has recognized that each atypical antipsychotic has a different risk profile, including for diabetes-related side effects; (ii) the November 10, 2003 mailing and the Risperdal package insert did not have a tendency to deceive South Carolina prescribing physicians; and (iii) the

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State's interpretation of the federal regulations governing a pharmaceutical manufacturer's duty to update its product label, which it presented to the jury, was erroneous;

(4) excluding post-2004 evidence regarding the risks of diabetes, hyperglycemia, and other side effects of various atypical antipsychotics, including Risperdal;

(5) precluding Janssen from introducing the testimony of Dr. Eugene Barrett;

(6) precluding Janssen from introducing evidence regarding the State's SCORxE Program;

(7) precluding Janssen from introducing additional evidence from Dr. William Wecker; and

(8) precluding Janssen from introducing certain testimony of Sheldon Bradshaw.

The particular trial exhibits and testimony that were the subject of the Court's evidentiary rulings are set forth in detail in the accompanying memorandum of law, which is incorporated herein by reference.

**Tenth**, the State's opening and closing statements prejudiced Janssen because they repeatedly referenced Defendants' revenues and profit margins, corporate integrity, and corporate ethics, and otherwise sought to have the jury base its decision on emotion and/or bias, rather than evidence.

**Finally**, the jury instructions were inadequate and flawed, and the verdict sheet was confusing and insufficiently specific.

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CRAWFORD COUNTY

WHEREFORE, for the reasons stated herein and in the accompanying memorandum of law, which is incorporated as though set forth fully herein, the Court should grant Janssen's Motion in its entirety and enter judgment in Janssen's favor notwithstanding the jury's verdict. In the alternative, the Court should order a new trial of the claim against Janssen.

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PHARMACEUTICALS, INC.

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April 1, 2011.

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANT ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC.'S MOTION FOR JUDGMENT NOTWITHSTANDING THE VERDICT OR, IN THE ALTERNATIVE, FOR A NEW TRIAL** |

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2009 APR -1 PM 4:41
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Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen"), by and through the undersigned counsel, hereby submits this Memorandum of Law in support of its Motion for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial.

## I. INTRODUCTION

Before trial, Plaintiff, the State of South Carolina (the "State"), chose to pursue only one claim against Janssen, a claim for violation of the South Carolina Unfair Trade Practices Act ("SCUTPA") based on: (1) the supposedly "deceptive" nature of one paragraph of a November 10, 2003 mailing from Janssen to South Carolina physicians (the "November 2003 mailing"); and (2) the purported "inadequacy" of the U.S. Food and Drug Administration ("FDA")-approved package insert for Risperdal® ("Risperdal package insert" or the "package insert"). According to the State, the November 2003 mailing was "deceptive" because it minimized the risk of diabetes associated with the use of Risperdal, and, in particular, because it stated that "[e]vidence also suggests that RISPERDAL is associated with a lower risk of diabetes than some other studied atypical antipsychotics."

The State also contended that the Risperdal package insert was "deceptive" because it did not adequately warn of certain risks, including the risks of weight gain, hyperglycemia, and diabetes.

At trial, however, the State made no attempt to prove that the statements in the letter and the package insert were "deceptive" – that they had a "tendency to deceive" South Carolina physicians. The State presented no evidence whatsoever about the impact of the statements on South Carolina physicians. Indeed, the State's counsel proclaimed, "[t]his isn't a case about science." And, "it was not about whether doctors were deceived." Instead, the State relied, almost exclusively, on the opinions of two litigation experts about the alleged "inadequacies" of the FDA-approved Risperdal package insert and on a "warning letter" sent by an employee of the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC") who characterized the November 2003 mailing as "false or misleading in violation of . . . the Federal Food, Drug, and Cosmetic Act." Moreover, to show "willfulness," the State introduced voluminous evidence, over Janssen's objections, of supposed violations of the FDA's marketing/promotion rules or nondisclosures to the FDA. That improper evidence included colorful commentary, by a vice-president of a sister company not personally involved in the matter, about Janssen's decision to send the November 2003 mailing.

The State's case, as presented to the jury, then, was not so much a case about "deceptive" statements and "inadequate" package inserts as it was a case about "breaking FDA rules" and "unfair" or "unethical" conduct. For a variety of reasons – including the SCUTPA regulated activity exemption, federal preemption, the "primary jurisdiction" of the FDA, the State's abuse of the discovery process, the State's failure to prove essential elements of its SCUTPA claim, and the statute of limitations – such a claim should never have been submitted to the jury and Janssen is now entitled to a judgment notwithstanding

the verdict. At a minimum, to the extent that the State's evidence was improperly admitted, Janssen should have a new trial.

Although the State's case was supposedly about "false or misleading" and "deceptive" and "unfair" statements, the State successfully objected to Defendants' efforts to show that the statements, in fact, were true. Indeed, the State successfully objected to Defendants' proof that the FDA has since conceded that the statements in the November 2003 mailing about "differing risk" were true. And the State successfully objected to virtually all of Defendants' efforts to show that the November 2003 mailing and the Risperdal package insert were not deceptive and did not have a "tendency to deceive" because the statements in the mailing came as no surprise to South Carolina physicians, who already knew that the different antipsychotics had different risks and that Risperdal's risk profile was better than that of some other medicines. At the State's insistence, the Court excluded almost all testimony from or about South Carolina physicians. The Court also excluded testimony about the State's knowledge of the differential risks. If nothing else, these limitations on Janssen's defenses compel a new trial.

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A new trial also is necessary because the Court's instructions were, in certain respects, incorrect, and in other respects, inadequate, and because the verdict sheet was insufficiently specific and failed to ask key questions. As a result, the jury was allowed to find liability based on impermissible considerations, flawed legal theories, improperly admitted evidence, or in the absence of the proof required by the statute. Indeed, the jury may well have returned its "mailing" verdict against Janssen simply because the FDA sent a letter saying that Janssen "broke the rules." Or, the jury may have concluded that the package insert was "unfair," even though Janssen complied with all of the FDA "rules." Or, the jury may have been swayed by the improper arguments of the State's counsel about the questionable "ethics" of corporate America and counsels' repeated references to

Defendants' sales and profits and the fact that they are not South Carolina companies.

Janssen is entitled to entry of a judgment in its favor, notwithstanding the jury verdict. At an absolute minimum, Janssen is entitled to a new trial.

## II. APPLICABLE STANDARD

A motion for judgment notwithstanding the verdict should be granted if the evidence presented at trial was "insufficient" to support the verdict. *See Watson v. Ford Motor Co.*, 389 S.C. 434, 455, 699 S.E.2d 169, 180 (2010) (finding the evidence was insufficient to support the jury's verdict). In ruling on a motion for judgment notwithstanding the verdict, the trial court shall "view the evidence and the inferences that reasonably can be drawn therefrom in the light most favorable to the party opposing the motions." *McMillan v. Oconee Mem'l Hosp., Inc.*, 367 S.C. 559, 564, 626 S.E.2d 884, 886 (2006) (internal citation omitted) (reversing the trial court's denial of a motion for judgment notwithstanding the verdict because the evidence did not support a finding of civil conspiracy).

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Under Rule 59(a) of the South Carolina Rules of Civil Procedure, a new trial may be granted "in an action in which there has been a trial by jury, for any of the reasons for which new trials have heretofore been granted, in the courts of the State." Rule 59(a), S.C.R.C.P. South Carolina courts have recognized that a new trial is warranted in a number of circumstances, including but not limited to: (1) when evidence that was improperly admitted amounted to prejudicial error, *see, e.g.*, *Mizell v. Glover*, 351 S.C. 392, 401-02, 570 S.E.2d 176, 181 (2002) (granting a new trial based on the admission of improper extrinsic evidence, which also constituted inadmissible hearsay); *Nelson v. Taylor*, 347 S.C. 210, 218, 553 S.E.2d 488, 492 (Ct. App. 2001) (granting a new trial based on improperly admitted deposition testimony); (2) when the verdict was inconsistent and demonstrated the jury's confusion, *Johnson v. Parker*, 279 S.C. 132, 134, 303 S.E.2d 95, 97 (1983); (3) when the trial court gave an erroneous charge, *Dixon v. Ford*, 362 S.C. 614, 624, 608 S.E.2d 879,

884-85 (Ct. App. 2005) (reversing and remanding for new trial because jury charge was a misstatement of the law that prejudiced plaintiffs); and (4) when the trial court failed to give a requested instruction to the prejudice of the objecting party, *Sanders v. W. Auto Supply Co.*, 256 S.C. 490, 497, 183 S.E.2d 321, 325 (1971).

In addition, the "thirteenth juror doctrine" permits a judge to grant a new trial when the judge concludes the evidence does not justify the verdict. *Youmans ex rel. Elmore v. S.C. Dep't of Transp.*, 380 S.C. 263, 272, 670 S.E.2d 1, 5 (Ct. App. 2008), *reh'g denied* (Dec. 19, 2008), *cert. granted* (July 9, 2009), *cert. dismissed*, 386 S.C. 640, 690 S.E.2d 582 (2010). Discussing this doctrine, South Carolina courts have acknowledged a "broad, inherent authority to grant a new trial for any prejudicial errors committed during the trial as a matter of fundamental fairness." *Ex parte Kent*, 379 S.C. 633, 640, 666 S.E.2d 921, 925 (Ct. App. 2008) (citation omitted).

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## III. ARGUMENT

### A. The State's SCUTPA Claim Based On The FDA-Approved Risperdal Package Insert Fails On Several Independent Grounds

The State's failure to prove its claim based on the FDA-approved Risperdal package insert is discussed below. Apart from the failures of proof, the "package insert" claim fails based on: (1) proper application of the regulated activity exemption; (2) the doctrine of primary jurisdiction; and (3) the lack of any duty to warn consumers/patients.

#### 1. The State's Claim Of "Deception" Or "Unfairness" To South Carolina Consumers Should Not Have Been Submitted To The Jury Because It Is Barred By The Regulated Activity Exemption

The regulated activity exemption provided at S.C. Code Ann. § 39-5-40 applies to and bars the State's claim based on the FDA-approved Risperdal package insert.

a. **This Court's Narrow Interpretation Of The Regulated Activity Exemption Violates Well-Accepted Tenets Of Statutory Construction**

In denying Defendants' motion for summary judgment, this Court held that the regulated activity exemption does not apply because "the FDA does not allow or permit deceptive activities in the marketing and labeling of drugs." Slip op. at 7-8 (Feb. 25, 2011). But every SCUTPA defendant necessarily is accused of committing an "unfair" or "deceptive" act. Indeed, if an act or practice is not unfair or deceptive, there could be no claim under SCUTPA and a regulated activity exemption would not be necessary.

The purpose of the exemption is to remove from the scope of SCUTPA "deceptive" acts and practices that are the subject of review and approval by federal and state agencies. The relevant inquiry for application of the exemption is simple and straightforward – whether the particular act or practice challenged as deceptive was permitted by a federal agency; if it was, the practice is not actionable, even if the attorney general believes that it was deceptive. *Ward v. Dick Dyer & Assocs., Inc.*, 304 S.C. 152, 155, 403 S.E.2d 310, 312 (1991) ("[T]he exemption is intended to exclude those actions or transactions which are allowed or authorized by regulatory agencies or other statutes.").

Any other interpretation is inconsistent with the *Ward* decision. There, the South Carolina Supreme Court held that "the intent of our Legislature was to exclude activities which would otherwise be allowed or authorized." *Id.* at 156, 403 S.E.2d at 312. The *Ward* court relied on the Tennessee case of *Skinner v. Steele*, 730 S.W.2d 335 (Tenn. Ct. App. 1987), which explained: "The purpose of the exemption is to insure that a business is not subjected to a lawsuit under the Act when it does something required by law, or *does something that would otherwise be a violation of the Act, but which is allowed under other statutes or regulations.*" *Ward*, 304 S.C. at 156, 403 S.E.2d at 312 (citing *Skinner*, 730 S.W.2d at 337) (emphasis added). Thus, as recognized by the *Ward* court, application of

the exemption specifically contemplates allegedly deceptive conduct. Otherwise, there would be no reason for the exemption at all.

In the present case, the label challenged as deceptive not only was permitted by the FDA but required by the agency – and was never found by the FDA to be inadequate, false, misleading, or deceptive. *See* Trial Tr. vol. VII, 1518:23-1520:2, Mar. 15, 2011 (testimony of Dr. Mahmoud); *see also* Trial Exs. D841, D843, D3180, P571 (various FDA approval letters requiring Janssen to use "identical" or "verbatim" language in Risperdal labeling). The State's own expert witness did not dispute that every version of the Risperdal package insert from product launch always was permitted by the FDA. *See* Trial Tr. vol. III, 541:3-7, 597:7-9, Mar. 9, 2011 (testimony of Dr. Wirshing). Moreover, even when it requested a class-wide label change in September 2003, the FDA did not take the position that the existing package insert was inadequate, i.e., that Janssen should have updated earlier its package insert to add a warning. Rather, the FDA simply requested, on a going-forward basis, that the package insert be revised to add additional warning language. *See* Trial Ex. P520 (Letter from R. Katz to C. McGowan). This, consistent with the *Ward* decision, was sufficient to bar the State's "package insert" claim.

**b. <u>Other Courts Have Found That The FDA's Specific Approval Of The Risperdal Package Insert Bars Claims Of Deceptive Or Misleading Conduct</u>**

Accepting the State's argument that there is no basis or precedent for applying the regulated activity exemption to a claim like the State's "package insert" claim, this Court held, in the summary judgment context, that "the mere fact that an FDA label may be in effect does not act as a complete bar to an action under SCUTPA." Slip op. at 7 (Feb. 25, 2011). But, in fact, courts repeatedly have found that FDA approval of a medicine's label precludes claims similar to those advanced here. *See, e.g., Prohias v. Pfizer, Inc.*, 490 F. Supp. 2d 1228, 1234-35 (S.D. Fla. 2007) (holding that the FDA's approval of an

amended product label barred portion of deceptive trade practice claim, explaining, "[G]iven the FDA's additional approvals of Lipitor, namely, to reduce the risk of heart attacks in certain patients, Pfizer's post-July 2004 advertisements were not misleading as a matter of law. . . . In sum, any way that I look at it, the change in Lipitor's approved label prevents the plaintiffs' [sic] from proceeding with claims that Pfizer's advertisements were misleading."); *Prohias v. AstraZeneca Pharm., Inc.*, 958 So. 2d 1054 (Fla. App. 2007) (pharmaceutical manufacturer's marketing activity supported by FDA-approved label within scope of safe harbor provision under Florida's consumer fraud statute as action "specifically permitted" by federal law); *Mylan Pharm., Inc. v. Procter & Gamble Co.*, 443 F. Supp. 2d 453, 460 (S.D.N.Y. 2006) ("In the context of pharmaceutical drugs, courts have generally rejected Lanham Act claims based on advertisements that merely repeat labeling information that has been approved by the FDA."); *Cytyc Corp. v. Neuromedical Sys., Inc.*, 12 F. Supp. 2d 296, 301 (S.D.N.Y. 1998) (holding, for consumer fraud and false advertising claims, that "representations by [defendant] that comport substantively with statements approved as accurate by the FDA cannot supply the basis for [plaintiff's] claims" and that statements that are "similar enough to the approved statements," even if not "precisely" the same as the FDA-approved labeling, are "neither false nor misleading" as a matter of law); *Am. Home Prods. Corp. v. Johnson & Johnson*, 672 F. Supp. 135, 144-45 (S.D.N.Y. 1987) ("In unfair competition actions under state statutory or common law, it has been consistently ruled that compliance with FDA warning requirements is a complete defense. . . . [I]f the intercession of a private attorney general is needed to press the FDA to perform that duty with respect to a particular product label, the quickest and most effective relief could be obtained through a direct petition to the agency and not through an unfair competition action against the manufacturer.").

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### c. The Evidence Presented Does Not Support An "Ability To Update" Exception To The Regulated Activity Exemption

The Court's refusal to apply the regulated activity exemption to prescription drug labels was based, at least in part, on the existence of a duty "to update . . . based on available information." *See* slip op. at 7-8 (Feb. 25, 2011) (citing 21 C.F.R. § 314.70 (c)(6)(iii)(A), (C)). Under this regulation, known as the changes being effected ("CBE") regulation, however, a pharmaceutical manufacturer is not required – or even permitted – to update a package insert based simply on "available information." Rather, a pharmaceutical manufacturer may update a package insert *only* when it has (i) "newly acquired information" that (ii) constitutes "evidence of a causal association [that] satisfies the standard for inclusion in the labeling under § 201.57(c) of this chapter." *Id.*

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Under 21 C.F.R. § 201.57(c)(6)(i), "the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established." Although the word "causal" did not appear before "association" until the regulation was revised in June 2006, the FDA has confirmed that it always was the FDA's policy to require such a "causal" association. *See* 73 Fed. Reg. 49603 (Aug. 22, 2008) at 49603 (CBE regulation was meant to "*codify* the agency's *longstanding* view concerning when a change to the labeling of an approved drug, biologic, or medical device may be made in advance of the agency's review and approval of such change" (emphasis added)). Significantly, the FDA's codification of the "newly acquired information" and "causal association" standard was "intended to ensure that scientifically valid and appropriately worded warnings will be provided in the approved labeling for medical products, *and to prevent overwarning*, which may deter appropriate use of medical products, or overshadow more important warnings." *Id.* at 49605-06 (emphasis added).

Thus, to show that Janssen had an obligation at some point in time after approval of the initial package insert by the FDA to update its package insert under the CBE regulation, the State was required to provide specific evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" between Risperdal and the risks of hyperglycemia, diabetes, weight gain, hyperprolactinemia, and alpha toxicity. Neither of the State's experts could identify with any specificity exactly what was "inadequate" about the Risperdal package insert, the specific "newly acquired information" Janssen possessed that provided "reasonable evidence of a causal association," or exactly "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing).[1] Dr. Wirshing actually testified that at the time of the FDA-mandated class label change, the evidence did not support a conclusion of a "causal" connection between Risperdal and diabetes. Trial Tr. vol. III, 496:25-497:10, Mar. 9, 2011 (evidence was "not conclusive" and it was "not causal"). Dr. Plunkett conceded that she was not retained to form a failure to warn opinion related to the Risperdal label. Trial Tr. vol. IV, 932:9-934:3, Mar. 10, 2011.

Both of the State's experts also testified that the Risperdal package insert was "inadequate" at the time of product launch. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing). As a matter of law, logic, and common sense, a pharmaceutical

[1] This lack of clarity alone should have kept the "package insert" claim from the jury. *See Schering-Plough Healthcare Prods., Inc. v. Schwarz Pharma, Inc.*, 586 F. 3d 500, 508 (7th Cir. 2009) ("But Schering has been coy about what it thinks the disclaimer should say, and its coyness makes us doubt that this is a matter that can be resolved intelligently without a decision by the FDA.").

manufacturer cannot have a duty to "update" the package insert the moment it is issued, when the FDA had just approved every word of the package insert and required that it be used "verbatim" by Janssen. Trial Ex. P571 (Initial approval letter). The State's expert testimony thus falls far short of establishing any obligation by Janssen to update its package insert as to the risks of hyperglycemia, diabetes, weight gain, hyperprolactinemia, and alpha toxicity.

The State attempted to satisfy its burden by repeatedly offering "evidence" as to Janssen's "awareness" of the risks of hyperglycemia, diabetes, weight gain, and hyperprolactinemia. *See, e.g.*, Trial Tr. vol. III, 624:15-626:13, Mar. 9, 2011 (testimony of Dr. Wirshing). As the FDA regulations and the FDA itself make clear, general awareness and knowledge of risks of the use of a prescription medicine are insufficient to require a manufacturer to update its package insert – and will not support the use of the CBE procedures. *See* 21 C.F.R. 314.70(c)(6)(iii)(A),(C); *id.* § 201.57(c)(6)(i); 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008).

* * *

The State's evidence at trial confirmed that: (1) at all times, the Risperdal package insert was approved and permitted by the FDA – when the medicine was first marketed and repeatedly thereafter; (2) the FDA has never determined that the Risperdal package insert was not properly updated by Janssen; (3) the FDA has never determined that the Risperdal package insert was false or misleading; and (4) the State did not present evidence that Janssen possessed "newly acquired information" that constituted "reasonable evidence of a causal association" as to any of the risks which the State alleged were inadequately disclosed. As the State did not introduce any evidence that Janssen was required – or even permitted – to update its label with a CBE submission, the SCUTPA regulated activity exemption barred the State's "package insert" claim.

### 2. This Court Should Have Deferred To The FDA's Primary Jurisdiction Over Prescription Drug Package Inserts

The FDA approves and permits *all* of the language that appears in a package insert for a prescription medicine. *See Wyeth v. Levine*, 129 S. Ct. 1187, 1196 (2009) ("*Wyeth*") ("The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label." (citing 21 U.S.C. § 355; 21 C.F.R. § 314.105(b))). In approving and permitting the exact language used, the FDA necessarily makes a determination that the language of the package insert is neither false nor misleading. *See* 21 C.F.R. § 314.125(b)(6) (stating that the FDA will refuse to approve a new drug application if it determines that "[t]he proposed labeling is false or misleading in any particular").

For this precise reason, courts repeatedly have acknowledged that the FDA, not courts or juries, has primary jurisdiction over claims of alleged falsity or deception as to a product label. *See, e.g., Wyeth v. Sun Pharm. Indus., Ltd.*, No. 09-11726, 2010 WL 746394, at *4 (E.D. Mich. Mar. 2, 2010) ("[I]t is solely the FDA's duty to investigate and prosecute allegations of misbranding or adulterating drugs."); *Mut. Pharm. Co. v. Watson Pharm. Inc.*, No. CV 09-5700, 2009 WL 3401117, at *5 (C.D. Cal. Oct. 19, 2009) ("Plaintiffs' contentions concerning the product labels and inserts are even weaker, both because the evidence of confusion is weaker and because disputes concerning the content of those labels and inserts falls even more squarely within the primary jurisdiction of the FDA."); *Pediamed Pharm., Inc. v. Breckenridge Pharm., Inc.*, 419 F. Supp. 2d 715, 726 n.14 (D. Md. 2006) ("The [FDA] has enforcement power over false and misleading labels. 21 U.S.C. § 352. To the extent that Plaintiff relies solely on the false label argument to find a Lanham Act violation . . . such a claim is essentially a mislabeling claim, which is within the jurisdiction of the FDA and thus would be precluded."). The South Carolina Supreme Court

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has long recognized that South Carolina courts should defer to existing, available, and comprehensive administrative frameworks rather than exercise jurisdiction over a particular matter. *See Smith v. S.C. Ret. Sys.*, 336 S.C. 505, 527, 520 S.E.2d 339, 351 (Ct. App. 1999) ("'Gratuitous interference' in the administrative process should be avoided.") (citation omitted). *See generally Isgett v. Atl. Coast Line R. Co.*, 223 S.C. 56, 64, 74 S.E.2d 220, 223 (1953) ("If the court should undertake to now decide the controversy, it would not bind the Board [established by the Railway Labor Act], to which the next similar controversy might be taken. It would seem that the presently firmly established rule of exclusive primary jurisdiction of the Board in such cases should be beneficial, in the long run, to both carriers and employees, and to the public.").

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This same result should have been reached here. As the State's counsel previously emphasized to this Court at a hearing on pretrial motions, the FDA-approved Risperdal package insert is used throughout the United States. *See* Hearing Tr., 160, Feb. 2, 2011 (State's counsel: "It's always important to remember that there's one Risperdal label and it's used everywhere in the United States. It's not a South Carolina specific label."). This Court should have recognized the FDA's primary jurisdiction in this matter; it should not have allowed the State to argue, to a jury, that South Carolina may make its own determinations about what should be said in a package insert for a prescription medicine, and how the label should be formatted.

If the State, through its attorney general, truly believed that the FDA-approved package insert was misleading, the attorney general (almost four years ago) could have availed himself of the FDA's administrative process specifically designed to raise such concerns to the FDA. *See generally Code Labs., Inc. v. Sebelius*, No. 10-CV-00147, 2010 WL 3119279, at *10 (D. Wyo. July 26, 2010) ("[P]laintiffs could can [sic] file a citizen petition at any time seeking FDA's views[.]"); 21 C.F.R. § 10.25(a) ("An interested person may

petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administration action."); 21 C.F.R. § 10.30 (Citizen petition). Having failed to use this existing administrative remedy, the State should be precluded from using a South Carolina jury to impose drug labeling requirements in this state different from those imposed, by FDA regulation, elsewhere in the nation. *See generally Graves v. Horry-Georgetown Tech. Coll.*, 391 S.C. 1, 704 S.E.2d 350 (Ct. App. 2010) (affirming trial court's grant of a directed verdict based on failure to exhaust administrative remedy).

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3. **The State's Claim Of "Deception" Or "Unfairness" To South Carolina Consumers Should Not Have Been Submitted To The Jury Because Pharmaceutical Manufacturers Have No Duty To Warn Consumers**

Janssen moved for a summary judgment as to the State's claim based on the FDA-approved Risperdal package insert, in part, because, while the State asserted that the FDA-approved Risperdal package insert violated SCUTPA because it purportedly failed adequately to disclose certain risks to "consumers," pharmaceutical manufacturers owe no duty to warn consumers about the risks of a prescription medicine. *See* Defs.' Mem. of Law in Support of Mot. for Summ. J. as to Pl.'s Unfair Trade Practices Claim Based on the FDA-Approved Risperdal Package Insert at § V.A. In denying this aspect of Janssen's motion for summary judgment, the Court did not directly address Defendants' argument, but stated, "Since this Court has determined that this cause of action is not an action for damages to any particular person, but is rather to penalize a company or individual for engaging in unfair or deceptive practices in the conduct of its trade or commerce, this cause of action does not require that anyone in particular has been the victim of this activity or has suffered any particular harm." Slip op. at 5 (Feb. 25, 2011). The Court then allowed the State to argue to the jury that the package insert could deceive consumers – patients –

because, in the Court's view, there was evidence that the package insert "winds up" in the hands of consumers. Trial Tr. vol. XI, 2606:14-16, Mar. 21, 2011 ("But the patients, though, do make decisions, sometimes, as to whether to swallow the pill or not."); Trial Tr. vol. XII, 2780:6-14, Mar. 22, 2011 ("I have consistently, throughout the case, felt like that, while the representations were primarily made to doctors, that the information is in the public realm and is available to members of the public. And there was testimony from the person who detailed the drugs that every sample contained the label; it would have been submitted to the public in that fashion.").

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Respectfully, Janssen maintains that the Court misconstrued both the relevant inquiry and Janssen's argument. The argument was *not* that "SCUTPA only applies if a consumer has been directly misled or defrauded by a defendant's actions in the market place" *or* that the State must show damages as part of its civil penalty action. Slip op. at 4 (Feb. 25, 2011). Rather, the argument was that Janssen, as a matter of law, cannot be found to have committed an unfair or deceptive trade practice based on conduct that is not actionable in the first instance.

The State has never contested that, as a matter of law, a pharmaceutical manufacturer has no duty to advise consumers of a prescription medicine as to the risks of a particular drug. *See, e.g., Brooks v. Medtronic, Inc.*, 750 F.2d 1227, 1231 (4th Cir. 1984) ("Although the South Carolina Supreme Court has not addressed the issue, we conclude it would adopt the rule, generally accepted and supported by sound policy, restricting the manufacturer's duty to warn to the prescribing physician."). Nor can the State coherently argue against the settled proposition that a package insert is written solely for physicians, not consumers. *See* 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008) ("FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the

agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."); *see also Morlino v. Med. Ctr. of Ocean Cnty.*, 152 N.J. 563, 580, 706 A.2d 721, 729-30 (1998) ("Drug manufacturers write explanations and warnings for doctors, not the general public.").

Thus, Janssen's argument was and remains simple and straightforward: because the package insert is not written for consumers, it cannot, as a matter of law, be considered "unfair" or "deceptive" as to consumers. No principle of South Carolina law supports the view that the State may use SCUTPA as a statutory sword to impose new obligations on pharmaceutical manufacturers. Indeed, the rule requiring strict construction of penal statutes stands in the way of such an interpretation of SCUTPA. *See S.C. Dep't of Revenue v. Collins Entm't Corp.*, 340 S.C. 77, 79, 530 S.E.2d 635, 636 (S.C. 2000) (applying principle of strict statutory construction to statute imposing cumulative penalty of $500 for each and every violation of statute reasoning that "'[t]he principle is well established that penal statutes are strictly construed, and one who seeks to recover a penalty for failure on the part of the defendant to discharge some duty imposed by law, must bring his case clearly within the language and meaning of the statute awarding the penalty. Such laws are to be expounded strictly against the offender and liberally in his favor . . . . And it is immaterial, for the purpose of the application of the rule of strict construction, whether the proceedings for the enforcement of the penal law, be criminal or civil.'" (citation omitted)); *State ex rel. Moody v. Stem*, 213 S.C. 468, 50 S.E.2d 175, 176 (1948) ("Any doubt as to the proper construction should be resolved in favor of the citizen against the state."); *see also Dykeman v. Wells Fargo Home Mortg., Inc.*, 381 S.C. 333, 673 S.E.2d 804 (S.C. 2009) (interpreting statute imposing penalty on mortgagor for failing to satisfy a mortgage as penal statute subject to strict construction). The State's theory of alleged "unfairness" or "deception" of South Carolina consumers in connection with the

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FDA-approved Risperdal package insert was and remains legally insufficient and should never have been submitted to the jury.

### B. The State's SCUTPA Claim Is Preempted By Federal Law

#### 1. The November 2003 Mailing

As presented, the State's SCUTPA claim as to the November 2003 mailing is based entirely on Janssen's supposed violations of federal law. Time and again, the State introduced or based its expert witnesses' testimony on the FDA's April 2004 warning letter ("DDMAC has concluded that the DHCP letter is false or misleading in violation of . . . the Federal Food, Drug, and Cosmetic Act") and merely had its experts agree with the statements in the letter. *See, e.g.*, Trial Tr. vol. V, 1057:23-1059:15, Mar. 11, 2011 (Dr. Plunkett's opinion that the November 2003 mailing was false and misleading is "based upon the FDA standard").

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The most striking, but not the only, example of the State's near-exclusive reliance on the April 2004 warning letter as the evidence of the alleged unfairness or deception of the November 2003 mailing is that the opinions of the State's experts as to whether the November 2003 mailing was false, misleading, or deceptive were their "agreement" with the April 2004 warning letter. As testified to by the State's expert, Dr. Wirshing:

> Q: I just want to ask you generally, Doctor, do you agree with the FDA's assessment that Janssen's November 10, 2003 letter was false and misleading?
>
> A. Absolutely, it was – in my opinion, it was designed to distinguish themselves from the class label, which is an absolute distinction to what the FDA wanted, they wanted a class label.
>
> . . . .
>
> Q. . . . According to the FDA, is that letter true or not?
>
> A. No, the FDA felt it was false and misleading.

Trial Tr. vol. III, 468:5-12, 488:22-25, Mar. 9, 2011. As also testified to by the State's other expert, Dr. Plunkett:

Q. Okay. Well, you can look on with me. Doctor, what is this document?

A. This is a warning letter that was sent by FDA to Janssen regarding their mailing of the Dear Doctor letter in November of 2003.

Q. And what does the FDA say about that letter?

A. I believe that they say that it's false and misleading and failed to disclose important information.

Q. It says, "Janssen's letter creates a serious public health issue also." Right?

A. Yes, that's correct.

Q. Now, Doctor, as an expert in the FDA regulations, do you agree with how the FDA interpreted its regulations in this case?

A. Absolutely, yes.

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Trial Tr. vol. IV, 759:22-760:13, Mar. 10, 2011. Any doubt as to the role of the 2004 warning letter as the centerpiece of the State's "November 2003 mailing" claim is eliminated by the State's examination of its last witness, a Janssen sales representative, who was asked to "defer" to the 2004 warning letter:

Q. Well, let me ask you this: If the FDA said it was, if it was false and misleading, will you defer to the FDA here today in front of this jury in Spartanburg County?

A. I would, but this is the package insert change. We were informing the customer and the doctor of what was going on, it was a package insert change.

Q. And all I'm asking you is – is, will you defer to the FDA in regards to Paragraph 4 and if they say it was misleading, you'll – you would defer to them, right?

A. Absolutely.

Q. Because it's for them to decide?

A. It is for them to decide.

Trial Tr. vol. V, 1182:20-1183:9, Mar. 11, 2011.

The State's reliance upon the 2004 warning letter was not limited to its own case. At the first hint of any damaging testimony, the State time and again turned to the April 2004 warning letter to attempt to discredit defense witnesses. For example, the State did not challenge Dr. Ramy Mahmoud, who signed the November 10, 2003 Dear Healthcare Provider Letter, as to the bases for the statements in the November letter. Rather, the State simply elicited the following:

Q. Did you take this [the April 2004 warning letter] seriously when you got it?

A. Yes.

Q. Did you feel bad?

A. Yes, I was concerned, because I didn't know how they could have come to this conclusion.

Q. Well, I mean, FDA said that your letter was false, right?

A. Right.

Q. Opposition of true, right?

A. DDMAC concluded the letter was false or misleading, yes.

Q. In other words, what DDMAC is saying to you is that the information you're providing the doctors in your Dear Doctor letter is a lie, right?

A. They concluded that the letter was false or misleading.

Trial Tr. vol. VII, 1625:23-1626:14, Mar. 15, 2011.

Similarly, when obviously dissatisfied as to the testimony of defense witnesses Michael Chester and David Fabbri, the State once again reached for the 2004 warning letter:

Q. All right. And your opinion is, that it wasn't false and misleading?

A. Correct.

Q. You just disagree with the FDA?

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A. Correct.

Trial Tr. vol. IX, 2024:16-20, Mar. 17, 2011 (testimony of M. Chester).

Q. Now, Mr. Fabbri, you became aware, did you not, that after these materials went out, after this letter went out, after the sales aids that your group designed to be used in conjunction with this letter and with this new message that went out, there came a time when it apparently was reviewed by DDMAC at FDA?

A. Um, yes.

Q. And you were aware, were you not, sir, that Janssen received a warning letter from DDMAC, basically saying that the use of this letter and the associated sales and promotional materials was inappropriate.

A. I'm not familiar with any associated sales materials. I know the letter.

Trial Tr. vol. X, 2364:21-2365:10, Mar. 18, 2011 (testimony of D. Fabbri).

Finally, when unable to challenge the expert testimony of the defense expert Dr. John Newcomer on the merits, the State was left with no other option but to invoke the 2004 warning letter:

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Q. You said it was true and accurate, right?

A. Yes.

Q. Are you aware the FDA has the exact opposite interpretation of that letter?

A. I'm not sure what you mean.

Q. Are you aware of a warning letter sent to Janssen because of that Dear Doctor letter?

A. I'm aware of a DDMAC letter that was sent, yes.

Q. Have you read it?

A. Yes.

Q. You have it in front of you, Doctor, and I will spare the jury a complete reading of this letter.

Is this the warning letter that you're aware of, Doctor?

A. This is the DDMAC letter, yes.

Q. And you're aware that DDMAC and the FDA take the position that the opinion you gave to this jury is wrong, right?

A. Uh, I don't believe that that's correct. I think that DDMAC is the regulatory piece of FDA which comments on whether or not pieces of communications have been part of the approved label.

Q. Okay. We'll make this real easy. You said the letter was true. The FDA concluded that the letter is false or misleading.

Do you see that?

A. I see what it says there.

Trial Tr. vol. X, 2507:1-2508:6, Mar. 18, 2011.

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The claim presented to the jury, then, was nothing more than a claim based on the FDA's conclusion that the November 2003 mailing was "false" or "misleading" in violation of federal law. The jury could not have understood it as anything else. But such a claim is preempted by federal law.

This Court, like many others, previously acknowledged that preemption would apply to a claim like this. *See State ex rel. McMaster v. Eli Lilly & Co.*, No. 2007-CP-42-1855, slip op. at 23, 2009 WL 6058384 (S.C. Ct. Com. Pl. Sept. 22, 2009) (Couch, J.) ("*Lilly*") (recognizing that "to the extent that the Plaintiff in this case might be seeking to bring a private cause of action based o[n] the [Federal Food, Drug, and Cosmetic Act (the 'FDCA' or the 'Act')] the motion [for summary judgment] would be granted"); *see also Weston v. Kim's Dollar Store*, 385 S.C. 520, 537, 684 S.E.2d 768, 778 (Ct. App. 2009) (holding that the circuit court correctly applied the doctrine of federal preemption).

Federal law provides that *only* the federal government may enforce federal drug labeling law and expressly prohibits attempts to use state law to enforce federal drug labeling law. The FDCA provides that any "proceedings for the enforcement, or to restrain violations, of this chapter [of the FDCA] shall be by and in the name of the United States." 21 U.S.C. § 337(a). As the United States Supreme Court has explained, Section 337(a)

"leaves no doubt that" the federal government has the exclusive authority to "file suit for noncompliance" with FDA regulations. *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349 n.4 (2001); *accord Lilly*, slip op. at 23, 2009 WL 6058384 (Couch, J.).

The State's entire claim as to the November 2003 mailing is inextricably intertwined with the April 2004 DDMAC warning letter. But that warning letter speaks only of purported violations of the FDCA. Thus, the State's claim is that the November 2003 mailing was "deceptive" because it was, in DDMAC's view, "false or misleading in violation of Sections 502(a) and 201(n) of the [FDCA]." Trial Ex. P232. The State, then, was improperly attempting to impose liability based on alleged violations of the FDCA. *Id.*

This is particularly inappropriate in the present case because DDMAC investigated all aspects of the November 2003 mailing and took no further steps after Janssen issued its July 2004 letter. Trial Tr. vol. IV, 838:13-23, Mar. 10, 2011. That is, DDMAC made a conscious decision not to pursue any of the panoply of remedies available to it. *See generally* FDA Regulatory Procedures Manual § 4-1-1. *See also* Trial Tr. vol. III, 838:13-23, Mar. 10, 2011 (If Janssen had not complied, the FDA could have pursued administrative enforcement actions).

Thus, Defendants are entitled to a judgment notwithstanding the jury verdict on the "November 2003 mailing" claim because such a claim is preempted by federal law.

**2. <u>The FDA-Approved Package Insert</u>**

The Supreme Court's decision in *Wyeth*, 129 S. Ct. at 1196, provides a narrow exception to principles of federal preemption when a plaintiff alleges that a pharmaceutical manufacturer had the sort of "newly acquired" information that would trigger the manufacturer's obligation to update its label under the CBE regulations. *Wyeth*, 129 S. Ct. at 1196-97. As noted above, the State's experts were unable to say exactly what was "inadequate" about the Risperdal package insert, could not identify the specific "newly

acquired information" Janssen possessed that provided "reasonable evidence" of any causal association with a serious health hazard, and were unable to pinpoint "when" the inadequacy existed as a result of the "newly acquired information." Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing). As explained below, the *Wyeth* decision does not apply to the State's claim here. But even if it did, the State's proof was manifestly insufficient, the State did not show that its claim falls within the "*Wyeth* exception," and the State's package insert claim thus is preempted by federal law.

But the *Wyeth* decision does *not* apply to the State's claim. In *Wyeth*, the Supreme Court determined that a negligence and strict liability "failure to warn" claim brought by a single personal injury plaintiff who had sustained actual injury would not be preempted as a matter of federal law. *Wyeth*, 129 S. Ct. at 1191-92, 1204. "In short," the Supreme Court held, "[Defendant] has not persuaded us that failure-to-warn claims like [plaintiff's] obstruct the federal regulation of drug labeling." The Supreme Court, however, did *not* hold that an action by a state's attorney general challenging the adequacy of an FDA-approved package insert – even if it might be characterized as a type of "failure to warn" claim – would be permitted. While an individual personal injury action based on a "failure to warn" might not interfere with the federal regulation of drug labeling, surely a "penalties" action by a state attorney general challenging the FDA's decisions as to the adequacy of a prescription drug label poses a quite different and much greater threat to the effectiveness and uniformity of FDA regulation of drug labeling. *Wyeth*, then, provides no exception to the application of "conflict preemption" principles here. The State's claim is preempted by federal law.

The State's claim also is preempted to the extent that it is based on: (1) the alleged failure to disclose to the FDA the results of two "studies" (referred to by the State as "RIS-113" and "ERI"); and (2) the supposed "off-label promotion" of Risperdal or other violations

of federal law or regulations. *See, e.g.*, Trial Tr. vol. III, 633:16-634:2, Mar. 9, 2011 (Dr. Wirshing testifying that results of "RIS-113" should have been disclosed to the FDA); Trial Tr. vol. V, 1074:21-1075:12, Mar. 11, 2011 (Dr. Plunkett testifying that results of "RIS-113" and "ERI" should have been disclosed to the FDA); Trial Tr. vol. IV, 861:5-22, Mar. 10, 2011 (Dr. Plunkett reviewing an internal Janssen document and agreeing with State's counsel that it appears as if Janssen was engaging in "off-label promotion"). The first simply is a "fraud on the FDA claim," which is barred by *Buckman* and this Court's decision in *Lilly*. *See Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 348 (2001); *Lilly*, slip op, at 23, 2009 WL 6058384; *see also* Trial Tr. vol. I, 56:10-12, 58:5, Mar. 7, 2011. The second is expressly preempted by the FDCA as an impermissible attempt to pursue a private cause of action for alleged violations of that Act. 21 U.S.C. § 337(a); *Buckman*, 531 U.S. at 349 n.4 (explaining that FDCA "leaves no doubt that it is the Federal Government" that is "authorized to file suit for noncompliance" with FDA regulations (quoting 21 U.S.C. § 337(a))).

The South Carolina Supreme Court recently held that "[w]hen a federal statute contains an express provision regarding preemption, the preemption inquiry must focus on the plain wording of that provision, which generally contains the most reliable evidence as to whether Congress intended to preempt state law." *City of Cayce v. Norfolk S. Ry. Co.*, 706 S.E.2d 6, 9 (S.C. 2011) (citation omitted). Given the express preemption set forth in 21 U.S.C. § 337(a), the State could not base any part of its SCUTPA claim on violations of federal law or regulations.

### C. First Amendment Considerations Dictate That Judgment Be Entered In Favor Of Janssen

The State sought to punish Defendants for: (1) opinions expressed in the November 2003 mailing as to the meaning and significance of scientific evidence about the

associations between Risperdal, other antipsychotics, and diabetes; and (2) statements about Risperdal and its association with various "risks" in the FDA-approved Risperdal package insert. A plaintiff who seeks to recover on a state law cause of action based on the defendant's speech on a matter of public concern, however, must satisfy the requirements of the First Amendment to the United States Constitution. *Snyder v. Phelps*, 131 S. Ct. 1207, 1215 (2011) (holding that state law cause of action seeking to impose liability on speech on a matter of public concern must also satisfy requirements of First Amendment); *Illinois ex rel. Madigan v. Telemarketing Assocs., Inc.*, 538 U.S. 600, 620, 621 n.10 (2003) (permitting consumer fraud action to proceed only because Illinois law provided sufficient breathing room for protected speech by requiring "exacting proof" of actual malice to recover presumed damages).

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Speech involves a matter of "public concern" if it relates to "any matter of political, social, or other concern to the community." *Connick v. Myers*, 461 U.S. 138, 146 (1983); *Parker v. Evening Post Publ'g Co.*, 317 S.C. 236, 452 S.E.2d 640 (Ct. App. 1994). Statements on scientific and medical research are, as a matter of law, statements on matters of public concern. *See, e.g., Bd. of Trs. of Leland Stanford Jr. Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991), *McMillan v. Togus Reg'l Office, Dep't of Veteran Affairs*, 294 F. Supp. 2d 305, 317 (E.D.N.Y. 2003), *aff'd* 120 F. App'x 849 (2d Cir. 2005) (government censorship of "the complex debate and interplay among the scientists that comprises modern science can only distort and confuse.").

Because the November 2003 mailing and the package insert address matters of public concern, these statements cannot be punished absent proof by clear and convincing evidence that they were made with actual malice. *Gertz v. Robert Welch, Inc.*, 418 U.S. 323, 342, 348-50 (1974); *Erickson v. Jones Street Publishers, LLC*, 368 S.C. 444, 467-68, 629 S.E.2d 653, 665-66 (2006). As the jury was not so instructed, the verdict cannot stand.

### D. The State Did Not Introduce Sufficient Proof Of Each Of The Elements Of Its SCUTPA Claim Based On Unfair Or Deceptive Trade Practices

South Carolina courts have repeatedly acknowledged the legislative mandate that in determining whether an act is unfair or deceptive for purposes of SCUTPA, "the courts will be guided by the interpretations given by the Federal Trade Commission and the Federal Courts to § 5(a)(1) of the Federal Trade Commission Act (15 U.S.C. § 45(a)(1)), as from time to time amended." *See* S.C. Code Ann. § 39-5-20(b); *see also Plowman v. Bagnal*, 316 S.C. 283, 287, 450 S.E.2d 36, 38 (1994) (relying on federal case construing Federal Trade Commission Act); *State ex rel. McLeod v. VIP Enters., Inc.*, 286 S.C. 501, 504, 335 S.E.2d 243, 244 (Ct. App. 1985) (same). That statutory mandate, obviously, does not require that South Carolina trial courts defer to interpretations of the Federal Trade Commission Act that are inconsistent with binding South Carolina authority, but it does call for deference to interpretations that are consistent with South Carolina decisional law or instructive where there is an absence of South Carolina law on the specific issue presented. This legislative mandate is particularly significant because, as outlined below, Federal Trade Commission Policy Statements and Federal Trade Commission Act decisions not only set specific requirements for the proof of the necessary elements of the State's claim of an unfair or deceptive practice or act but also establish the insufficiency of the evidence offered by the State.

Stated another way, these standards set forth the applicable evidentiary burden for the State. And it is a burden that could not be satisfied with "expert" opinion testimony alone as to whether a particular act or practice is "unfair" or "deceptive"; instead, the State was required to present *facts* supporting each of the elements of its SCUTPA claim. As the State's evidence failed to establish the essential elements of either a deceptive trade

practice claim or an unfair trade practice claim, judgment in favor of Janssen is mandated. *Guffey*, 364 S.C. at 163, 612 S.E.2d at 697.

### 1. The State Did Not Present Sufficient Facts As To Its Unfair Trade Practices Claim

The State's claim that the November 2003 mailing and the Risperdal package insert are "unfair" acts or practices should not have been submitted to the jury. "Unfair" acts or practices cannot be "inferred." *Wingard v. Exxon Co., U.S.A.*, 819 F. Supp. 497, 506 (D.S.C. 1992). And "SCUTPA does not prohibit all business activities that someone may consider 'unfair.'" *Miller v. W.H. Bristow, Inc.*, 739 F. Supp. 1044, 1055 (D.S.C. 1990). The State was required to prove the essential elements of an unfair trade practice, which can easily be determined by reference to both the Federal Trade Commission Act as well as to a long-standing Federal Trade Commission Policy Statement. *See* 15 U.S.C.A. § 45(n) (Federal Trade Commission Act); Federal Trade Commission Policy Statement on Unfairness (1980).

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#### a. Use Of An FDA-Approved Package Insert Cannot Be The Basis Of An "Unfair" Trade Practice

Regardless of the definition given to an "unfair" act, it is difficult to fathom how the use of a federally mandated, FDA-approved package insert can give rise to a violation of a state consumer protection law. Yet, that is exactly what the Court's evidentiary rulings and the Court's instructions allowed.

This Court relied on *Gentry v. Yonce*, 337 S.C. 1, 522 S.E.2d 137 (1999) for the definition of an "unfair" act: one that is offensive to public policy or immoral, unethical, or oppressive. *Id.* at 12, 522 S.E.2d at 143 (citing *Harris v. NCNB*, 85 N.C. App. 669, 355 S.E.2d 838 (1987)). But the *Gentry* court, itself relying on North Carolina law rather than statutorily-mandated Federal Trade Commission interpretation, did nothing more than provide a basic definition for the term. Because the conduct at issue on its face violated an

existing South Carolina statute, it was not necessary for the Court to explain what a differently-situated plaintiff would be required to prove to be successful on a SCUTPA "unfair trade practices" claim. *Id.* That additional guidance, as the legislature has specifically directed and South Carolina courts have expressly acknowledged, must come from interpretations given by the Federal Trade Commission and the federal courts to 15 U.S.C. 45(a)(1). S.C. Code Ann. § 39-5-20.

That did not happen in this case. And in the absence of proper instruction as to the requirements of a claim for "unfair" trade practices under SCUTPA, the jury was left to believe that using an allegedly "inadequate" package insert, even one that had been approved by the FDA, could serve as the basis for a violation of SCUTPA. Such a verdict, however, finds no basis in the law and cannot stand.

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**b. Lack Of Evidence Of The Essential Elements Of An Unfair Trade Practice**

In construing SCUTPA, the South Carolina Supreme Court has found decisions from Tennessee courts to be persuasive authority. *See, e.g.*, *Ward*, 304 S.C. at 156, 403 S.E.2d at 312 (citing *Skinner v. Steele*, 730 S.W.2d 335 (Tenn. App. 1987)). In defining what constitutes an unfair trade practice, Tennessee courts have adopted the elements set forth in 15 U.S.C. § 45(n) (part of the Federal Trade Commission Act). *Tucker v. Sierra Builders*, 180 S.W.3d 109 (Tenn. App. 2005). As held by the court in *Tucker*:

> In the 1994 legislation reauthorizing the Federal Trade Commission, Congress undertook to codify the Commission's policy statement on unfairness by stating that an act or practice should not be deemed unfair "unless the act or practice causes or is likely to cause substantial injury to consumers which is not reasonably avoidable by consumers themselves and not outweighed by countervailing benefits to consumers or to competition." 15 U.S.C.A. § 45(n). Following the mandate of Tenn. Code Ann. § 47-18-115, we will use this description of unfairness to guide our interpretation of Tenn. Code Ann. § 47-18-104(a).

*Id.* at 116-117. As further explained by the court:

> To be considered "substantial," consumer injury must be more than trivial or speculative. Substantial injury usually involves monetary injury or unwarranted health and safety risks. Consumer injury will be considered substantial if a relatively small harm is inflicted on a large number of consumers or if a greater harm is inflicted on a relatively small number of consumers. Even if an act or practice causes or is likely to cause substantial injury, it will not be considered unfair unless the injury is not reasonably avoidable by consumers themselves. Consumers cannot reasonably avoid injury when a merchant's sales practices unreasonably create or take advantage of an obstacle to the free exercise of consumer decision-making. Practices that unreasonably interfere with consumer decision-making include (1) withholding important information from consumers, (2) overt coercion, or (3) exercising undue influence over a highly susceptible class of consumers.

*Id.* at 117 (citations omitted).

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The evidence the State presented in support of its unfair trade practice claim falls far short of proof of any of these essential elements. First, any alleged "substantial" injury to consumers from either the November 2003 mailing or the Risperdal package insert is nothing more than speculation. Second, any alleged "substantial" injury is more than outweighed by the undisputed benefits to South Carolina residents from the availability and use of Risperdal. The State's expert, Dr. Wirshing, in particular testified in great detail as to the substantial medical benefits of Risperdal. Trial Tr. vol. III, 561:7-568:2, 624:7-14, Mar. 9, 2011. Finally, the State introduced no evidence whatsoever from which a reasonable jury could have concluded that any aspect of the November 2003 mailing or the Risperdal package insert "unreasonably interfered" with either a consumer's or a physician's decision to choose an antipsychotic medicine.

### c. Alleged Violations Of Public Policy Alone Are Not A Basis Upon Which The Jury Can Make A Finding That An Act Or Practice Is "Unfair"

Ever since they were first advanced, only a few weeks before trial, the State's "public policy" arguments – that Janssen's conduct is offensive to public policy, immoral, unethical, or oppressive – have been unclear and have shifted depending on the particular issue raised. *See, e.g.*, Pl.'s Opp'n to Defs.' Mot. *in Limine* to Preclude Irrelevant and Unfairly

Prejudicial Evidence at 18 ("[T]he State is entitled to introduce evidence of loss and harm sustained by the South Carolina Medicaid program to show that Defendants' labeling of Risperdal prescriptions paid or reimbursed by the State violated S.C. Code Ann. § 39-5-20(a) because it was unethical, immoral, and offensive to South Carolina's public policy of not defrauding public agencies that protect the health and welfare of its citizens."); Pl.'s Opp'n to Defs.' Mot. for Summ. J. as to Pl.'s Unfair Trade Practices Claim Based on the November 2003 Mailing at 21 ("In its April 2004 Warning Letter to Janssen, the FDA recognized the significant and detrimental impact of the November 2003 "Dear Doctor" letter on the South Carolina public: 'The healthcare community relies on ["Dear Doctor"] letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers *is a serious public health issue.*'"). At trial, the State had nothing but speculative public policy concerns as the basis of its unfairness claim. The Federal Trade Commission Act, as well as the Federal Trade Commission's "unfairness" policy statement, unequivocally confirm, however, that a violation of public policy alone is not a basis upon which the jury can find that the November 2003 mailing or the Risperdal package insert was an unfair trade practice. 15 U.S.C.A. § 45(n); Federal Trade Commission Policy Statement on Unfairness (1980). Similarly, a violation of public policy cannot be the primary basis upon which the jury can find that the November 2003 mailing was an unfair trade practice. 15 U.S.C.A. § 45(n). Because, after all the State's evidence was in, there was nothing more than vague, conclusory assertions of a violation of some unspecified "public policy," the State's unfair trade practice claim should not have been submitted to the jury.

## 2. The State Failed to Present Sufficient Evidence As To The Essential Elements Of Its Deceptive Trade Practices Claim

Well-settled law provides that to establish liability for a deceptive trade practice, "the [Federal Trade Commission] must establish that (1) there was a representation; (2) the representation was likely to mislead customers acting reasonably under the circumstances; and (3) the representation was material." *FTC v. Tashman*, 318 F.3d 1273, 1277 (11th Cir. 2003) (citations omitted). The "Federal Trade Commission" law is not inconsistent with South Carolina law, and the State therefore was required to establish these elements.

### a. Lack Of An Actionable Representation

The November 2003 mailing expressed Janssen's opinion as to the conclusions that could be drawn from a certain "body of evidence from published peer-reviewed epidemiology research." *See* Trial Ex. P1736 (November 2003 mailing). Equally significant, the November 2003 mailing also cited to each of the published peer-reviewed epidemiological research studies, thereby fully disclosing the entire scientific basis for Janssen's opinion. *Id.* Because Janssen's statement of its opinion was accompanied by a disclosure of the sources upon which the opinion was based – allowing any reader of the November 2003 mailing to draw his own conclusions about the scientific evidence – the mailing cannot be considered deceptive. *See Bruette v. Stokes, Kia, Isuzu, Subaru, Inc.*, No. 2001-CP-10-1800, slip op. at 9, 2002 WL 34128304 (S.C. Ct. Com. Pl. Nov. 6, 2002) ("When the alleged unfair trade practice 'is a misrepresentation, the claimant is not entitled to recover if he had an equal and ample opportunity to ascertain the truth but failed to exercise proper diligence to do so.'" (citation omitted)); *see also Pizza Hut, Inc. v. Papa John's Int'l, Inc.*, 227 F.3d 489, 496 (5th Cir. 2000) (holding, under analogous Lanham Act, 15 U.S.C.A. § 1125(a): "Bald assertions of superiority or general statements of opinion cannot form the basis of Lanham Act liability. Rather the statements at issue must be a

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'specific and measurable claim, capable of being proved false or of being reasonably interpreted as a statement of objective fact.'" (citations omitted)); *Cytyc Corp.*, 12 F. Supp. 2d at 300 ("In the actual statement, contained in a press release, Cytyc identified the specific screening site, and the numbers of positive cases diagnosed with the pap smear and with ThinPrep. The inclusion of such specific evidence means that this statement could not be found to be misleading."). This is especially true where the opinions relate to scientific and medical research. *See, e.g.*, *McDonagh v. Bergan*, No. 03 C 146, 2003 WL 21798735, at *3 (N.D. Ill. July 25, 2003) ("disagreements of this type amongst medical professionals should be settled by discussion and research in the medical community, not by the courts").

The statements in the Risperdal package insert, like the statements in the November 2003 letter, reflect judgments, by Janssen and/or the FDA, about the meaning and significance of the scientific evidence. As to the package insert, neither of the State's experts even attempted to argue that the statements about diabetes, hyperprolactinemia, etc. were based on anything other than extensive medical research and information as to the use of Risperdal, although they took issue with the wording of certain parts of the package insert and the prominence of the "risk" information in it. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Dr. Wirshing). This should have been dispositive of the State's deceptive trade practice claim.

This case illustrates precisely the logical and, equally important, constitutional problem with the entirety of the State's SCUTPA claim – the State improperly seeks to punish reasonable expressions of scientific opinions by Janssen. The jury was allowed to choose among the different experts' positions in the scientific debate, and the State now seeks to have this Court punish Janssen for having a different – yet scientifically supported

– view. Nothing under applicable law supports this conclusion or result. As the complete absence of a provably false factual representation that could "deceive" the persons to whom it was made precludes the State's deceptive trade practice claim in the first instance, the jury's verdict is flawed.

**b. Absence Of Evidence That The November 2003 Mailing Or The Risperdal Package Insert Had A "Tendency To Deceive" Or Were "Likely To Deceive" South Carolina Physicians**

Under South Carolina law, the test for SCUTPA liability is whether the challenged statement or act "has a tendency to deceive." *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (Ct. App. 2000). Whether an act has a "tendency to deceive" or is "likely to deceive" "depends upon the surrounding facts and the impact of the transaction on the marketplace." *Id.* Consideration of "the surrounding facts and the impact of the transaction on the marketplace," in turn, requires consideration of the knowledge, experience, and sophistication of the relevant audience. *See* Federal Trade Commission Policy Statement on Deception, 2 Fed. Trade Comm'n App. D-2 (2009); S.C. Code Ann. § 39-5-20(b) ("the courts will be guided by the interpretations given by the Federal Trade Commission . . . to § 5(a)(1) of the Federal Trade Commission Act . . .."). Pursuant to the Federal Trade Commission Policy Statement, "a practice or representation directed to a well-educated group, such as a prescription drug advertisement to doctors, would be judged in light of the knowledge and sophistication of that group." *Id.* The relevant audience, or "marketplace," for the State's SCUTPA claim necessarily is South Carolina physicians because: (1) Risperdal can only be obtained by prescription; (2) the November 2003 mailing was sent to physicians; and (3) the package insert is written for physicians.

As part of its proof, therefore, the State was required to present evidence that the November 2003 mailing and the Risperdal package insert actually had a "tendency to

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deceive" or were "likely to deceive" South Carolina physicians. *See TC X, Inc. v. Commw. Land Title Ins. Co.*, 928 F. Supp. 618, 625 (D.S.C. 1995), *aff'd without op.*, 86 F.3d 1152 (4th Cir. 1996) (granting summary judgment for the defendant on a SCUTPA claim, stating that "[t]here is no evidence that Commonwealth deceived TC X or anyone else regarding its interpretation of the policy").

The State, however, did not prove that either the November 2003 mailing or the Risperdal package insert had a tendency to deceive or were likely to deceive South Carolina physicians. The State's experts took the position that the November 2003 mailing was somehow inherently "deceptive" and that the Risperdal package insert was "inadequate" as to certain risks. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Dr. Wirshing). But they provided no testimony whatsoever about the knowledge, experience, and sophistication of South Carolina physicians, and no testimony as to whether the November 2003 mailing or the Risperdal package insert, with their statements as to the scientific evidence, actually deceived or were "likely to deceive" those physicians. *See generally* Trial Tr. vols. IV & V, Mar. 10-11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, Mar. 9, 2011 (testimony of Dr. Wirshing). Without supporting facts, the speculation of experts as to whether a statement is "deceptive" was insufficient to satisfy the State's evidentiary burden. Under the plain language of the *deBondt* decision the State was required to present *facts* showing impact on the physician "marketplace." *See* 342 S.C. at 269, 536 S.E.2d at 407. As discussed *infra*, the State's failure of proof would have been made even more clear if the Court had allowed Janssen to introduce affirmative evidence that neither the November 2003 mailing nor the FDA-approved Risperdal package insert had a tendency to deceive South Carolina physicians.

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The *only* evidence in this case regarding the impact – or lack thereof – the November 2003 mailing had on the South Carolina marketplace was evidence presented by the Defendants, through the stipulation as to Dr. Wecker's calculations of "market share" and the testimony of Dr. Robert Bank and Dr. Brenda Ratliff.[2] As an initial matter, the parties stipulated to Dr. Wecker's calculations showing that there was no change in Risperdal's share of prescriptions for antipsychotics filled for South Carolina Medicaid and State Health Plan participants after the November 2003 mailing *or* after Janssen sent a follow-up letter in July 2004. *See* Trial Ex. D7337. That is, the State's database shows that the November 2003 mailing had no impact on the relevant marketplace. Equally significant, Dr. Bank and Dr. Ratliff testified that South Carolina physicians knew, before the November 2003 mailing was sent, about the associations between various antipsychotics and weight gain and diabetes. Dr. Bank testified that as each atypical antipsychotic was introduced into the marketplace, he observed the diabetes-related effects associated with that particular medicine within the first year or two of prescribing the medicine. Trial Tr. vol. IX, 2112:12-23, Mar. 17, 2011. He also testified that by 2002, other physicians who prescribed atypical antipsychotics also had observed diabetes-related side effects, including weight gain, in their patients. *Id.* at 2118:11-18, 2119:4-6. Indeed, Dr. Bank testified that the only thing "new" in the Consensus Statement, which was published in February 2004, "was that the American Diabetes Association and the American Psychiatric Association had concurred that this [observing a relationship between atypical antipsychotics and diabetes] was the experience of a community of physicians that are represented by this document." *Id.* at

[2] Dr. Bank is the current medical director of the South Carolina Department of Mental Health ("DMH"), and Dr. Ratliff is the former medical director of DMH. Trial Tr. vol. IX, 2109:4-13, 2155:22-2157:6, Mar. 17, 2011. DMH is the largest provider of treatment services for the mentally ill population of South Carolina. *Id.* at 2109:20-23.

2125:2-23. Dr. Ratliff also testified that the Consensus Statement was consistent with her observations and with what she had discussed with her colleagues. *Id.* at 2161:21-2163:13. The State presented no contrary evidence.

The evidence, then, shows that the November 2003 mailing did not have – and could not have had – any impact whatsoever on the South Carolina marketplace. Thus, it did not have a "tendency to deceive." For that reason alone, the State's SCUTPA claim as to the November 2003 mailing should not have been submitted to the jury.

**c. Lack Of Evidence Of Materiality**

A material claim is one that is "likely to affect" a party's "conduct or decision with regard to a product or service." Federal Trade Commission Policy Statement on Deception at 2. The State introduced no evidence that either the November 2003 mailing or the Risperdal package insert was material to a single prescribing decision by a South Carolina physician. Although it was not their burden to disprove materiality, Defendants introduced the "market share" evidence demonstrating that the mailing was not material. *See, e.g.*, *Raab v. Gen. Physics Corp.*, 4 F.3d 286, 289 (4th Cir. 1993) (finding that "statements such as these generally lack materiality because the market price of a share is not inflated by vague statements predicting growth"); *In re Boston Scientific Corp. Sec. Litig.*, 708 F. Supp. 2d 110, 128-29 (D. Mass. 2010) (concluding that plaintiffs could not establish "materiality," in part, because there was "no evidence that the disclosures made during the Class Period had any 'material' impact on the Company stock price"). Janssen would have introduced additional evidence as to the lack of materiality but for the Court's evidentiary rulings as explained in more detail below. For this reason as well, the State's deceptive trade practice claim fails.

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## E. There Was A Complete Absence Of Sufficient Evidence To Establish That The Alleged Unfair Or Deceptive Trade Practices Adversely Affected The Public Interest

The State was required to show that the challenged practice has the potential for repetition or that it otherwise affected the public interest. Slip op. at 4 (Feb. 25, 2011). The potential for repetition may be proven by showing: (1) the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) the defendant's procedures created a potential for repetition of the unfair and deceptive acts. *See, e.g., Singleton v. Stokes Motors, Inc.*, 358 S.C. 369, 595 S.E.2d 461 (2004).

### 1. Repetition: The November 2003 Mailing

As to the November 2003 mailing, the State did not introduce any evidence that any similar kind of "deceptive act" occurred in the past. Nor did the State introduce any evidence that any procedure of Defendants created a potential for repetition. Indeed, the State introduced no evidence that any prior or subsequent letter to physicians ever has been challenged by anyone, including the FDA. In over a decade of communications with physicians as to the risks of Risperdal, the single piece of correspondence challenged by the State is insufficient to establish that the November 2003 mailing "has the potential for repetition."

The January 5, 1999 DDMAC letter, which raised a concern, in the view of a DDMAC reviewer, about "a campaign that markets Risperdal for geriatric patients," Trial Ex. P200, was not sufficient evidence to satisfy SCUTPA's "capable of repetition" element under the decision of *Burbach v. Investors Management Corp.*, 326 S.C. 492, 484 S.E.2d 119 (Ct. App. 1997). Under *Burbach*, the January 5, 1999 DDMAC letter is insufficient – and inadmissible – evidence to satisfy the "capable of repetition" element because: (1) it was issued over five years before the 2004 warning letter; (2) there is no similarity whatsoever between the two letters – the 1999 letter concerned certain marketing materials

in connection with geriatric patients and the 2004 warning letter concerned a mailing to healthcare professionals about changes to the Risperdal package insert as to the risks of diabetes, hyperglycemia, and weight gain; and (3) in over sixteen years, these are the only two isolated instances where the FDA ever raised any concern as to Janssen's activities in relation to Risperdal. *Id.* at 498 n.3, 484 S.E.2d at 122 n.3.

2. **Repetition: The Risperdal Package Insert**

The State's "package insert" claim suffers from the same lack of evidence. The evidence showed that the agency charged with determining the sufficiency and accuracy of the label, the FDA, never took any issue with the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. And again, the State could not identify a single Janssen "procedure" that purportedly would result in an unfair or deceptive Risperdal package insert in the future.

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The mere fact that the challenged Risperdal package insert remained in use was insufficient to establish the essential element that the "deceptive" practice be capable of repetition. *See, e.g., Jefferies v. Phillips*, 316 S.C. 523, 529, 451 S.E.2d 21, 23-24 (Ct. App. 1994) ("In the course of human endeavor, every action has some potential for repetition. The mere proof that the actor is still alive and engaged in the same business is not sufficient to establish this element.").

3. **Adverse Effect On The Public Interest**

In the absence of a showing that the challenged conduct has the potential for repetition, to establish a SCUTPA violation, the alleged unfair act or deceptive practice must have otherwise affected the public interest. That is, the State was required to "establish, *by specific facts*, that members of the public were adversely affected" by Janssen's alleged unfair trade practice. *Bessinger v. Food Lion Inc.*, 305 F. Supp. 574, 584 (D.S.C. 2003), *aff'd*, 115 F. App'x 636 (4th Cir. 2004) (emphasis added).

But the mere invocation of such words as "public interest," "public policy," and "public health issue" by the State's experts, without specific facts supporting such conclusory statements, is insufficient. *Orangeburg Pecan Co. v. Farmers Inv. Co.*, 869 F. Supp. 359, 362 (D.S.C. 1994) ("Plaintiff here has done little more than chant phrases like 'public interest' and 'public impact' without producing a shred of evidence that such alleged wrongdoing is capable of repetition, or was, in fact, repeated."). *See, e.g.*, Trial Tr. vol. IV, 760:7-9, Mar. 10, 2011 (Dr. Plunkett merely agreeing with State's counsel that DDMAC's 2004 letter says November mailing "creates a serious public health issue").

A SCUTPA claim cannot be speculative. Yet, the State presented no factual evidence that either the November 2003 mailing or the Risperdal package insert had an *actual* adverse affect on the public or on physicians. *See* Trial Tr. vol. V, 993:16-994:8, 995:10-17, 999:3-8, 1024:21-1025:10, Mar. 11, 2011 (Dr. Plunkett testifying that she had no contact with any South Carolina physicians regarding the Risperdal label or any of the matters that are the subject of the lawsuit; no specific knowledge of any South Carolina resident experiencing hyperprolactinemia or diabetes after receiving Risperdal). At most, one of the State's experts testified that the November 2003 mailing "potentially" was a serious public health issue. Trial Tr. vol. III, 473:17-20, Mar. 9, 2011 (testimony of Dr. Wirshing). In addition, the Court's evidentiary rulings, as discussed more fully below, prevented Janssen from introducing additional evidence that the public interest was not adversely affected by the allegedly "unfair" or "deceptive" conduct.

As the State completely failed to establish the required SCUTPA element of an adverse impact on the public, no reasonable jury could have found a SCUTPA violation. *See, e.g.*, *Omni Outdoor Adver. Inc. v. Columbia Outdoor Adver. Inc.*, 974 F.2d 502, 507 (4th Cir. 1992) ("Omni suggests that the practice of double billing inflates costs to the advertisers and hence to consumers. Omni, however, cites no evidence in the record to

support this proposition. It offers no basis other than sheer speculation to conclude that the total advertising costs of the affected companies rose as a result of the alleged COA practices. South Carolina courts have consistently rejected speculative claims of adverse public impact and required evidentiary proof of such effects.") (citations omitted).

### F. The State Failed To Introduce Sufficient Facts For The Jury To Find Willful Conduct

The State also failed to introduce sufficient evidence as to the essential element of a "willful" violation of SCUTPA. A SCUTPA violation is willful "when the party committing the violation knew or should have known that his conduct was a violation of [the South Carolina Unfair Trade Practices Act]." S.C. Code Ann. § 39-5-140(d). As held by South Carolina courts, conduct is willful for purposes of SCUTPA only "[i]f in the exercise of due diligence, a person of ordinary prudence engaged in trade or commerce could have ascertained that his conduct violates the Act." *State ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 290 S.C. 124, 128, 348 S.E.2d 381, 384 (Ct. App. 1986) ("*Nest Egg*").

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The Court required the State to prove only that Defendants knew or should have known that the labeling was "unfair" or "unethical" or "deceptive." But the limited South Carolina decisions interpreting this element of SCUTPA have interpreted the element of a willful violation far more narrowly – a violation is willful only where the defendant's conduct violated a specific South Carolina statute that expressly prohibits the precise practice that the Attorney General alleges is a violation of SCUTPA. *See Nest Egg*, 290 S.C. at 124, 348 S.E.2d at 381 (willful conduct was a pyramid scheme expressly proscribed by S.C. Code Ann. § 39-5-30). *See generally Gentry*, 337 S.C. at 12, 522 S.E.2d at 143. Even more significant, the South Carolina Supreme Court has made clear that conduct is not willful if it is not prohibited and there is evidence that the conduct challenged as unfair or deceptive is a common practice in the defendants' trade or business. *Haley Nursery Co., Inc. v. Forrest*,

298 S.C. 520, 525, 381 S.E.2d 906, 908 (1989) ("[Defendant's] conduct is not prohibited and there is evidence it is in accord with the common practice of the trade. Applying the statutory definition, we hold the record supports the trial judge's finding the violation was not willful.").

The State presented no evidence that the Risperdal package insert was ever "prohibited" by the FDA or anyone else. The State's expert, in fact, acknowledged the contrary: the FDA has never taken any action as to the Risperdal package insert. Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011. Further, not only is the use of a package insert in accord with the "common practice of the trade," but it is required for prescription medicines such as Risperdal. *See* 21 U.S.C.A. § 355(b)(1)(F) (new drug application shall include "specimens of the labeling proposed to be used for such drug"); *see also* 21 C.F.R. §§ 201.56, 201.57 (labeling requirements for prescription drugs); 21 C.F.R. § 314.54 (procedure for submission of an application requiring investigations for approval of a new indication for, or other change from, a listed drug); 21 C.F.R. § 314.70 (supplements and other changes to an approved application). Accordingly, the State has not introduced any evidence from which a jury could find that Defendants committed a willful violation of SCUTPA in connection with the Risperdal package insert.

As to the November 2003 mailing, the State failed to introduce any evidence that Janssen knew or should have known that the statements in the mailing were false. States with statutes similar to SCUTPA that also impose a "willfulness" requirement have held that, at a minimum, a plaintiff must establish that a defendant knew or should have known that the representations challenged as deceptive were false. *See, e.g., Adamson v. Worldcom Commc'ns, Inc.*, 78 P.3d 577, 583 (Or. App. 2003); *State ex rel. Corbin v. United Energy Corp. of Am.*, 725 P.2d 752, 758-59 (Ariz. App. 1986).

Neither of the State's experts testified that the materials cited by Janssen in the November 2003 mailing did not support the statements made by Janssen. The testimony, in fact, was to the contrary. For example, although Dr. Wirshing testified that the word "infrequently" may not be the best word to describe the occurrence rate for hyperglycemia, he admitted that "it wasn't really common at any rate." Trial Tr. vol. III, 457:20-458:4, Mar. 9, 2011.[3] He also admitted that it was fair to say that the primary conclusion from the eight articles cited in the mailing were supportive "to a degree" of the middle paragraph of the November 2003 mailing and that six of the eight articles support the statement that Risperdal has a lower diabetes risk than Zyprexa. *Id.* at 613:15-614:4. And, Dr. Wirshing conceded that Risperdal does have a lower risk of weight gain than Zyprexa. *Id.* at 405:25-406:18; 600:3-601:6, 627:22-628:7. As such, any conduct as to the November 2003 mailing also was not "willful." No reasonable jury could have found that Janssen committed a willful violation of SCUTPA in connection with either the Risperdal package insert or the November 2003 mailing.

[3] There is a well-recognized definition as to what constitutes an infrequent event. Specifically, an infrequent event is one that occurs in less than one percent (1%) of individuals. Trial Tr. vol. III, 480:23-24, Mar. 9, 2011 ("One in a hundred to one in a thousand is infrequent[.]") (Dr. Wirshing testimony); Trial Tr. vol. VII, 1520:19-21, 1592:2-9, Mar. 15, 2011 (Dr. Mahmoud testimony) ("If it's infrequent, it's between 1 in 100 and 1 in a thousand so between 1 percent and 0.1 percent."); Trial Tr. VIII, 1763:1-3, Mar. 16, 2011 (Dr. Caers testimony) ("Infrequently is below 1 percent and above .1 percent. So above 1 out of every thousand and less than 1 of every 100.").

## G. The State's Entire SCUTPA Claim Was Barred By The Statute Of Limitations And The Court Erred In Granting The State's Motion For A Directed Verdict On The Statute Of Limitations Defense

### 1. Janssen Was Entitled To A Directed Verdict Because The State's Claim Was Barred By The Applicable Statute Of Limitations

A SCUTPA claim must be filed no more than three years after discovery of the unlawful conduct. S.C. Code Ann. § 39-5-150. Any alleged "deception" as to the November 2003 mailing would have been apparent on the face of the document as the letter states *both* (1) Janssen's opinion as to the conclusions "suggest[ed]" by a certain "body of evidence from published peer-reviewed epidemiology research" *and* (2) the identification of – and citations to – that "published peer-reviewed epidemiology research." *See* Trial Ex. P1736 (November 2003 mailing). Certainly, any of the physicians and other prescribers to whom the letter was addressed – and the State – had the ability to review the publicly available published studies to which Janssen pointed them and to "discover" any alleged deception in the opinion Janssen offered about them. As such, the limitations period began to run at the time of dissemination of the November 2003 mailing. *See Prestwick Golf Club, Inc. v. Prestwick Ltd. P'ship*, 331 S.C. 385, 393, 503 S.E.2d 184, 188 (Ct. App. 1998) (limitations period began to run on SCUTPA claim when defendant "announced its intention"); *see also Gibson v. Bank of Am., N.A.*, 383 S.C. 399, 407-08, 680 S.E.2d 778, 782-83 (Ct. App. 2009) (limitations period began to run at time of receipt of bank statements showing withdrawals that were the subject of claim). Thus, the SCUTPA claim based on the November 2003 mailing was time-barred.

The State's package insert claim also was time-barred. According to the State's experts, the Risperdal package insert was "inadequate" from Day One in 1994. Trial Tr. vol. V, 1084:4-24, Mar. 11, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 624:15-625:15, Mar. 9, 2011 (testimony of Dr. Wirshing). Also, according to the State's experts, the precise

risks which the State alleges were inadequately disclosed were both predictable and actually known based on: (1) the chemical compound of Risperdal itself; and (2) instances of weight gain, hyperglycemia, and hyperprolactinemia that were seen in the pre-marketing clinical studies of Risperdal. Trial Tr. vol. IV, 687:22-687:25, 691:16-23, 689:19-690:6, Mar. 10, 2011 (testimony of Dr. Plunkett); Trial Tr. vol. III, 475:24-477:23, 528:14-25, Mar. 9, 2011 (Dr. Wirshing testifying that weight gain warning should have been made earlier based on pre-marketing clinical trials; risk of alpha toxicity "inherent in the molecule"; risk was known "in the 80s"). The statute of limitations, therefore, began to run on the State's package insert claim at the time of the initial Risperdal package insert in 1994. *Prestwick Golf Club, Inc.*, 331 S.C. at 393, 503 S.E.2d at 188; *see also Gibson*, 383 S.C. at 407-08, 680 S.E.2d at 782-83. As the alleged deceptive conduct occurred more than three years prior to the initiation of this action, the State's entire package insert claim also was time-barred.

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### 2. The Court Erroneously Granted The State's Motion For A Directed Verdict

This Court erroneously granted the State's motion for a directed verdict. First, the Court determined that the State is not on notice of a claim until the attorney general himself has notice. But there simply is no authority for such a special rule as to when the State is on notice for purposes of the statute of limitations. In fact, the only South Carolina court to address the issue held that the State is subject to the same principles governing the application of the statute of limitations as anyone else. *Willcox v. Stroup*, 358 B.R. 824 (D.S.C.), *aff'd*, 467 F.3d 409 (4th Cir. 2006); *see also State of Delaware ex rel. Brady v. Pettinaro Enters.*, 870 A.2d 513, 532 (Del. Ch. 2005) (finding that attorney general is not entitled to preferential treatment in connection with stale claims under the state's consumer protection statute). The notice that starts the statute running is notice to the State, not to

any particular state official. Second, this Court's determination that a plaintiff, including the attorney general, must have actual knowledge of wrongdoing, Trial Tr. vol. XI, 2580:16-2585:7, Mar. 21, 2011, is inconsistent with well-settled South Carolina law, *see Prestwick Golf Club, Inc.*, 331 S.C. at 393, 503 S.E.2d at 188; *Gibson*, 383 S.C. at 407-08, 680 S.E.2d at 782-83.

Third, this Court erroneously found that the statute of limitations was equitably tolled. Equitable tolling is a doctrine to be sparingly applied. *See Hooper v. Ebenezer Senior Svcs. & Rehab. Ctr.*, 386 S.C. 108, 117, 687 S.E.2d 29, 33 (2009). It was particularly inappropriate to remove the issue of statute of limitations from the jury's consideration because, as this Court acknowledged, there was no evidence that anyone was misled; instead, the evidence adduced established that the recipients of the letter knew of the adverse risks which the State now says were "hidden." Specifically, the Court explained:

> All of the individuals who testified on behalf of the Defendant from the State as to what they knew and when they knew it, all of them testified as to the fact that they were aware that atypical antipsychotics, the second generation of drugs, had an issue or a problem involving diabetic adverse events.
>
> And that particular fact appears to have been known by the medical community for some period of time before this action was filed. However, none of them testified that they ever felt at any time that they had been – the facts had been misrepresented by Janssen or that Janssen had committed any type of fraud or made misleading statements in the marketplace. None of them – in fact, I suspect if they were asked today, they would state that they are unaware of those events occurring.
>
> Therefore, I find it difficult to say that their knowledge of the side effects going over a period of time would somehow raise an issue as to a letter mailed in 2003 when they didn't apparently feel that they were being misled or having false statements being made to them at any time in the process.
>
> . . . .
>
> Also, again, the evidence given by the witnesses from the State did not indicate that they felt like the labeling was ever misleading, in specific,

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and there is, again, no evidence that that information was transmitted of a possible deception in the label to the Attorney General.

Trial Tr. vol. XI, 2582:4-2583:3, 2584:22-2585:2, Mar. 21, 2011. In reality, those findings required that the entire case be taken from the jury and Defendants' Motion for a Renewed Directed Verdict be granted – the opposite of what happened in this case.

H. **This Court's Evidentiary Rulings Taint The Jury's Verdict As To Janssen**

The Court's first, overarching evidentiary error was its failure to limit the State's SCUTPA claim to the conduct the State consistently identified in discovery as the basis of its SCUTPA violation: Janssen's purportedly "deceptive" conduct in the dissemination of the November 2003 mailing and the FDA-approved Risperdal package insert. The Court further erred in admitting various categories of evidence, including but not limited to, documents and testimony related to: (1) informal, advisory letters from DDMAC; (2) the number of Risperdal prescriptions in South Carolina; (3) Defendants' sales, revenues, profits, and business plans; (4) e-mails sent by Dr. Scott Reines, the former vice president of one of Janssen's sister companies, who did not participate in any aspect of the November 2003 mailing; (5) alleged off-label and otherwise improper and deceptive promotional and marketing activities; and (6) purported nondisclosures to the FDA.

At the same time, the Court improperly excluded relevant evidence, including documents and testimony that would have shown that: (1) the FDA has recognized that each atypical antipsychotic has a different risk profile, including for diabetes-related side effects; (2) the November 10, 2003 mailing and the Risperdal package insert did not have a tendency to deceive South Carolina prescribing physicians; and (3) the State's interpretation of the federal regulations governing a pharmaceutical manufacturer's duty to update its product label, which it presented to the jury, was erroneous. These numerous

and incurable errors irreparably damaged Janssen's ability to defend itself against the State's claim.

### 1. The Court Abused Its Discretion And Erred In Failing To Limit The State's Case To The Conduct And Evidence The State Repeatedly Identified Throughout Discovery As The Bases For Its Claims

In responding to no fewer than nine of Janssen's discovery requests, the State limited its SCUTPA claim to (1) the November 2003 mailing and (2) the Risperdal package insert. *See, e.g.*, Pl.'s Supplemental Answers to Janssen's Fifth Set of Interrogs., No. 9 (identifying the "Risperdal package insert and the November 2003 Dear Doctor Letter" in response to request to identify "all statements, representations and promotional schemes by Defendant Janssen that, you contend, were unfair, deceptive, false, incomplete, misleading, and untrue"); *see also id.* at Nos. 10-13, 28-29, 31-32. Moreover, the State also made clear that it viewed Janssen's "promotional activities" as "irrelevant" to the State's claim. *See id.* at No. 15 (objecting to interrogatory seeking identification of "all alleged false and deceptive promotional activity" as "seeking irrelevant information").

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Similarly, throughout its discovery responses, the State repeatedly asserted that its SCUTPA claim *was* based *only* on a claim that Janssen's conduct was "deceptive." *See, e.g.*, Pl.'s Answers to Janssen's Sixth Set of Interrogs., No. 1 ("Each Risperdal package insert constitutes a separate violation of SCUTPA *because it tends to deceive* recipients . . . ." (emphasis added)); Supplemental Answers to Janssen's Fourth Set of Interrogs., No. 6 ("The State asserts that every package insert . . . disseminated in South Carolina and every dissemination of Defendants' November 2003 Dear Doctor Letter *tended to deceive* pursuant to S.C. Code Ann. Section 39-5-20." (emphasis added)).

Relying on the State's discovery responses, Janssen prepared for trial on the understanding that the State's SCUTPA claim was based only on Janssen's purported "deceptive" conduct regarding the dissemination of November 2003 mailing and the

Risperdal package insert. But on the eve of trial, in opposition to a motion for summary judgment, the State suddenly asserted that its SCUTPA claim was based on conduct by Janssen that purportedly was "deceptive" and/or "unfair" and that myriad categories of evidence were now relevant. The Court denied Janssen's subsequent motion to limit the State's SCUTPA claim to the conduct identified in the State's discovery responses, and the result was a trial that was a "guessing game" and "one of surprise" for Janssen – the very type of trial the discovery rules are designed to prevent. *See In re Anonymous Member of S.C. Bar*, 346 S.C. 177, 193, 552 S.E.2d 10, 18 (2001). In failing to limit the State's claim, the Court erred. *See Samples v. Mitchell*, 329 S.C. 105, 114, 495 S.E.2d 213, 217-18 (Ct. App. 1997) (trial court imposed an overly lenient sanction that likely would not deter such discovery abuses in the future) (citing *Downey v. Dixon*, 294 S.C. 42, 45-46, 46 n.2, 362 S.E.2d 317, 318, 318 n.2 (Ct. App. 1987) ("The rights of discovery provided by the Rules were not protected in any way. Neither was Ms. Downey accorded the rights of discovery provided by the Rules, nor was the sanction imposed against Mr. Dixon a meaningful deterrent to those who might fail to submit to discovery in the future. . . . Indeed, it can be argued that the sanction imposed in the instant case tended to encourage, rather than discourage, noncompliance with the Rules.")).

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2. **The Court Erred In Allowing The Introduction Of, References To, And Testimony Regarding Informal and Advisory Letters From DDMAC**

In the absence of any actual evidence of a "tendency to deceive" or unfairness, the State relied on – and the Court erroneously allowed the introduction of – three informal and advisory letters from a division of the FDA: the 1994 DDMAC letter, the 1999 DDMAC letter, and the 2004 DDMAC letter. By allowing these letters to be admitted and testified to during trial, the Court allowed the State to base its SCUTPA claim on these letters, which discuss DDMAC-perceived violations of federal regulations and standards.

The 1994 DDMAC letter is a letter from a DDMAC employee regarding "Janssen's *proposed* introductory campaign for Risperdal (risperidone) Tablets." *See* Trial Ex. P1027 (emphasis added). In this letter, the author noted that the materials she reviewed were "tentative" and "final comments cannot be provided until review of the final materials." *Id.* The author concluded that some of the statements in the proposed materials were "misleading." *Id.* Notably, this comment related to pre-launch materials that Janssen never used in connection with the promotion of Risperdal. Trial Tr. vol. IV, 696:2-6, Mar. 10, 2011 (counsel for the State: "It's a letter that relates to the first proposed set of Risperdal advertising that was submitted to the FDA as part of the approval process. Those advertising pieces weren't ultimately used.").

The 1999 DDMAC letter was written by another DDMAC employee. This letter – which is referred to as an untitled letter – contained a summary of the conclusions the author reached after reviewing various promotional materials relating to a purported geriatric campaign. *See* Trial Ex. P200. The author concluded that these materials were "false, misleading, and/or lacking in fair balance, and in violation of the [FDCA] and the regulations promulgated thereunder." *Id.*

The 2004 DDMAC letter – which is referred to as a warning letter – was written by yet another DDMAC employee. *See* Trial Ex. P232. In the 2004 DDMAC letter, the author concluded the November 2003 mailing was "false or misleading in violation of Sections 502(a) and 201(n) of the [FDCA]." *See id.* The author also opined that the mailing "fails to communicate" certain safety information and "minimizes risks associated with Risperdal" and that the eight peer-reviewed, epidemiological studies cited in the mailing "do not represent the weight of the pertinent scientific evidence." *Id.*

a. **The Court Erroneously Allowed The Introduction Of The DDMAC Letters As Evidence Supporting The State's SCUTPA Claim**

As a threshold matter, in discovery and at trial, the State specifically denied that it was relying on any violation of federal statutes and FDA regulations as support for its SCUTPA claim. *See, e.g.*, Trial Tr. vol. XI, 2551:25-2552:17, Mar. 21, 2011 ("[T]he State does not contend that Janssen's breach of any FDA-promulgated rule, regulation, or statute provides for the basis of Janssen's violation of the South Carolina Unfair Trade Practices Act."). Having disclaimed reliance on violations of federal law, the State was not entitled to introduce, and the jury was not entitled to rely on, the DDMAC letters to establish a SCUTPA violation.

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Moreover, the State has not, and cannot, evade the universally recognized fact that such correspondence by the FDA is neither a determination of liability nor evidence of deceptive or unfair conduct. The Supreme Court of Appeals of West Virginia has held that the very same 2004 warning letter at issue here was merely "informal and advisory." *State ex rel. McGraw v. Johnson & Johnson*, 704 S.E.2d 677, 689-90 (W. Va. 2010). Other courts similarly have held that such correspondence cannot be used as evidence of final agency action or solely as evidence of "falsity." *See, e.g., Schering-Plough Healthcare Prods. v. Schwarz Pharma*, Inc., 586 F.3d 500, 508 (7th Cir. 2009) ("We can set aside the letters from subordinate officials of the FDA; the letters are not final agency action binding on the district court, as there has been no final agency action, let alone action that has been or could be judicially reviewed."); *Bracco Diagnostics, Inc. v. Amersham Health, Inc.*, 627 F. Supp. 2d 384, 471 (D.N.J. 2009) ("[Plaintiff] cannot prove falsity simply by relying on statements made in FDA letters that apply FDA standards."); *Genendo Pharm. N.V. v. Thompson*, 308 F. Supp. 2d 881, 885 (N.D. Ill. 2003) ("Statements of lower-level [FDA]

agency officials likewise do not rise to the level of final agency action – even when they are contained in warning letters or other official regulatory correspondence.").

The FDA's Regulatory Procedures Manual supports these conclusions: "A Warning Letter is informal and advisory. It communicates the agency's position on a matter, but it does not commit FDA to taking enforcement action. For these reasons, FDA does not consider Warning Letters to be final agency action on which it can be sued." *See* Trial Ex. D4337, Ch. 4 *FDA Regulatory Procedures Manual: Advisory Actions* at 4-2 (2010). An untitled letter such as the 1999 DDMAC letter "cites violations that do not meet the threshold of [regulatory significance for] a Warning Letter" and carries even less significance than warning letters. *See id.* at 4-26. And the 1994 DDMAC letter, which did not even rise to the level of an untitled letter, falls even lower on the regulatory significance scale.

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The 2004 DDMAC letter, the 1999 DDMAC letter, and the 1994 DDMAC letter, therefore, could not be used by the State for any of the purposes for which they were introduced; namely, to show the November 2003 mailing was deceptive, capable of repetition, willful, and had an adverse public impact because it created a "public health risk." *See, e.g.*, Pl.'s Opp'n to Defs.' Mot. for Directed Verdict at 19 (citing 2004 warning letter). Thus, this correspondence was insufficient evidence upon which the jury could impose liability upon Janssen as to the November 2003 mailing.

**b. <u>The DDMAC Letters Constituted Inadmissible Hearsay</u>**

The Court further erred in admitting the DDMAC letters because they are classic hearsay. They are out-of-court statements by DDMAC employees that the State offered to prove the truth of the matter asserted – that Janssen engaged in "false" or "misleading" promotion of Risperdal and the November 2003 mailing was "false" and "misleading." *See* Rule 801(c), SCRE; *see also, e.g.*, Trial Tr. vol. III, 467:21-468:12, Mar. 9, 2011 (testimony of Dr. Wirshing, reviewing 2004 DDMAC letter and "[a]bsolutely" agreeing with the FDA's

assessment that November 2003 mailing was "false and misleading"); Trial Tr. vol. IV, 702:22-703:6, Mar. 10, 2011 (testimony of Dr. Plunkett agreeing that in 1994 DDMAC letter, FDA said some claims were "misleading"); Trial Tr. vol. V, 1098:23-1100:12, Mar. 11, 2011 (testimony of Dr. Plunkett, reviewing 1999 DDMAC letter and stating that DDMAC made "exact determination" that materials addressed by the letter were "false, misleading, and/or lacking in fair balance and in violation of the law").

The DDMAC letters do not fall within the narrow public records and reports hearsay exception, which permits admission of "[r]ecords, reports, statements, or data compilations, in any form, of public offices or agencies, setting forth . . . matters observed pursuant to duty imposed by law as to which matters there was a duty to report . . . *provided, however,* that investigative notes involving opinions, judgments, or conclusions are not admissible." *See* Rule 803(8), SCRE. Records or reports that contain "opinions, judgments, or conclusions," are ineligible for the exception and, therefore, remain inadmissible hearsay. *Id.*; *State v. Morris*, 376 S.C. 189, 207, 656 S.E.2d 359, 368-69 (2008). The public records and reports exception does not apply to the DDMAC letters because they contain the authors' "opinions, judgments, and conclusions." Rule 803(8); *see also* Trial Ex. P1027 (1994 DDMAC letter, containing author's conclusion that some proposed promotional materials are "misleading"); Trial Ex. P200 (1999 DDMAC letter, containing author's conclusions that various promotional materials relating to purported geriatric campaign were "false, misleading, and/or lacking in fair balance, and in violation of the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder"); Trial Ex. P232 (2004 DDMAC letter, containing author's legal conclusion that November 2003 mailing is "false or misleading in violation of Sections 502(a) and 201(n) of the [FDCA]" and his opinions that the mailing "fails to communicate" certain safety information and "minimizes risks of

Risperdal" and that the eight peer-reviewed, epidemiological studies cited in the mailing "do not represent the weight of the pertinent scientific evidence").

### c. The Probative Value Of The DDMAC Letters Was Substantially Outweighed By The Danger Of Unfair Prejudice

Admission of the DDMAC letters also was erroneous because any probative value of the letters was substantially outweighed by the danger of unfair prejudice. Rule 403, SCRE; *Jamison v. Ford Motor Co.*, 373 S.C. 248, 269, 644 S.E.2d 755, 766 (Ct. App. 2007), *reh'g denied* (May 17, 2007), *cert. granted* (July 10, 2008), *cert. dismissed*, 385 S.C. 238, 683 S.E.2d 803 (2009) (affirming trial court's decision to exclude evidence where prejudice outweighed any probative value).

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As Janssen has explained repeatedly, the FDA regulations governing prescription drug promotion attach a particular meaning to the phrases "false," "misleading," and "lacking in fair balance." *See, e.g.*, 21 U.S.C. §§ 321(n), 352(a); 21 C.F.R. §§ 201.1 *et seq.*, 202.1 *et seq.* Nonetheless, the State repeatedly and consistently showed the "false and misleading" language to the jury and asked witnesses if the letters said Janssen's materials were "false" or "misleading." *See, e.g.*, Trial Tr. vol. IV, 702:22-703:6, Mar. 10, 2011 (testimony of Dr. Plunkett agreeing that in 1994 DDMAC letter, FDA said the "excellent safety profile claim" is "misleading"); Trial Tr. vol. V, 1098:23-1100:12, Mar. 11, 2011 (testimony of Dr. Plunkett reviewing 1999 DDMAC letter and stating that DDMAC made "exact determination" that materials addressed by the letter were "false, misleading, and/or lacking in fair balance and in violation of the law"); *id.* at 1156:23-1157:7, 1157:25-1158:19 (testimony of Janssen sales representative, who had never seen 2004 DDMAC letter, reading "false and misleading" language of letter to jury at request of counsel for the State).

The repeated use of the DDMAC letters at trial conveyed the appearance of presumptive wrongdoing under SCUTPA and surely confused the jury about the applicable

standards of liability, resulting in severe prejudice to Janssen. This prejudice was compounded by the Court's charge that the jury's verdict could be based solely on "immoral, unethical, or oppressive" conduct, Trial Tr. vol. XII, 2815:11-15, Mar. 22, 2011, and the State's opening and closing statements encouraging the jury to punish Janssen for "break[ing] the rules" or "breaking the law, and not abiding by the rules," Trial Tr. vol. II, 193:17-20, Mar. 8, 2011; Trial Tr. vol. XI, 2728:21-22, Mar. 21, 2011. The Court's narrow – and belated – instruction at the end of trial that the State's case was not an action brought under or to enforce any federal laws and regulations did nothing to cure this prejudice.

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**d. The 1994 DDMAC Letter And 1999 DDMAC Letter Were Not Admissible To Show Janssen's Conduct Was Capable Of Repetition**

The 1994 DDMAC letter and 1999 DDMAC letter also were not relevant to show that Janssen's conduct related to the November 2003 mailing was capable of "repetition," which the State had to prove. *See* slip op. at 4 (Feb. 25, 2011). In *Burbach v. Investors Management Corp. International*, 326 S.C. 492, 484 S.E.2d 119 (Ct. App. 1997), the South Carolina Court of Appeals set forth the factors that trial courts are to consider when "determining the admissibility of prior similar conduct under [SC]UTPA claims":

(a) the length of time between each of the past incidents, and the incident under consideration;

(b) the degree of similarity between the facts of the previous incidences [sic] and the incident under consideration;

(c) the degree of similarity between the conduct of the defendant in each of the incidents;

(d) the degree of similarity between the advantage foreseeably obtained under the facts of each prior incident by the unfair conduct in each case;

(e) the degree of similarity of harm to others in each incident; and

(f) the number of prior incidents as compared with the relative number of prior opportunities to conduct the unfair conduct.

*Id.* at 498 n.3, 484 S.E.2d at 122 n.3.

An analysis of these factors shows that neither the 1994 DDMAC letter nor the 1999 DDMAC letter was admissible to show repetition. The November 2003 mailing discussed the associations between the use of various atypical antipsychotics and diabetes-related conditions, whereas the 1994 DDMAC letter addressed proposed introductory promotional materials and the 1999 DDMAC letter addressed a purported geriatric campaign. Neither the 1994 DDMAC letter or the 1999 DDMAC letter mentioned diabetes, hyperglycemia, or weight gain. Equally important, the November 2003 mailing was sent more than nine years after the 1994 DDMAC letter and nearly five years after the 1999 DDMAC letter.

### 3. The Court Erred In Allowing The Introduction Of All Manner Of Evidence That Was Purportedly Relevant Only To The Issue Of "Willfulness"

The jury had to decide two separate questions in order to render a verdict against Janssen: (1) whether Janssen's conduct violated S.C. Code Ann. § 39-5-20, and if so, (2) whether Janssen acted "willfully." *See* slip op. at 4 (Feb. 25, 2011). South Carolina law provides that when evaluating the second question – whether a defendant has engaged in willful conduct sufficient to constitute a SCUTPA violation – "courts consider only the actions at the time of the transaction in question." 28 S.C. Jur. Unfair Trade Practices Act, Section 10 (citing *Ward*, 304 S.C. at 152, 403 S.E.2d at 310). Despite this temporal limitation, the Court allowed virtually unlimited evidence and testimony that purportedly went to the issue – and *only* to the issue – of "willfulness." *See, e.g.*, Trial Tr. vol. I, 87:3-5, Mar. 7, 2011 (Court: "I'm not going to allow it, but I will allow it on the issue of willfulness in terms of internal documents that you referenced."). Over Janssen's standing objections, *see, e.g.*, Trial Tr. vol. II, 150:4-151:7 (Mar. 8, 2011), the Court allowed the introduction of multiple categories of evidence as to this issue, including the 1994 and 1999 DDMAC letters discussed above and evidence relating to: (1) the number of Risperdal prescriptions in

South Carolina from 1994 to 2007[4]; (2) Defendants' sales, revenues, profits, and business plans[5]; (3) e-mails sent by Dr. Reines, the former vice president of one of Janssen's sister companies, who had no personal involvement in any of the matters at issue;[6] (4) alleged off-label marketing and promotion and other allegedly improper marketing and promotion of Risperdal[7]; and (5) alleged nondisclosures to the FDA.[8]

The admission of all of this evidence solely as to the issue of willfulness, and without regard to the temporal limitation governing its admissibility, resulted in severe prejudice to Janssen. Moreover, given the voluminous documents and testimony the Court allowed as to this issue, the jury simply could not have disregarded them when initially determining whether Janssen engaged in unfair or deceptive acts.

These categories of evidence were also inadmissible for additional, independent reasons:

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[4] Evidence in this category was presented through the testimony of Dr. David Patterson and exhibits P2670, P2671, and P2672. Dr. Patterson's testimony was also the subject of a separate motion, Defendants' Motion to Strike Plaintiff's Witness, W. David Patterson, Ph.D., with Incorporated Memorandum. The Court, however, permitted Dr. Patterson to testify. Trial Tr. vol. V, 1132:15-21, Mar. 11, 2011, Trial Tr. vol. VI, 1287:1-1288:1, Mar. 14, 2011.

[5] Evidence in this category was presented through the following trial exhibits and related testimony: P77, P415, P416, P435, P815, and P1105 (sales and/or revenues); P1035, P1078, P1264, P1299, P1321, P1552, and P2594 (profits); and P1670, P1681, P2587, P2591, P2603, P2618, P2626, P2632, and P2651 (business plans).

[6] Evidence in this category includes the following trial exhibits and related testimony: P462, P477, P1061, P2363, P2364, P2613, P2614, P2615, and P2677.

[7] Evidence in this category includes the following trial exhibits and related testimony: P8, P28, P108, P161, P200, P206, P228, P232, P254, P307, P316, P357, P387, P388, P436, P438, P814, P825, P826, P1027, P1038, P1075, P1273, P1294, P1654, P1662, P1700, P1703, P1712, P1731, P1734, P1739, P2602, P2649, P2673, P2676, and P2717.

[8] Evidence related to this category includes the following trial exhibits and related testimony: P145, P146, P151, P152, P153, P164, P165, P166, P167, P170, P172, P208, P273, P427, P442, P1728, P1735, P1741, P2628, P2653, and P2682.

**Number of prescriptions.** The number of Risperdal prescriptions filled in the State of South Carolina, if relevant at all, is relevant only in determining the amount of civil penalties that should be awarded, which is an issue for this Court and was not an issue for the jury.[9] *See* S.C. Code Ann. § 39-5-110(a); slip op. at 4 (Feb. 25, 2011). Allowing the jury to consider this irrelevant evidence likely led to confusion of the issues, and in any event, was severely prejudicial to Janssen.

**Evidence of Defendants' profits, sales, and revenues.** Evidence as to the net worth of a defendant is relevant only to an award of punitive damages, which was *not* at issue in this case. *See Branham v. Ford Motor Co.*, 390 S.C. 203, 239-40, 701 S.E.2d 5, 24-25 (2010). And even if evidence of net worth would have been admissible, information related to income, sales, and revenues is not appropriate under any circumstances – even when punitive damages may be awarded – to avoid constitutional concerns. *Id.*

**Reines E-mails.** In the e-mails introduced by the State, Dr. Reines never questioned the scientific accuracy or the truthfulness of the statements in the November 2003 mailing. But he did express his personal view – using dramatic and colorful language – that the November 2003 mailing was not well-handled, as a matter of Janssen's relationship and interaction with its primary federal regulator, the FDA. Clearly the State introduced these documents solely due to their inflammatory language, not because the e-mails provided relevant evidence as to the issues to be decided by the jury. *See, e.g., In re Boston Scientific Corp. Sec. Litig.*, 708 F. Supp. 2d at 126 n.15 (noting that "Monday morning remorse, such as that expressed in [an individual's] email, and the regret that [Defendants] had not done more earlier, does not establish - or event suggest - that the

[9] As will be explained during the penalty phase, the number of prescriptions will not be relevant even to penalties, because the FDA-approved Risperdal package insert was not distributed when prescriptions were filled by pharmacies.

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Defendants had knowledge or acted in reckless disregard of a meaningful prospect of recall"). The use of such evidence in this fashion constitutes the classic circumstances under which Rule of Evidence 403 is implicated.

### 4. The Court Erred In Excluding Categories Of Evidence Relevant To The Elements Of The State's SCUTPA Claim

#### a. Post-2004 Evidence Regarding The Diabetes-Related Risks And Side Effects Of Risperdal And Other Atypical Antipsychotics

At the beginning of trial, the State announced for the first time that it was limiting its claim regarding weight gain and diabetes warnings in the Risperdal package insert to the time period between 1994 and 2004. Trial Tr. vol. I, 43:3-61:20, Mar. 7, 2011. The Court then excluded post-2004 evidence relating to weight gain, diabetes, and other metabolic risks associated with Risperdal and other atypical antipsychotics. *See, e.g., id.* at 61:21-62:4.

If Janssen had been allowed to offer post-2004 evidence related to weight gain, diabetes, and other metabolic risks associated with atypical antipsychotics, it would have offered evidence from scientific literature and otherwise demonstrating that the statements in the November 2003 mailing were true. And, it would have offered evidence showing that the FDA has acknowledged there are differences in the diabetes-related side effects associated with the various atypical antipsychotics. As to that specific point, Janssen would have introduced evidence to show that in 2007, the FDA required Eli Lilly & Co., Inc., which manufactures Zyprexa®, to add language to the warning section of its package insert acknowledging the differences in the diabetes-related risks associated with the various atypical antipsychotics. *See, e.g.*, Proposed Trial Ex. D4011 at 8 (2009 Zyprexa Package Insert) ("While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and

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olanzapine appears to have a greater association than some other atypical antipsychotics."). Janssen also would have introduced evidence to show that in 2010, the FDA required Sunovion Pharmaceuticals Inc., which manufactures Latuda®, to add language to the same section of its package insert that also acknowledged these differences. *See, e.g.*, Proposed Trial Ex. D6367 at 5 (2010 Latuda Package Insert) ("While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile."). This evidence would have gone directly to whether the statements in the November 2003 mailing – including the statement that Risperdal has less diabetes-related risk than some other atypical antipsychotics – were true and would have mitigated, if not negated, the impact of the April 2004 DDMAC letter.

The exclusion of post-2004 evidence regarding diabetes-related side effects was also erroneous because the State presented evidence that placed it directly at issue. In particular, the State presented testimony and evidence designed to create the impression that there is no difference between Risperdal and Zyprexa regarding weight gain. For example, on multiple occasions the State introduced evidence to support its implication that the FDA has always – including to this day – viewed all atypical antipsychotics as presenting equal diabetes-related risks. *See, e.g.*, Trial Tr. vol. IV, 761:22-25, Mar. 10, 2011 (testimony of Dr Plunkett); Trial Tr. vol. III, 488:22-489:4, Mar. 9, 2011 (testimony of Dr. Wirshing); Trial Tr. vol. VII, 1634:24-1635:5, Mar. 15, 2011 (questioning of Dr. Mahmoud on cross-examination).

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**b. <u>The Testimony Of Dr. Eugene Barrett</u>**

The testimony presented at trial showed that, in November 2003, a Consensus Panel comprised of medical experts from various disciplines met to discuss the diabetes-related side effects associated with the various atypical antipsychotics. The panel reached an agreement regarding the relative incidences of these side effects during the meeting and

then published its findings in February 2004. As part of its findings, the panel published a chart showing that Zyprexa had a higher incidence of weight gain than Risperdal did. *See* Trial Tr. vol. IV, 874:19-875:23, 950:22-955:5, Mar. 10, 2011; *see also* Trial Ex. P1750. During trial, the State elicited testimony to create the impression that if two purported "studies" – the incomplete ERI and the failed RIS-USA-113 – had been submitted to the Consensus Panel, it would have affected the conclusions of the Consensus Statement.

To rebut this, Janssen attempted to call Dr. Eugene Barrett, who was chair of the Consensus Panel and a representative of the American Psychiatric Association. If Dr. Barrett had been allowed to testify, he would have explained, from his perspective, why ERI and RIS-USA-113 would not have affected the conclusions reached in the Consensus Statement. *See* Trial Tr. vol. IX, 2227:1-2229:20, Mar. 17, 2011. The Court erred in excluding this evidence, as it was in direct rebuttal to the State's late-developed theory on this issue.

### c. Evidence Relating To Whether The November 2003 Mailing And The Risperdal Package Insert Tended To Deceive The Relevant Audience

Under South Carolina law, the test for SCUTPA liability is whether the challenged statement or act "has a tendency to deceive," and whether an act has a "tendency to deceive" or is "likely to deceive" "depends upon the surrounding facts and the impact of the transaction on the marketplace." *deBondt*, 342 S.C. at 269, 536 S.E.2d at 407. In this case, the relevant "marketplace" or audience necessarily is South Carolina physicians because: (1) Risperdal can only be obtained by prescription; (2) the November 2003 mailing was sent to physicians; and (3) the package insert is written for physicians.

The Court erroneously excluded evidence from and about this relevant audience, including: (1) testimony and documents relating to Dr. William Wecker's statistical survey of South Carolina physicians; (2) the testimony of twenty prescribing physicians who were

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deposed as a part of Dr. Wecker's statistical survey; and (3) the testimony of Dr. Gerard Jebaily. The testimony of Dr. Wecker, the twenty prescribing physicians, and Dr. Jebaily would have shown that South Carolina prescribing physicians have long been aware of the risks associated with Risperdal and with other antipsychotics, including the diabetes-related risks and the risks of hyperprolactinemia. It would have shown that the November 2003 mailing did not mislead any of the members of its intended audience. It would have shown that the package insert was not, in fact, misleading. And it would have rebutted the allegations of misleading and/or off-label promotion. The evidence was therefore directly probative of whether Janssen's November 2003 mailing and the Risperdal package insert had a "tendency to deceive," and it was error for the Court to exclude this evidence.[10]

**d. Evidence Regarding The State's SCORxE Program**

At trial, the State offered the testimony of James Assey, a pharmacist, former Division Director for Pharmacy Services of the South Carolina Department of Health and Human Services ("DHHS"), and current consultant for DHHS. One of the areas Mr. Assey testified to was the State's SCORxE program. Trial Tr. vol. VI, 1216:21-1219:18, Mar. 14, 2011. Mr. Assey described the SCORxE program as a "pilot" project in a "handful" of counties where pharmacists visit certain physicians to discuss with them literature regarding prescription medicines. *Id.*

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[10] Dr. Wecker's testimony was excluded, at least in part, because the Court questioned Dr. Wecker's methodology. There was no basis, in the record, for a determination that the methodology was flawed, and no reason to exclude the survey and survey-related testimony. Similarly, the Court excluded Dr. Jebaily's testimony, in part, because it concluded that he could not competently testify about other physicians' prescribing decisions. But Dr. Jebaily is knowledgeable about such matters – e.g., he has taught residents and other physicians for years. *See* Defs.' Offer of Proof for the Expert Test. of Gerard C. Jebaily, M.D., M.H.S.A., C.M.D.

Despite the fact that the State elicited testimony from its own witness regarding this program, the Court erroneously excluded testimony from Janssen's proposed witnesses: Sophie Robert, a clinical pharmacy consultant for the SCORxE Academic Detailing Program, and Sarah Ball, Program Director for the SCORxE program since 2007. *See* Trial Tr. vol. IX, 2195:6-2201:14-15, Mar. 17, 2011; *see also* Defs.' Offers of Proof for the Testimony of Sophie Robert and Sarah Ball. If the Court had allowed the testimony of Ms. Robert and Ms. Ball, Janssen would have presented rebuttal evidence regarding the State's SCORxE program. Ms. Robert and Ms. Ball would have testified in detail about the purpose and operations of this ongoing program, which is an educational outreach program that presents healthcare providers with balanced, evidence-based information to assist with best practices and best prescription decisions. They also would have testified that SCORxE provides information regarding the side effects associated with atypical antipsychotics. Ms. Robert would have further testified that around early 2000, she became aware of the perceived relationship between atypical antipsychotics and diabetes-related side effects, and that by 2004, she was well aware of these concerns.

Not only was this testimony admissible in response to the evidence introduced by the State, it was also admissible because it was relevant to whether the November 2003 mailing and the Risperdal package insert had a tendency to deceive South Carolina physicians. Finally, it was relevant to Janssen's statute of limitations defense, as it was probative of when the State knew, or should have known, about the side effects associated with Risperdal and other atypical antipsychotics.

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e. **Additional Testimony Of Dr. William Wecker**

The Court made several other erroneous rulings related to the testimony of Dr. Wecker that led to the impermissible exclusion of almost all of Dr. Wecker's proposed testimony. In addition to the erroneous conclusion that Dr. Wecker's proposed testimony

regarding his statistical survey of South Carolina prescribing physicians was not admissible, the Court also erroneously excluded Dr. Wecker's testimony about his statistical analyses of the South Carolina Medicaid and State Health Plan claims data and his evaluation of the incidence of side effects the State alleged to be associated with Risperdal in three separate patient groups. The Court also erred in excluding Dr. Wecker's testimony as it related to his review and analysis of the statistical conclusions contained in the eight epidemiological studies Janssen cited in the November 2003 mailing. Both of these areas of testimony should have been allowed because they were directly relevant to the issues of whether the statements in the November 2003 mailing were true and whether the November 2003 mailing adversely impacted the public interest.[11]

**f. Certain Testimony Of Sheldon Bradshaw**

The Court erroneously granted the State's request to strike certain answers of Mr. Bradshaw and instructed the jury to disregard the answers because they "violate[d] a previous ruling." *See* Trial Tr. vol. IX, 2050:12-2051:14, 2058:2-2060:1, Mar. 17, 2001 (Mr. Bradshaw's testimony); *id.* at 2060:12-2076:10 (Court's ruling). The Court's ruling as to this testimony was based on the erroneous representation by the State's counsel that the federal regulations governing a pharmaceutical manufacturer's duty to update its product label did not require a "causal" association between use of the medicine and the specific risk at issue and that the word "causal" did not appear in any version of the regulation until 2008. *Id.* at 2065:11-2066:3, 2069:21-2070:4.

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[11] Dr. Wecker, an expert statistician, is competent to testify as to each of these matters. *See* Defs.' Offer of Proof for the Expert Testimony of Dr. William E. Wecker. Although the State took issue with his methodology as to the "side effects" analysis, the State presented no competent or persuasive evidence that his methodology was in any way flawed.

The State had presented expert testimony that the Risperdal package insert was inadequate, in some respects, through at least 2007. *See, e.g.*, Trial Tr. vol. III, 624:20-626:13, Mar. 9, 2011. Mr. Bradshaw's stricken testimony directly rebutted the State's claim that, because of Janssen's knowledge of certain risks associated with the use of Risperdal, Janssen had a duty under the federal regulations to update the Risperdal package insert and failed to do so.

## I. The Court Erred In Allowing The State To Make Arguments During Opening And Closing Statements That Janssen Should Be Found Liable Solely Because It Is A Large, Profitable, And Out-Of-State Corporation

As previously discussed, at the beginning of trial the Court ruled that certain categories of evidence, including evidence relating to Risperdal sales volume and Defendants' revenues was admissible because it went to the question of willfulness. *See* Trial Tr. vol. I, 87:3-5, Mar. 7, 2011. Janssen subsequently placed a standing objection to the admissibility of this evidence on the record. *See* Trial Tr. vol. II, 150:19-20, Mar. 8, 2011.

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Counsel for the State then argued during opening statements that the jury should find Defendants liable because they are large and profitable corporations. *See* Trial Tr. vol. II, 193:21-25, Mar. 8, 2011 ("This case is about corporate responsibility, being a good corporate citizen, not going out and trying to break the rules and lie to people and deceive people all in pursuit of the almighty dollar."); *id.* at 194:7-9 ("This case is about a very large company that developed a little pill that brought them huge, huge profits."); *id.* at 208:7-20 ("And at the time they were writing this [November 2003] letter, they were around $3 billion a year. But it wasn't just what they had made, it was what they were planning to make."); *id.* at 237:6-7 ("And it is about Janssen's putting profits over safety.").

Counsel for the State also argued during closing statements that a message had to be sent to Defendants – not because Defendants violated SCUTPA, but because

Defendants were big, out-of-state corporations and because corporations have questionable "ethics." Specific statements included:

- "Little pill, big profits. Little pill, big profits." Trial Tr. vol. XI, 2637:1-2, Mar. 21, 2011.
- "This e-mail, ladies and gentlemen, gives you a direct window to the soul of these two companies. It's all about the money." *Id.* at 2657:25-2658:2.
- "Sometimes it was hard to listen to everything, and so, you know, we started out this case with, Thou shall not lie. Maybe we should have said, Don't sell your soul for the almighty dollar. And Mr. Pugh wants to talk about the, Whose bread I eat, whose song I sing. I think that's pretty instructive." *Id.* at 2729:3-10.
- "You're asked to bring your common sense and experience into the case. Corporate ethics is an issue that's current. It's affected our nation and South Carolina for the last three or four years. That's what we're talking about in this case. It's not science; it's corporate ethics." *Id.* at 2729:17-22.
- "Now, when you listen to the charge by Judge Couch at the end of this case, see if his charge matches up with this side, the science. Or see if his charge matches up against bad behavior, misrepresentation, false claims, breaking the law, and not abiding by the rules. Profits over safety." *Id.* at 2728:17-22.
- It's like the Bible study David and Goliath. For four years I have thought about this case, and I've thought about them as Goliath, and our little trial team with the Attorney General from the great State of South Carolina being David." *Id.* at 2730:1-5.
- "I would suggest to you this, and I do this respectfully. He whose bread I eat, whose song I sing." *Id.* at 2735:8-11.
- "Here is the deal. Here is the message: They wanted to expand their market and they wanted doctors – not psychiatrists – pediatricians, geriatric doctors, internists, to prescribe the drug Risperdal for indications that weren't approved by the FDA. And if they did that, it would become this billions and billions of dollars of revenue. And they had to do it within a certain period of time because the patent ran out, and when the patent ran out, everybody could make it. It had a shelf life." *Id.* at 2737:3-15.
- "The end shouldn't justify the means in this case." *Id.* at 2738:2-3.

As the Supreme Court of South Carolina has stated, "It is improper for counsel to make a 'closing argument to the jury . . . calculated to arouse passion or prejudice.'" *Branham*, 390 S.C. at 234, 701 S.E.2d at 21 (quoting *Gathers v. Harris Teeter*

*Supermarket, Inc.*, 282 S.C. 220, 231, 317 S.E.2d 748, 755 (Ct. App. 1984)). In fact, this alone – inviting the jury to base a verdict on passion rather than reason – is independent grounds for a new trial. *See id.* at 235, 701 S.E.2d at 22 ("The closing argument invited the jury to base its verdict on passion rather than reason. The closing argument denied Ford a fair trial.").

### J. Errors In The Jury Instructions And The Verdict Sheet Render The Jury's Verdict Uninterpretable

#### 1. This Court's Failure To Charge The Jury As To Each Of The Necessary Elements Of The State's Claim Confused The Jury And Prejudiced Janssen

This Court's instruction on the law was confusing to the jury and prejudicial to Janssen. First, the charge did not enumerate the precise claims of the State. As noted, the State's claim was based only on: (1) one paragraph of the November 2003 mailing; and (2) an assertion that the FDA-approved Risperdal package insert was "inadequate." After weeks of testimony about topics not relevant to the initial question to be answered by the jury – if relevant at all – it was necessary to instruct the jury as to what exactly the State alleged gave rise to its claim that Janssen violated SCUTPA. *See, e.g.*, Trial Tr. vol. XII, 2782:19-25, Mar. 22, 2011.

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Second, the instruction combined – or eliminated – numerous separate and distinct elements of the State's claim. For example, Janssen asked that this Court charge the jury as to the specific elements of the SCUTPA claim and that it charge separately the elements of "unfair" and "deceptive" acts and practices. *See, e.g.*, Trial Tr. vol. XII, 2779:17-23, Mar. 22, 2011. Janssen also asked that the Court provide a full charge on willfulness, *id.* at 2781:13-21, 2786:16-20, including that an action or statement is not willful unless there is a statute in South Carolina that affirmatively prohibits it or if it is the ordinary and normal practice in the industry, *Haley Nursery Co.*, 298 S.C. at 520, 381 S.E.2d at 906. The

Court's refusal to give these specific charges of what the State was required to prove made particularly prejudicial the Court's instruction as to what the state did not have to prove with respect to the elements of fraud. Trial Tr. vol. XII, 2781:5-11, Mar. 22, 2011. The jury specifically noted its confusion with the charge by asking for clarification on more than one occasion. *Id.* at 2800:13-2802:16, 2804:23-2818:19.

In addition, Janssen requested that the Court specifically charge, pursuant to *deBondt v. Carlton Motorcars, Inc.*, 342 S.C. 254, 269, 536 S.E.2d 399, 407 (Ct. App. 2000) and the Federal Trade Commission's Policy Statement on Deception, that the intended audience of the statement must be considered. *See, e.g.*, Trial Tr. vol. XII, 2779:25-2780:5, Mar. 22, 2011. Consistent with *Ruberg v. Brown*, 50 S.C. 397, 27 S.E. 873 (1897), Janssen requested a charge that opinions are not actionable under the law of South Carolina. Trial Tr. vol. XII, 2780:19-22, Mar. 22, 2011. Janssen also requested that the Court charge the jury that South Carolina law, *Bruette v. Stokes Kia, Isuzu, Subaru, Inc.*, No. 2001-CP-10-1800, slip op. at 9, 2002 WL 34128304 (S.C. Ct. Com. Pl. Nov. 6, 2002), would not allow the State to recover if the jury found that the recipient of the statements had an equal and ample opportunity to ascertain the truth but failed to exercise proper diligence to do so. See, e.g., Trial Tr. vol. XII, 2782:4-11, Mar, 22, 2011. Finally, Janssen requested that this Court charge the jury: (1) that expert opinions must be based on facts, *id.* at 2777:11-15; (2) that attorneys' questions are not evidence, *id.* at 2775:21-25; (3) that the State's claim may be barred by the regulated activity exemption, *id.* at 2783:6-18; and (4) on the actual CBE regulations, including a corrective instruction as to the testimony of Defendants' regulatory expert Sheldon Bradshaw, *id.* at 2785:6-16, 2785:19-2786:7. Failure to give these instructions also confused the jury and prejudiced Janssen.

Third, the charge did not make clear that willfulness was the only purpose for which the numerous FDA references were admitted, i.e., warning letters, alleged nondisclosures,

alleged off-label marketing or promotion, and promotional material. While this Court and the State acknowledged the limited purpose for which this "evidence" was admitted, it so pervaded the State's presentation that no reasonable jury could be expected, without some clarification, to separate the allegations of FDA misconduct from the evidence (if any) of an actual violation of SCUTPA. The Court's charge that "[this is] not an action that has been brought under federal law or federal regulations, and this is not an effort to enforce any federal laws or regulations," *Id.* at 2764:2-5, was meaningless without any context as to how the FDA "evidence" should have been used. In other words, any reasonable juror would be left to ask herself why she listened to weeks of testimony if it had no bearing on Janssen's liability. The instruction did nothing to protect Janssen from what ultimately happened: being found liable for violating SCUTPA when the only evidence of "deception" introduced by the State related to FDA letters. At a minimum, the Court should have instructed the jury specifically that a violation of federal law or FDA regulations could not be the basis for a violation of SCUTPA. *See, e.g., id.* at 2778:16-23, 2783:21-2784:8, 2784:12-19.

Fourth, the charge did not apprise the jury of the First Amendment issues that should have guided its deliberations, including the fact that Janssen was entitled to express its disagreement with the FDA. *See, e.g., id.* at 2781:23-2782:3, 2784:20-2785:5. As explained in more detail above, because the State sought to punish Defendants for speech on a matter of public concern, the First Amendment required the State to prove that Janssen's speech was false and to present clear and convincing evidence of actual malice.

The jury was not properly instructed as to the matters at issue and the limited evidence it was entitled to consider to determine whether SCUTPA was violated by Janssen. Given the complexity of the action, for the jury to have properly understood the limited issues it was deciding, Defendants' proposed jury instructions should have been used by the Court. *See* Defendants' Proposed Jury Instructions.

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### 2. The Verdict Sheet Was Not Specific Enough To Ensure That The Jury's Verdict Was Supported By The Evidence

A verdict sheet must be specific enough that it permits the court and the parties to ensure that the verdict is supported by the evidence. In *Branham v. Ford Motor Co.*, the trial court refused Ford Motor Co.'s request for special interrogatories and, instead, asked the jury to apportion liability among Ford and its alleged joint tortfeasor because "of a need to ensure that any punitive damage award was supported by a negligence cause of action, and not the strict liability claim." 390 S.C. 203, 235-36, 701 S.E.2d 5, 22-23 (2010). The Supreme Court of South Carolina held that the verdict form was improper. *Id.* at 236, 701 S.E.2d at 23. It explained, "A proper verdict form would have avoided the confusion caused by having the jury apportion blame between jointly and severally liable defendants. More to the point, Ford's requested special verdict form would have avoided the very real risk that the jury (unaware of joint and several liability principles) would take the cue from the apportionment question and inflate the actual damage award to ensure [the plaintiff] received a full recovery from the one deep-pocket defendant. The actual damage award causes genuine concern as to the effect on the jury of the improper verdict form." *Id.* at 237, 701 S.E.2d at 23.

Here, the verdict sheet prejudiced Janssen because it was not sufficiently specific. *See, e.g.*, Trial Tr. vol. XII, 2789:9-23, Mar. 22, 2011. The verdict sheet did not require that the jury find each of the separate elements of the State's SCUTPA claim. Janssen is entitled to judgment if the State fails on any single element of its claim, *Guffey v. Columbia/Colleton Reg'l Hosp., Inc.*, 364 S.C. 158, 163, 612 S.E.2d 695, 697 (2005). The verdict sheet, which asked only whether Janssen committed an "unfair" or "deceptive" practice in violation of SCUTPA, when considered in light of the charge, which did not

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sufficiently identify the specific elements of the State's claims, prejudiced Janssen by confusing the jury as to exactly what elements the State was required to prove.

Similarly, the verdict sheet did not require that the jury separately consider whether Janssen's conduct was "unfair" or "deceptive," although claims for "unfair" and "deceptive" trade practices have separate and distinct elements. Given the Court's charge and combined verdict form, it is entirely possible to conclude that the jury's entire verdict against Janssen is based on some speculative public policy concern, e.g., a concern about "corporate ethics." But, as noted above, a violation of public policy alone is not a basis upon which the jury could find that the November 2003 mailing or the Risperdal package insert were an unfair trade practice. 15 U.S.C.A. § 45(n); Federal Trade Commission Policy Statement on Unfairness (1980). This possibility alone renders the jury's verdict hopelessly uninterpretable. Finally, for the reasons already stated, not including the First Amendment considerations in the verdict sheet – e.g., questions about "opinions" and "actual malice" – also prejudiced Janssen. Thus, the failure to use the verdict sheet proffered by Janssen, or a similar verdict sheet, and the submission of an improper verdict sheet to the jury also requires that the jury verdict be set aside.

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## IV. CONCLUSION

For the foregoing reasons, Janssen respectfully requests that this Court enter judgment in favor of Janssen and against the State notwithstanding the jury's verdict. In the alternative, Janssen respectfully requests that this Court enter an Order granting a new trial.


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April 1, 2011.


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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA ex. rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>PLAINTIFF,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, LP and JOHNSON & JOHNSON, INC.,<br><br>DEFENDANTS. | ) IN THE COURT OF COMMON PLEAS<br>)<br>)FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>Civil Action No.: 2007-CP-42-1438<br><br>PLAINTIFF'S PRE-TRIAL BRIEF TO THE COURT<br><br>(CIVIL PENALTY PHASE) |

The Plaintiff State of South Carolina, by and through its undersigned counsel of record hereby submits this, its Pre-Trial Brief, to the court in advance of the scheduled hearing on the civil penalty phase of the trial of this case. This pre-trial brief is being submitted to the court solely for its use pursuant to Rule 16(c), SCRCP.

**1. A concise, non-argumentative statement of the facts of the case.**

On March 22, 2011, a Spartanburg County jury rendered a verdict in favor of the Plaintiff State of South Carolina and against the Defendant Ortho-McNeil-Janssen (f/k/a Janssen Pharmaceutical, Inc. and/or Janssen, LP) in the liability phase of this proceeding. More specifically, the jury found that the Defendant Janssen violated the South Carolina Unfair Trade Practices Act ("SCUTPA") by engaging in unfair or deceptive acts or practices in the conduct of its trade or commerce with respect to the "Dear Doctor Letter" of November 10, 2003 and that such violations were willful in nature. The jury likewise found that the Defendant violated SCUTPA in connection with its label (also known as

the "product label," "package insert," or "prescribing information") and that these violations were also willful in nature. As a result, this court has scheduled the hearing for Monday, April 18, 2011 for the purpose of determining the number of violations involved and to assign a civil penalty to such violations in an amount deemed appropriate by this court up to a statutory maximum of $5,000 per violation.

**2. Objective statement of facts in controversy.**

The dispute before the court in the upcoming hearing will be the number of violations of SCUTPA arising out of Defendant Janssen's use of its label(s) in the State of South Carolina together with the publication of the November 10, 2003 "Dear Doctor Letter" to South Carolina prescribers as well as the severity of the civil penalties which should be imposed. Plaintiff has attached a summary outline of its intended offer of proof as to the relevant acts and transactions. This offer of proof is attached as Exhibit A. The court's attention is drawn to the fact that the Plaintiff will provide both the total number of any such relevant transactions as well as a breakdown of those transactions for particular periods of time, which relate to the Defendant Janssen's state of knowledge or the egregiousness of conduct.

**3. The legal issues involved.**

This proceeding is governed by the applicable provisions of the South Carolina Unfair Trade Practices Act, specifically including Section 39-5-110. In addition, please see the collected cases attached as Exhibit B for factors and considerations relevant to the imposition of the civil penalties.

**4. A listing of exhibits and listing of witnesses who may be called.**

(a) Exhibits

(1) Plaintiff will refer to numerous trial exhibits and testimony already in evidence from the liability phase of the trial.

(2) Plaintiff will offer evidence of transactions (prescriptions, sales calls, sample boxes distributed, etc.) as computed by Solutions Plus from data provided by Defendant as well as CMS prescription data maintained by the South Carolina Attorney General's office.

(3) Plaintiff will offer public records as to the number of prescribers in the State of South Carolina, Defendant's required financial reports, and Defendant's prior bad acts.

(b) Witnesses

(1) J. Woodlock – Solutions Plus, will testify as to the numbers of prescriptions in the State of SC according to IMS Per Doctor Prescription Data given to the State by the Defense via Discovery, the number of sample boxes of Risperdal disseminated in the State of SC as well as the number of times samples were disseminated according to the Sample Distribution Data given to the State by the Defense via Discovery, and will proffer an analysis of the Call Note Data set produced by the Defense which will include the number of instances when Janssen Representatives gave healthcare professionals marketing/ promotional materials/ label materials during a sales call.

(2) Jay Smith – Analyst for the South Carolina Attorney General's Office, may testify as to the numbers of Medicaid prescriptions filled

according to CMS data and reimbursement cost to the state through Medicaid as enumerated in the CMS data.

(3) Dr. David Patterson – Division Director for the South Carolina Office of Research and Statistics may testify regarding the numbers of prescriptions filled under Medicaid and the State Employee Health Insurance Plan as maintained by the State.

**5. Any unusual problems relating to the evidence to be introduced.**

Most of the exhibits to be offered in the upcoming hearing have already been admitted in the trial of this case at the liability phase. With respect to the documents being submitted from publically available sources, the State would request that this court take judicial notice of same and that those exhibits be admitted pursuant to Rules 901 and 902, SCRE, and South Carolina Code of Law Section 19-5-10, Section 19-5-510 and 19-5-610, all as applicable.

**6. Any unusual question or matter which should be brought to the attention to the court.**

None known at this time.

**7. Statement of settlement negotiations were attempted before the date of the pre-trial hearing and status of settlement negotiations.**

Not applicable under these circumstances.

Respectfully submitted,

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April 15, 2011

Attorneys for the State of South Carolina

Spartanburg, South Carolina

# EXHIBIT A

The State of South Carolina takes the position, consistent with the jury verdict in this case, that every time the defendant Janssen's Risperdal product label or November 10, 2003 "Dear Doctor Letter" was published within the State of South Carolina, there occurred a separate and distinct SCUTPA violation. South Carolina contends that the relevant time period for these violations extends from product launch in 1994 until the label was finally modified to include a specific prolactinemia warning at the end of 2006.

**Total numbers of potential violations:**

1. As to the Risperdal label:

| | | |
|---|---|---|
| (a) Distribution of Sample Boxes (1998 – April 23, 2007) | | 497,477 |
| (b) Sales Calls on South Carolina Prescribers | | |
| Sample Drop (1998 – April 23, 2007) | | 63,260 |
| Presentation (PL required) (1994- April 23, 2007) | | 183,144 |
| (c) Prescriptions (tainted): | | |
| OSR Records (Patterson) | | |
| Medicaid (1994-2006) | | 566,619 |
| SHP (1995-2006) | | 53,719 |
| TOTAL | | 620,338 |
| SCAG per CMS (Jay Smith) | | |
| Medicaid (1994 – 1st Quarter 2007) | | 664,565 |
| IMS Prescription Data (J. Woodlock) (2001-2006) | | 514,644 |
| Janssen Interrogatory Response (September 1, 2001 – September 30, 2008) | | 722,433 |

2. As to the November 10, 2003 DDL:

| | |
|---|---|
| Number of letters mailed in South Carolina | 7,194 |
| Number of Licensed SC Healthcare Providers with access to letter on Defendant's website | 26,676 |

Physicians – 12,930
Physician Assistants – 381
Advanced Practice Registered Nurse – 2,376
Pharmacists – 5,256
Pharmacy Technicians – 5,733

Sales calls between November 10, 2003 and July 21, 2004
When letter published (Presentation (PL required)) 36,372

With respect to the severity of penalty called for by Defendant Janssen's conduct, the State of South Carolina takes the position that some of these violations are more egregious than others. This position is based upon the evidence as to the state of Defendant's knowledge at the time as well as its marketing strategies in light of its underlying knowledge.

## EXHIBIT B

**I. FTC case(s) on civil penalty considerations:**

In determining the size of civil penalties, the Court must consider a number of factors including: (1) the good or bad faith of the defendant; (2) the injury to the public; (3) the defendant's ability to pay; (4) the desire to eliminate the benefits derived by a violation; and (5) the necessity of vindicating the authority of the Federal Trade Commission ("FTC"). United States v. Papercraft Corp., 540 F.2d 131, 141 (C.A.3, 1976); United States v. J. B. Williams Company, Inc., 498 F.2d 414, 438 (C.A.2, 1974); Federal Trade Commission v. Consolidated Foods Corp., 396 F.Supp. 1353, 1356-57 (S.D.N.Y.1975); United States v. Swingline, 371 F.Supp. 37, 46 (E.D.N.Y.1974)

U. S. v. Reader's Digest Ass'n, Inc., 494 F. Supp. 770, (D. Del. 1980) aff'd, 662 F.2d 955 (3d Cir. 1981)

**II. SOUTH CAROLINA CASE(S):**

State ex rel. Medlock v. Nest Egg Soc. Today, Inc., 290 S.C. 124, 348 S.E.2d 381 (S.C. Ct. App. 1986)

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG | IN THE COURT OF COMMON PLEAS<br>FOR THE SEVENTH JUDICIAL CIRCUIT |
| STATE OF SOUTH CAROLINA ex rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>Plaintiff,<br><br>v.<br><br>ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA INC., and/or JANSSEN, L.P. and JOHNSON & JOHNSON, INC.,<br><br>Defendants. | Civil Action No. 2007-CP-42-1438<br><br>**JANSSEN'S PENALTY HEARING BRIEF** |

Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. ("Janssen"), by and through its undersigned counsel, hereby submits this Memorandum of Law in opposition to the request of Plaintiff, the State of South Carolina (the "State"), for an award of civil penalties against Janssen.

## I. INTRODUCTION

The imposition of civil penalties is warranted only to deter – to penalize prior conduct to avoid future similar instances. Here, the State acknowledges that, for the entire period of Risperdal's use in South Carolina – more than 17 years – not a single South Carolina resident actually was deceived by any alleged unfair or deceptive conduct, not a single South Carolina resident suffered a personal injury as a result of any alleged unfair or deceptive conduct, and the State incurred not a single dollar of economic loss as a result of any alleged unfair or deceptive conduct. Moreover, one of the two "unfair" or "deceptive" acts of which the State complains, the November 2003 mailing, was a one-time event, more than seven years ago, involving a dispute with an arm of the U.S. Food and Drug

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Administration ("FDA") that was reflected in a "warning letter." The "warning letter" was the only such letter ever sent about Risperdal, the dispute was resolved promptly and cooperatively, and the FDA considered the matter "closed." The other "unfair" or "deceptive" act, the use of an FDA-approved package insert said, by the State, to be "inadequate" in some respects, ended, by the State's own account, four years ago. The FDA itself never took issue with the "adequacy" of the package insert.

There is no need for "deterrence" in this case. The State surely had no fear of actual or imminent harm to the public; it never made any attempt to obtain injunctive relief. Nevertheless, it seems that the State will now ask this Court to impose extraordinarily large civil penalties on Janssen. South Carolina law, however, will not permit the assessment of exceptionally large penalties – or, indeed, any substantial amount of penalties – in circumstances like these. Indeed, such penalties would be unconstitutional – prohibited by the due process and excessive fines clauses of the South Carolina and Federal constitutions. Under both decisional law and constitutional law, punishment, if there is to be any at all, may only be that which is necessary to avoid future similar conduct.

## II. APPLICABLE STANDARDS

Under well-settled "damages" principles, awards based on speculation or conjecture are impermissible:

> While proof, with mathematical certainty, of the amount of loss or damage is not required, in order for damages to be recoverable the evidence should be such as to enable the court or jury to determine the amount thereof with reasonable certainty or accuracy. Neither the existence, causation nor amount of damages can be left to conjecture, guess, or speculation.

*Gauld v. O'Shaugnessy Realty Co.*, 380 S.C. 548, 559, 671 S.E.2d 79, 86 (Ct. App. 2009) (citations omitted). The same principles must apply to awards of civil penalties.

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This Court has discretion to impose a civil penalty amount that is reasonable and appropriate in light of all the facts and circumstances of the case. *See, e.g., State ex rel. McLeod v. C & L Corp.*, 280 S.C. 519, 528, 313 S.E.2d 334, 340 (confirming that penalty within limits "was a matter of the judge's discretion"). SCUTPA, however, imposes an upper limit on the exercise of the Court's discretion – the penalty may not exceed "five thousand dollars per violation." S.C. Code Ann. § 39-5-110(a).

The limited South Carolina law on civil penalties demonstrates that penalty awards are not mere arithmetical calculations. *See State ex rel. Medlock v. Nest Egg Soc'y Today, Inc.*, 290 S.C. 124, 348 S.E.2d 381 (Ct. App. 1986) ("*Nest Egg*") (awarding a civil penalty of $45,000 under SCUTPA – less than $5.00 per violation); *see also Midlands Util., Inc. v. S.C. Dep't of Health & Envtl. Control*, 313 S.C. 210, 212, 437 S.E.2d 120, 121 (Ct. App. 1993) ("[E]ach fine must be analyzed individually to determine if it is appropriate under the circumstances. The assessment of a civil penalty for violation of an environmental statute is committed to the informed discretion of the circuit court; in exercising this discretion, the court should give effect to the major purpose of a civil penalty – deterrence."). When determining a penalty amount, courts must also consider the particular circumstances of the conduct at issue. *See C & L Corp.*, 280 S.C. at 524, 313 S.E.2d at 337 (noting that the penalty imposed ($55,000) was appropriate because: (1) "sales of the lots went forward in plain violation of the law" despite the fact that county officials had advised "on more than one occasion" that the conduct at issue was in violation of an ordinance; and (2) defendant's sales agents brazenly "told prospective buyers whatever they felt the buyers wished to hear in order to conclude a sale").

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## II. ARGUMENT

### A. The State Did Not Disclose Its Penalty Calculations

Early in this litigation, Janssen requested that the State identify the damages it was seeking. *See* Defs.' First Set of Interrogs. No. 92. On December 6, 2007, the State objected to the request as "properly the subject of expert testimony" but stated that it "will supplement its response as necessary." *See* Ex. A, Pl.'s Resp. to Defs.' First Set of Interrogs. No. 92. Although Janssen was entitled to that information, the State has never supplemented its response by providing an itemization or calculation of the monetary relief it is seeking. *See* Explanatory Note to Rule 33(b)(5), SCRCP ("Rule 33(b)(5) amends present Circuit Court Rule 90 to require an 'itemized' statement of all special damages exclusive of pain and suffering."); *see also* Rule 26(e), SCRCP (noting that a party's obligation to supplement interrogatory answers "shall be deemed to continue . . . until the time of trial of the action").

Janssen also requested that the State "[i]dentify the number of Janssen-manufactured Risperdal package inserts which you contend constitute a violation of SCUTPA." Defs.' Sixth Set of Interrogs. No. 4. The State responded that "because this Answer is dependent on certain of Defendants' prescription data which the State has requested in discovery, the State cannot fully respond to this Interrogatory until Defendants have made the requested production." *See* Ex. B, Pl.'s Resp. to Defs.' Sixth Set of Interrogs. No. 4. The State, again, never provided a supplemental response. Yet it now seeks penalties based on the number of package inserts that "violated SCUTPA."

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SCUTPA itself requires that the Attorney General file a separate petition that sets forth the request for penalties. *See* S.C. Code Ann. § 39-5-110(a) ("If a court finds that any person is willfully using or has willfully used a method, act or practice declared unlawful by § 39-5-20, the Attorney General, *upon petition to the court*, may recover on behalf of the

State a civil penalty of not exceeding five thousand dollars per violation." (emphasis added)). The State may argue that its Second Amended Complaint constitutes the required petition. But the Second Amended Complaint merely asks for the maximum "five thousand dollars per violation." That is, it merely asks that the Court impose the maximum allowable amount of penalties per "violation," without providing any information about what penalties, in total, the State would seek or how they would be calculated.

The State has not disclosed the specific amount of civil penalties it seeks in this action. Nor has the State identified the basis for any requested civil penalties. Having failed to comply with its disclosure obligations, the State should not now be permitted to ambush Defendants with an eleventh-hour calculation supposedly "supporting" an eight- or nine-figure penalty award.

B. **There Is No Basis for A Substantial Penalty Award**

No penalty, or no substantial penalty, should be imposed because:

- there is no evidence that the State or its mental health professionals were deceived or misled by the November 2003 mailing or the Risperdal package insert, Trial Tr. vol. XI, 2581:18-2583:3, 2583:17-2584:3, 2584:22-2585:2, Mar. 21, 2011;
- the State does not claim that any South Carolina resident suffered any personal injury, Trial Tr. vol. II, 236:22-24, Mar. 8, 2011; Trial Tr. vol. IX, 1993:10-17, Mar. 17, 2011; Trial Tr. vol. XI, 2728:4-6, Mar. 21, 2011;
- the State has no evidence of any economic loss to South Carolina, Trial Tr. vol. VI, 1308:5-8, Mar. 14, 2011 (no contention that any Risperdal prescription was medically unnecessary);
- the State has no evidence that any South Carolina physician or resident relied, to his or her detriment, on the November 2003 mailing or the Risperdal package insert, Trial Tr. vol. II, 204:14-19, Mar. 8, 2011 (no need to show any reliance);
- the State has no evidence that any South Carolina physician or resident actually was deceived by either the November 2003

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mailing or the Risperdal package insert, Trial Tr. vol. II, 234:12-15, 236:25-237:1, Mar. 8, 2011; Trial Tr. vol. IX, 1993:10-17, Mar. 17, 2011; Trial Tr. vol. XI, 2728:6-7, Mar. 21, 2011;

- the only evidence in the record regarding the impact of Janssen's November 2003 mailing on the South Carolina marketplace is that the marketplace was unaffected, *see, e.g.*, Defs.' Trial Ex. 7337; and

- the only evidence of record shows that Janssen submitted all required Risperdal safety information to the FDA, including safety information related to RIS-USA-113, Trial Tr. vol. VII, 1412:9-1413:4, 1414:17-1417:15, Mar. 15, 2011 (Mahmoud testimony); Defs.' Trial Ex. 7294.

In short, the uncontradicted evidence, including the State's own proof, admissions, and concessions, establishes that there is no conduct of Janssen that needs to be deterred, which is the primary purpose of a civil penalty. *See Midlands*, 313 S.C. at 212, 437 S.E.2d at 121 ("[T]he court should give effect to the major purpose of a civil penalty – deterrence.").

South Carolina case law does not support the State's anticipated request for massive civil penalties. In *Nest Egg*, 290 S.C. at 126, 348 S.E.2d at 382, the Court of Appeals of South Carolina affirmed a penalty award that had been specifically tailored to the harm caused by the defendants' conduct. Specifically, the trial court held that the defendants had violated SCUTPA by operating an unlawful pyramid scheme. The defendants' pyramid scheme was widespread throughout South Carolina, with 1039 members who had paid approximately $45,000 in membership dues to the defendants. *Id.* at 127, 348 S.E.2d at 383. Despite the $5,000 per violation maximum provided for by SCUTPA, the court imposed a total civil penalty of only $45,000. *Id.* at 126, 348 S.E.2d at 382.

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At most, the State is entitled to a nominal civil penalty in this case. First, there is no evidence that the November 2003 mailing or package insert caused any actual harm to the public. Second, the conduct at issue in this case – involving the provision of information

about the side effects of a prescription medicine – most certainly does not equate to the deliberate conduct of an explicitly forbidden pyramid scheme. And third, this case is novel: there was no precedent – not a single authority – that so much as suggested that an FDA-approved package insert could be the subject of a state-law deceptive trade practices claim. *See generally State v. Am. Recycling Techs., Inc.*, No. CV040832985, 2009 WL 1532330, at *6 (Conn. Super. Ct. May 5, 2009) (imposing civil penalty of $50,000 for violation of unfair trade practices act and solicitation of charitable funds act after the court concluded "that this is the first case in Connecticut construing the SCFA, and that defendant conceivably could have been uncertain of the applicability of some of its provisions to it").

### C. The Court Should Defer To The FDA's Determination As To The Appropriate Remedies

The FDA approves and permits *all* of the language that appears in a package insert for a prescription medicine. *See Wyeth v. Levine*, 129 S. Ct. 1187, 1196 (2009) ("The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label." (citing 21 U.S.C. § 355; 21 C.F.R. § 314.105(b))). In approving and permitting the exact language used, the FDA necessarily makes a determination that the language of the package insert is not false or misleading. *See Prohias v. Pfizer*, 490 F. Supp. 2d 1228, 1235 n.6 (S.D. Fla. 2007) ("The information included in the labeling of a new drug reflects a determination by the FDA that the information is not false or misleading.'" (citing 21 C.F.R. § 314.125(b)(6))).

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For this precise reason, courts repeatedly acknowledge that the FDA, not courts or juries, has primary jurisdiction over claims of alleged falsity or deception as to an approved or permitted product label. *See, e.g., Wyeth v. Sun Pharm. Indus., Ltd.*, No. 09-11726, 2010 WL 746394, at *4 (E.D. Mich. Mar. 2, 2010) ("[I]t is solely the FDA's duty to investigate and prosecute allegations of misbranding or adulterating drugs."); *Mut. Pharm. Co. v.*

*Watson Pharm. Co.*, Civ. A. No. CV 09-5700, 2009 WL 3401117, at *5 (C.D. Cal. Oct. 19, 2009) ("Plaintiffs' contentions concerning the product labels and inserts are even weaker, both because the evidence of confusion is weaker and because disputes concerning the content of those labels and inserts falls even more squarely within the primary jurisdiction of the FDA."); *Pediamed Pharm., Inc. v. Breckenridge Pharm., Inc.*, 419 F. Supp. 2d 715, 726 n.14 (D. Md. 2006) ("The FDCA has enforcement power over false and misleading labels. 21 U.S.C. § 352. To the extent that Plaintiff relies solely on the false label argument to find a Lanham Act violation . . . such a claim is essentially a mislabeling claim, which is within the jurisdiction of the FDA and thus would be precluded."); *Heller v. Coca-Cola Co.*, 646 N.Y.S.2d 524, 526 (N.Y. Ct. App. 1996) (The trial court "properly deferred the issues presented concerning the appropriateness of the labeling of beverages containing Aspartame and the use of Aspartame in aged soft drinks to the FDA. This will ensure that there will be national uniformity in the labeling of Aspartame and will utilize the special expertise of the FDA in evaluating the relevant factors for approving food additives. This is especially true given the fact that the FDA considered for over a decade the stability characteristics of Aspartame.").

Similarly, the FDA has primary responsibility for "Dear Healthcare Provider" letters like the letter in the November 2003 mailing. Even the State's "regulatory" expert, Dr. Laura Plunkett, acknowledged that the FDA's Division of Drug Marketing, Advertising and Communications ("DDMAC") regulates a pharmaceutical manufacturer's communications about its medicine. Trial Tr. vol. III, 466:11-17, Mar. 9, 2011. The trial, of course, focused extensively on one such instance of DDMAC regulation, namely, DDMAC's April 2004 warning letter. Pl.'s Trial Ex. 232.

The South Carolina Supreme Court has long recognized that its courts should defer to existing, available, and comprehensive administrative frameworks rather than exercise

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jurisdiction over a particular matter subject to regulation by an administrative agency. *See Smith v. S.C. Retirement* Sys., 336 S.C. 505, 527, 520 S.E.2d 339, 351 (Ct. App. 1999) ("'Gratuitous interference' in the administrative process should be avoided." (citation omitted)). *See generally Isgett v. Atl. Coast Line R. Co.*, 223 S.C. 56, 64, 74 S.E.2d 220, 223 (1953) ("If the court should undertake to now decide the controversy, it would not bind the Board [established by the Railway Labor Act], to which the next similar controversy might be taken. It would seem that the presently firmly established rule of exclusive primary jurisdiction of the Board in such cases should be beneficial, in the long run, to both carriers and employees, and to the public."). Here, the Court should defer to the FDA's determinations as to both the November 2003 mailing and the Risperdal package insert.

1. **November 2003 Mailing**

At trial, there was extensive testimony as to what DDMAC considered to be the appropriate remedy for its concerns as to the November 2003 mailing. Specifically, DDMAC requested, and Janssen agreed, that there would be a "corrective" letter sent to health care providers, including, obviously, those in South Carolina, which reported what DDMAC had said in its warning letter. *See, e.g.*, Trial Tr. vol. VII, 1499:13-1504:23, Mar. 15, 2011 (Mahmoud testimony); Pl.'s Trial Ex. 438 (July 2004 letter). Once the corrective letter was sent by Janssen, DDMAC considered the "matter closed" and took no further enforcement action. Trial Tr. vol. IV, 838:13-23, Mar. 10, 2011 (Plunkett testimony that the FDA could have taken enforcement action if Janssen refused to send corrective letter); Trial Tr. vol. VII, 1504:11-23, Mar. 15, 2011 (Mahmoud testimony that the FDA did not attempt to collect a fine or penalty); Trial Tr. vol. VIII, 1910:6-1911:1, Mar. 16, 2001 (Chester testimony that the FDA may institute enforcement action if requested actions are not taken); Trial Tr. vol. IX, 2087:4-6, Mar. 17, 2011 (Bradshaw testimony that purpose of warning letter is "to try to just get voluntary compliance and to open up the dialogue with the company"); Defs.'

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Trial Ex. 6253. This Court should defer to the determination of Janssen's primary regulator that a corrective letter was all that was needed to remedy any possible deception or public harm. Alternatively, this Court could effectively defer to DDMAC's view about the need for "punishment" by treating the November 2003 mailing as a single act and imposing only one penalty; the Court need not and should not impose a separate penalty for each letter sent in the course of the single mailing.

2. **Package Insert**

As to the Risperdal package insert, the State presented testimony that the package insert did not contain "adequate" warnings as to certain risks for certain periods of time. *See, e.g.*, Trial Tr. vol. III, 355:22-357:21, 362:21-365:20, 367:4-368:24, 370:19-381:24, Mar. 9, 2011 (Wirshing testimony). On multiple occasions, however, the FDA either suggested package insert revisions (as with the September 2003 request for additional warnings as to hyperglycemia and diabetes) or accepted revisions proposed by Janssen. *See, e.g.*, Defs.' Trial Exs. 841, 843, 3180; *see also, e.g.*, Trial Tr. vol. IV, 899:12-901:2, Mar. 10, 2011 (Plunkett testimony that Janssen changed label as to cerebrovascular events on its own prior to any request from the FDA); Trial Tr. vol. VII, 1519:10-1520:2, Mar. 15, 2011 (Mahmoud testimony that when Janssen learned of safety concerns that should be added to the label, it would use the changes being effected procedure to change the label); Trial Tr. vol. VIII, 1780:16-1781:8, Mar. 16, 2011 (Caers testimony that in 2002 Janssen went to the FDA to request a label change as to the issue of hyperglycemia).

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The FDA considered and approved each of the many changes to the Risperdal package insert. In the FDA's view, these package insert revisions provided adequately for the safe and effective use of Risperdal. To the extent that new warnings may have been needed from time to time, the FDA took the position that they could be provided by modifications to the package insert on a "going forward" basis. In fact, the FDA has *never*

said that Janssen should have updated its package insert to add any warnings earlier. *See* Trial Tr. vol. VII, 1518:23-1520:2, Mar. 15, 2011 (Mahmoud testimony); *see also* Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011 (Plunkett testimony). This Court should defer to the FDA's determination that the periodic, prospective changes to the Risperdal package insert were sufficient.

### D. The Failure Of The Jury To Make Separate Findings As To Unfair Trade Practices And Deceptive Trade Practices Precludes Any Award Of Civil Penalties

The State opposed Janssen's request that the jury decide separately (A) whether the November 2003 mailing was (1) an unfair trade practice or (2) a deceptive trade practice and (B) whether the Risperdal package insert was (1) an unfair trade practice or (2) a deceptive trade practice. *See* Defs.' Requested Verdict Sheet. The failure to require the jury to make separate findings is significant; the jury easily could have determined only that the November 2003 mailing or package insert was somehow "unfair," particularly given the Court's instruction that a practice may be found "unfair" "if it offends established public policy or it is immoral, unethical, or oppressive." Trial Tr. vol. XII, 2815:12-15, Mar. 22, 2011. The State's failure to request, or at least agree, that the jury should have made separate and distinct findings as to an unfair trade practice and a deceptive trade practice for both the November 2003 mailing and the package insert should preclude the State from seeking any penalties for either the November 2003 mailing or the package insert.

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As stated by the South Carolina Supreme Court in *Branham v. Ford Motor Co.*, 390 S.C. 203, 237, 701 S.E.2d 5, 23 (2010):

> A detailed verdict form would have specified whether a finding of negligence against Ford was based on the seatbelt sleeve claim or the design defect claim, or both. A proper verdict form would have avoided the confusion caused by having the jury apportion blame between jointly and severally liable defendants. More to the point, Ford's requested special verdict form would have avoided the very real risk that the jury

> (unaware of joint and several liability principles) would take the cue from the apportionment question and inflate the actual damage award to ensure Branham received a full recovery from the one deep-pocket defendant.

*See also S.C. Dep't of Transp. v. First Carolina Corp. of S.C.*, 372 S.C. 295, 303, 641 S.E.2d 903, 907-08 (2007) ("[A] special verdict question may be so defective in its formulation that its submission results in a prejudicial effect which constitutes reversible error.").

As it is impossible to determine the basis upon which the jury determined that Janssen was liable for a violation of SCUTPA – a problem of the State's own making – any award of civil penalties would be nothing more than impermissible speculation. This is particularly true for the Risperdal package insert where the use of a non-specific verdict form makes it factually impossible to determine: (1) whether the jury concluded that Janssen's conduct violated SCUTPA because it was "unfair" or because it was "deceptive," (2) why the jury found that the conduct was unfair or deceptive, and (3) the period of time during which the package insert was unfair or deceptive. This verdict sheet's insufficiency is important because the State's experts testified that the label was "inadequate" only for certain risks and, with respect to each risk, only for certain periods of time. For example:

> Q. Between ***1994*** and ***2004***, were the risks of Risperdal use in diabetes adequately warned of in your opinion?
>
> A. No, for reasons we talked about already.
>
> Q. Between ***1994*** and ***2006***, were the risks of Risperdal causing death in the elderly adequately warned of in your opinion?
>
> A. No.
>
> Q. And between ***1994*** and ***2007***, were the risks of Risperdal and –
>
> A. Can I go back to that last one?

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Q. Sure.

A. The risks of death were not known in '94. The risks of death were not known until about *'97* when the first protocols were accomplished, so if you change it to *'97* through whatever it was.

Q. Sure. Nevertheless, at no time before 2006, was there a warning in Risperdal's label about the risk of death in the elderly, was there?

A. No.

Q. Were the risks of hyperprolactinemia-related adverse events adequately warned of in your opinion in Risperdal's label between *1994* and *2007*?

A. No, sir.

Trial Tr. vol. III, 624:15-625-15, Mar. 9, 2011 (Wirshing testimony) (emphasis added).

Inconsistent with its own expert testimony, the State's counsel also argued to the jury, and to the Court, that the alleged inadequacy of the Risperdal package insert for both diabetes and the elderly ended in *2003*. Trial Tr. vol. X, 2278:2-11, Mar 18, 2011 ("The point of that, though, is that occurred in early of 2003, specifically April of 2003. And, obviously, once the warning is changed, once the label is changed and once that fact is communicated out to doctors through the Dear Doctor letter referenced in that earlier slide we were talking about, the State's claim on that particular issue is extinguished because then you have an adequate warning as to use in the elderly"); Trial Tr. vol. XI, 2673:22-15, Mar. 21, 2011 ("You know that the label from 1994 – 1993 until *2003* did not contain a warning for diabetes and hyperglycemia. That's not in dispute." (emphasis added)); Trial Tr. vol. I, 44:13-19, Mar. 7, 2011 ("To the extent the State seeks penalties for violations of SCUTPA, because of the absence of diabetes language in the labeling, our request for those penalties ends in July of *2004*. After that, we seek no penalties for that deficiency." (emphasis added)).

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There simply is no way of knowing whether the jury determined that the package insert was "unfair" because Janssen should have "updated" the diabetes warnings in 1994, or perhaps in 1999 or 2000 (in response to the RIS-USA-113 topline report or the ERI numbers); or whether the jury concluded that the package insert was "unfair" because the discussion of hyperprolactinemia appeared in the "precautions" section of the label, rather than the "warnings" section, since 1994; or whether the jury decided that a "mortality in the elderly" warning should have been added in 1997, or maybe in 2003, rather than in 2005. Or perhaps the jury was persuaded by the argument that the FDA-prescribed type size was "unfairly" small. Trial Tr. vol. II, 202:10-15, Mar. 8, 2011 (argument by Mr. Coggins, counsel for the State); Trial Tr. vol. IX, 2189:20-2190:2, Mar. 17, 2011 (Ratliff testimony); Trial Tr. vol. X, 2299:11-2300:8, Mar. 18, 2011 (Fabbri testimony). Any award of civil penalties for the Risperdal package insert, therefore, would be entirely speculative.[1] Because the State resisted a more specific verdict form -- because it insisted that the jury be asked only whether the label was ever "unfair" or "deceptive" – the State should be limited to, at most, a penalty based on one "violation" for each different package insert that might have been "unfair." Pl.'s Trial Exs. 643 (1994 original package insert), 2061 (April 1995), 649 (September 1996), 656 (July 2002), 657 (March 2003), 661 (December 2003), 662 (February 2005).[2]

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[1] For this reason, any evidence as to the number of Risperdal samples or number of calls on physicians will not be informative: there is no way of tying those samples or call notes to the label "inadequacy" upon which the verdict rests.

[2] The State also introduced a package insert from October 2006, Pl.'s Trial Ex. 665, which reflected a package insert change as to hyperprolactinemia. This change presumably ended the alleged "unfairness" and, as such, this package insert should not be the subject of a civil penalty.

## E. The State Is Not Entitled To A Civil Penalty For Every Risperdal Prescription Filled

The only insight into the relief requested by the State came from its previous assertion that it could seek a $5,000 penalty for every prescription filled in South Carolina, thereby entitling it to literally billions of dollars in penalties. *See* Ex. C, Pl.'s Suppl. Answer to Interrog. No. 17 of Defs.' Fifth Set of Interrogs. ("[T]he State contends that each Risperdal prescription filled since 1994 constitutes a separate and distinct violation of the South Carolina Unfair Trade Practices Act."). This "contention" is of no moment, however, because it was based on the false premise that a Risperdal package insert accompanied every prescription filled for a patient. The State's own witnesses flatly contradicted any such assertion. For example, James Assey testified to the following:

> Q. I want to ask you a couple of follow-up questions to what Mr. Coggins asked you. Bear with me a moment. Mr. Coggins asked you at one point about the package insert. And these folks during the course of trial have heard a bit about the package insert, but I want to see if we can make sure we just clear up what might be a discrepancy here. The package insert, as you understand it, is that the document that is FDA-approved and generated by the drug manufacturer?
>
> A. Yes, sir.
>
> Q. Okay. And that package insert, as we've just defined it, that's something that is different than the document that a patient receives upon having a prescription filled at the pharmacy, correct?
>
> A. Patient counseling document.
>
> Q. Right. So that document that you get from CVS or Eckerd's, Walgreens, wherever, that patient information is not something that's generated by the manufacturer, correct?
>
> A. Uh, no, it is not.

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Trial Tr. vol. VI, 1221:10-1222:8, Mar. 14, 2011. One of the State's other witnesses, Dr. W. David Patterson, similarly testified that the number of prescriptions filled is not the same as the number of package inserts distributed:

> Q. Doctor, do you have any way for any of the data that your office stores, do you have any way of telling the jury how many Risperdal package inserts were distributed in South Carolina?
>
> A. No, sir, we don't have that data.

*Id.* at 1309:1-5. Accordingly, the State is not entitled to a civil penalty based in any respect on the number of Risperdal prescriptions filled for participants in the South Carolina Medicaid program or the State employee health plan.

### F. Penalties Should Not Be Imposed For The Truthful Statements In the Risperdal Package Insert Or The November 2003 Mailing

#### 1. Package Insert

The State's only claim as to the Risperdal package insert was that it was somehow "inadequate." The State did not even attempt to prove that any statement in the package insert was untrue and, in fact, everything contained in the package insert was true. Penalties should not be imposed for truthful statements, particularly here, where the FDA approved – and mandated – the specific wording in the package insert, the formatting of the package insert, and even the type size that was used. *See generally* 21 U.S.C. § 355(b)(1)(F) (new drug application shall include "specimens of the labeling proposed to be used for such drug"); 21 C.F.R. §§ 201.56, 201.57 (labeling requirements for prescription drugs).

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#### 2. November 2003 Mailing

In the absence of a specific finding by the jury that the mailing was deceptive, the truth of the November 2003 mailing properly may be considered by the Court at the

penalties stage. In this regard, the Court should contrast the State's evidence as to the truth of the November 2003 mailing with Janssen's.

The State's experts' testimony was either general and conclusory or limited and qualified. Specifically, Dr. Wirshing testified:

> Q. According to you, Doctor, was that letter true or not true?
>
> A. No, it was not true then and it's not true now.

Trial Tr. vol. III, 489:1-4, Mar. 9, 2011. When asked specific questions, however, Dr. Wirshing contradicted himself and testified that the statements from the November 2003 mailing were supported by the studies identified by Janssen:

> Q. Is it fair to say that the primary conclusion from those eight articles is supportive of the middle paragraph of the November 10 letter?
>
> A. To a degree. I mean, the bottom line of the – of those articles, indeed, of the entire literature is that risperidone has a somewhat higher signal than some medications and a somewhat lower signal in terms of diabetes than other medications, and I think that that's reflected in those articles.
>
> Q. Is it fair to say that six of those eight articles based upon your review of them support the contents of the November 10 letter?
>
> A. Well, they support that risperidone has lower than olanzapine.
>
> Q. Lower what than olanzapine?
>
> A. Lower diabetic risk than olanzapine. They don't support the statement that it has equivalent risk to olanzapine or if it has equivalent risk to conventional antipsychotics, but I think it supports a portion of what's in the second paragraph.

*Id.* at 613:15-614:11. Dr. Plunkett only provided a limited conclusion as to the truth of the statements in the mailing "based on ERI and based on 113":

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Q. . . . But based on the peer-reviewed epidemiological research, based on ERI and based on 113, do you have an opinion as to whether the representations in this letter are true?

A. Yes, I do.

Q. What is your opinion?

A. That it is not an accurate representation. It's not true based on the information they had, and especially when you consider the whole body of information they had.

Trial Tr. vol. IV, 747:14-24, Mar. 10, 2011.

In contrast to the cursory, conflicting, and limited opinion testimony of the State's experts, Janssen's expert, Dr. Newcomer, reviewed every piece of literature available at the time and concluded that the November 2003 mailing was scientifically accurate:

Q. Dr. Newcomer, have you been asked to review Dr. Ramy Mahmoud's November 10, 2003 letter?

A. I was.

Q. And were you asked to offer an opinion as to whether that letter was adequate and appropriate?

A. I was.

Q. Okay. Were you asked to determine whether it was scientifically accurate?

A. Yes.

Q. And do you have an opinion in that regard?

A. I think the letter was scientifically accurate and scientifically appropriate.

Q. What did you review in coming to your opinion?

A. My review really -- let me back up. I, on a weekly basis, near daily basis, my laboratory has a process for sort of capturing out of the peer-reviewed published literature all of the new papers that come out that are relevant to our area of interest. So essentially coming across my desk or e-mail each day are all of these new papers. And then the ones that are relevant, you know, I

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essentially put into a pile and collect so we stay current with that literature. So I was able to review the -- what I think is the totality of the available peer-reviewed published literature relevant to the 10 topic that I was asked to review.

Trial Tr. vol. X, 2403:6-2404:10, Mar. 18, 2011. Dr. Newcomer also testified that the eight studies cited in the November 2003 mailing supported the statements challenged as deceptive:

Q. Now, Doctor, is it your opinion that the eight studies that Dr. Mahmoud cited in that letter support the position and the statements he made in that letter?

A. I think they do support it. And I was aware before I ever saw the letter, that these, at that point, were the only pharmacoepi studies that directly informed on this question that were available in the peer-reviewed literature. So when I got the literature, I wasn't surprised to see it.

*Id.* at 2449:6-15.

Imposition of any significant penalty as to the November 2003 mailing also is inappropriate because Dr. Plunkett confirmed that the statement challenged by the State as deceptive -- that Risperdal is different from Zyprexa -- has been confirmed to be accurate by her own "weight of the evidence" analysis:

Q. And employing a weight-of-the-evidence assessment, am I correct that you have found that with regard to weight gain caused by Risperdal on one hand and Zyprexa on the other, studies show that Zyprexa causes more weight gain than Risperdal?

A. Yes, based upon my weight-of-the-evidence analysis that was done in -- well, those particular analyses would have been done in '07, '08, '09, so later 2000s. My view of the scientific literature is there's a cause-and-effect association between Risperdal and -- as well as Zyprexa -- and weight gain, diabetes. Risperdal and hyperprolactinemia as well. And that it does appear based upon the current evidence that olanzapine or Zyprexa has a greater risk of producing weight gain and diabetes in individuals. However, that doesn't mean that all of the

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> information says that, and it doesn't mean that the clinical trial data says that. But certainly, the entire body of the literature in 2000 – I believe the Risperdal assessment was done in 2008 or '9 – would have led me to that conclusion.

Trial Tr. vol. V, 1036:24-1037:22, Mar. 11, 2011.

Significantly, the Federal Trade Commission ("FTC") has made clear that evidence that confirms the truth of earlier statements is appropriately considered in evaluating a defendant's conduct. As stated by the FTC:

> The goal of the advertising substantiation requirement is to assure that advertising is truthful, however, and the truth of [sic] falsity of a claim is always relevant to the Commission's deliberations. Therefore, it is important that the agency retain the discretion and flexibility to consider additional substantiating evidence . . . .
>
> . . . .
>
> [U]sing post-claim evidence to evaluate the truth of a claim, or otherwise using such evidence in deciding whether there is a public interest in continuing an investigation or issuing a complaint, is appropriate policy.
>
> . . . .
>
> [T]he Commission may use post-claim evidence in determining the need for or appropriate scope of an order to be entered against a firm that lacked a reasonable basis. Thus, when additional evidence offered for the first time at trial suggests that the claim is true, the Commission may frame a narrower order than if there had been no post-claim evidence.

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FTC Policy Statement Regarding Advertising Substantiation Program, 49 Fed. Reg. 30999, 31001 (Aug. 2, 1984). As succinctly stated by the FTC, "For other charges, such as falsity, when evidence was developed is irrelevant to its admissibility at trial." *Id.* at n.5.

As noted, there was substantial scientific evidence supporting the statement, in November 2003, that Risperdal's diabetes-related risks differed from those of some other antipsychotics, and there was even more evidence developed after 2003. One of the most

important pieces of confirmatory evidence is the FDA's acknowledgement, in 2007, that a "one size fits all" warning was inappropriate. In 2007, the FDA required Eli Lilly to modify the "class" warning in the Zyprexa package insert. Specifically, the Warnings and Precautions section of the post-2007 Zyprexa label was changed to provide:

> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. . . . Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics. *While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.*

Defs.' Offer of Proof for the Post-2007 FDA-Approved Package Insert for Zyprexa and the 2010 FDA-Approved Package Insert for Latuda (emphasis added) ("Defs.' Offer of Proof for Zyprexa and Latuda Labels").

Similarly, in October 2010, when the FDA approved a new atypical antipsychotic, Latuda, the FDA required Sunovion to include language in the Warnings and Precautions section of the Latuda label that recognized the differences in the metabolic-related side effects associated with the various atypical antipsychotics:

> Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/ cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. *While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.*

Defs.' Offer of Proof for Zyprexa and Latuda Labels. Under these circumstances, no punishment is warranted for a mailing that was true when sent, and that is true today – a mailing that the jury may have found "deceptive" or "unfair" based on a position taken by the FDA in 2004, but later abandoned.

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G. **The State Is Not Entitled To A Civil Penalty For Samples Of Risperdal Given To Consumers Because Pharmaceutical Manufacturers Have No Duty To Warn Consumers**

During trial, the Court allowed the State to argue to the jury that the package insert could deceive consumers – patients – because, in the Court's view, there was evidence that the package insert sometimes winds up in the hands of patients. Trial Tr. vol. XI, 2606:14-16, Mar. 21, 2011 ("But the patients, though, do make decisions, sometimes, as to whether to swallow the pill or not."); Trial Tr. vol. XII, 2780:7-14, Mar. 22, 2011 ("[W]hile the representations were made primarily to doctors . . . the information is in the public realm and is available to members of the public"; "there was testimony from the person who detailed the drugs that every sample contained the label; it would have been submitted to the public in that fashion"). Despite the Court's liability-phase decision, a penalty award cannot be based on the number of samples of Risperdal that contain a package insert.

Awarding civil penalties for alleged unfairness or deception as to consumers is improper because, as a matter of law, a pharmaceutical manufacturer has no duty to advise consumers of a prescription medicine of the risks of a particular drug. *See, e.g., Brooks v. Medtronic, Inc.*, 750 F.2d 1227, 1231 (4th Cir. 1984) ("Although the South Carolina Supreme Court has not addressed the issue, we conclude it would adopt the rule generally accepted and supported by sound policy, restricting the manufacturer's duty to warn to the prescribing physician."); *see also, e.g., Odom v. G.D. Searle & Co.*, 979 F.2d 1001, 1003 (4th Cir. 1992) ("[T]he manufacturer's duty to warn extends only to the prescribing physician, who then assumes responsibility for advising the individual patient of risks associated with the drug or device."). The State also cannot contest the settled proposition that a package insert is written solely for physicians, not consumers. *See* 73 Fed. Reg. 49603, 49604 (Aug. 22, 2008) ("FDA's comprehensive scientific evaluation is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific

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evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively."). *See generally Morlino v. Med. Ctr. of Ocean Cnty.*, 152 N.J. 563, 580, 706 A.2d 721, 729-30 (1998) ("Drug manufacturers write explanations and warnings for doctors, not the general public."); *Martin v. Hacker*, 83 N.Y.2d 1, 9, 628 N.E.2d 1308, 1311 (1993) ("Warnings for prescription drugs are intended for the physician, whose duty it is to balance the risks against the benefits of various drugs and treatments and to prescribe them and supervise their effects.").

### H. The State Is Not Entitled To Substantial Penalties For The Risperdal Package Insert Because The Alleged "Inadequacy" Of The Package Insert Concerns Risks Of Adverse Events That Are Infrequent

The State's sweeping request for civil penalties in connection with the Risperdal package insert also is disproportionate to the potential "harm" that the "unfair" package insert could possibly have caused. The side effects associated with the purportedly inadequately disclosed risks were "infrequent" events. Indeed, there is no evidence in the record that Risperdal has actually caused any South Carolina patients to experience adverse events related to the alleged risks.

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For example, the State's expert, Dr. Wirshing, freely admitted that the "risk of death" in the elderly was not based in fact but was merely a supposition:

> Q. And it's your opinion that it's the alpha toxicity that, at least in part, causes these adverse events warned of in this black box, right?
>
> A. Again, it's some supposition, but, yes, at least in part all drugs that have alpha blockades seem to be associated with these untoward cardiac and vascular outcomes.

Trial Tr. vol. III, 529:1-7. Mar. 9, 2011. Dr. Wirshing also agreed that diabetes-related adverse events were infrequent:

Q. The next paragraph says, "Hyperglycemia-related adverse events have infrequently been reported in patients receiving Risperdal." Do you see that?

A. Yes, sir.

Q. Do you have any idea what "infrequently" means?

A. Infrequently, I presume, means what it usually means, which is not frequently.

Q. Do you know what Dr. Mahmoud meant by that statement?

A. Directly what he meant, no. My presumption is that what he meant by it is that it has not happened very often. These events have not been reported frequently.

Q. Do you agree with that implication, not happening very often?

A. Um, it's – it's – they weren't reported terribly frequently. They were certainly in the literature, we had reported it, it certainly had been reported to the FDA, they certainly had been reported to Janssen. You know, the statement really hinges on the word "infrequently." Um, it's probably not the best word of choice, but it wasn't really common at any rate.

*Id.* at 457:4-458:4.

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An infrequent event is one that occurs in less than one percent of individuals. Trial Tr. vol. III, 480:23-24, Mar. 9, 2011 (Wirshing testimony that "One in a hundred to one in thousand is infrequent[.]"); Trial Tr. vol. VII, 1520:19-21, 1592:2-9, Mar. 15, 2011 (Mahmoud testimony that "If it's infrequent, it's between 1 in 100 and 1 in a thousand so between 1 percent and 0.1 percent."); Trial Tr. vol. VIII, 1763:1-3, Mar. 16, 2011 (Caers testimony that "Infrequently is below 1 percent and above .1 percent. So above 1 out of every thousand and less than 1 of every 100."); *see also* Pl.'s Trial Exs. 643, 656, 657, 661, 662, 665, 2049, 2061 (Risperdal package inserts stating that "infrequent adverse events are those occurring in 1/100 to 1/1000 patients").

Finally, the State presented no testimony that contradicted the testimony of Defendants' expert, Dr. Newcomer, that problems relating to elevated prolactin are reversible by discontinuing the medicine. Trial Tr. vol. X, 2433:4-7, Mar. 18, 2011 ("[T]he prolactin elevation is a completely reversible thing, if you stop the medicine, or treat it, it can go down, and prolactin elevation and its symptoms go away.").

This Court, when imposing penalties, might well consider the "impact" on the patient population of the liability-creating "inadequacies" of the package insert. But there is no proof, on this record, that the inadequacies had any impact, much less a substantial one. Because (1) the State introduced no evidence as to the frequency of the occurrence of the adverse events associated with the risks it claims were "inadequately" disclosed and (2) the only evidence of record is that those adverse events *might* affect only a small fraction of patients using Risperdal, there is no basis for an award of substantial penalties.

## I. The Testimony Of The Twenty Prescribers And The SCORxE Witnesses Confirms That Substantial Civil Penalties Are Not Warranted

During the liability phase, Defendants sought to introduce additional evidence to support the assertion that neither the November 2003 mailing nor the Risperdal package insert had a "tendency to deceive" or an "adverse public impact." Specifically, Janssen proffered (1) testimony from 20 South Carolina prescribing physicians and (2) testimony as to South Carolina's SCORxE program. Although the Court excluded this evidence as irrelevant to the determination of liability, the Court should consider it when determining what penalty, if any, should be imposed upon Janssen. The evidence shows that the "unfair" and "deceptive" practices that are the subject of the State's claim could not have had any impact whatsoever on South Carolina physicians.

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First, the testimony of the 20 prescribers shows that Janssen's alleged conduct in fact had no effect on the South Carolina physicians who wrote 33% of the Medicaid and

State Health Plan prescriptions for antipsychotics because they have long been aware of the relative risks associated with Risperdal and other antipsychotics, including the risks of diabetes-related side effects. *See* Defs.' Wecker Offer of Proof (outlining responses from prescriber depositions); Trial Tr. vol. XI, 2523:15-2525:6, Mar. 21, 2011) (oral offer of proof by Mr. Pugh, counsel for Janssen, as to 20 prescribers).

Second, the testimony as to the State's SCORxE program establishes that the State's own experts have recognized the benefits of Risperdal and, in particular, that the SCORxE program recommends as a "best practice" that an atypical antipsychotic such as Risperdal be used first for the treatment of schizophrenia. This testimony also establishes that a perceived relationship between atypical antipsychotics and hyperglycemia and diabetes was known in the early 2000s and was well known in 2004, after publication of the Consensus Statement. Finally, this evidence also is significant because, notwithstanding active and ongoing education of South Carolina physicians as to the appropriate use of atypical antipsychotics, the Attorney General's Office never advised anyone within the SCORxE program that the information being provided to physicians was incomplete or deficient in any respect. *See* Defs.' Offer of Proof for the Testimony of Sarah Ball and Sophie Robert.

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All of this evidence belies any assertion by the State that either the November 2003 mailing or the alleged "inadequacies" as to the Risperdal package insert had a widespread impact, or any impact, in South Carolina. For this reason, this additional evidence negates the State's request for significant civil penalties.

## J. The State's Evidence Of Janssen's "Willful" Conduct Does Not Warrant The Imposition Of Civil Penalties

### 1. The Evidence Establishes that There Were Differences in Weight Gain And Diabetes Risk Between Risperdal and Zyprexa

Through the erroneous introduction of numerous marketing documents, the State attempted throughout the trial to portray Janssen's conduct as "willful" for purposes of SCUTPA. In particular, the State pursued as a trial theme that, for more than a decade, Janssen engaged in an unsubstantiated effort to differentiate its atypical antipsychotic, Risperdal, from Eli Lilly's atypical antipsychotic, Zyprexa, with respect to weight gain and diabetes risk. *See, e.g.*, Trial Tr. vol. I, 68:12-16, 69:14-71:10, 78:3-5, Mar. 7, 2011 (argument by Mr. Coggins, counsel for the State, that unfairness is creating deceptive view in the marketplace as to competitors); Trial Tr. vol. XI, 2644:12-16, Mar. 21, 2011 (closing statement: "Their core message is we want doctors to think about Zyprexa when they think about diabetes, we want them to think about Risperdal as not causing diabetes and prescribe Risperdal.").

The State may now argue that the amount of civil penalties should be substantial by reason of this alleged "willful" conduct. But the evidence from the trial, including from the State's own witnesses, establishes that there were in fact substantial differences between Risperdal and Zyprexa. For example:

- the State's expert, Dr. Wirshing, testified that the available data suggested that Risperdal use was associated with a lower amount of weight gain than Zyprexa and that, when lecturing to physicians, he gave the opinion that Zyprexa caused weight gain at a higher rate than Risperdal, Trial Tr. vol. III, 405:24-406:6, 627:22-628:7, Mar. 9, 2011;
- Dr. Wirshing testified that the analysis of his own research group was that Zyprexa had more than twice the amount of weight gain as Risperdal, and that he continues to believe that to the present day, *id.* at 600:3-601:6;

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- the State's other expert, Dr. Plunkett, testified that there is a clinically significant difference in weight gain among atypicals – i.e., there is not a class effect, Trial Tr. vol. V, 988:10-991:3, Mar. 11, 2011;

- Dr. Plunkett testified that "in this question of what is relative risk [among atypicals], it's much more complex than just looking at one particular study. You need to look across all of the studies and determine whether or not you can find that kind of nonclass effect or differences in risk," *id.* at 980:15-981:13;

- Dr. Plunkett testified that under her own "weight of the evidence" analysis, Zyprexa causes more weight gain than Risperdal, *id.* at 1036:24-1037:22;

- the FDA specifically agreed to remove a key sentence from the proposed class labeling in the Fall of 2003 as to Risperdal, thereby indicating that there were differences between Risperdal and the other atypicals, Trial Tr. vol. VIII, 1938:4-1941:12, Mar. 16, 2011 (Chester testimony);

- the Consensus Statement, published in February 2004, included a chart that reflected the difference in weight gain between Risperdal and Zyprexa, Pl.'s Trial Ex. 1750, Defs.' Trial Ex. 7185;

- two State physicians (Dr. Bank and Dr. Ratliff) testified that the results of the Consensus Statement were consistent with the observations from their own practices in South Carolina, Trial Tr. vol. IX, 2123:20-2126:19, 2127:7-14, 2161:2-2163:13, Mar. 17, 2011; and

- Defendants' expert, Dr. John Newcomer:

    - confirmed, after reviewing "the entire available literature," that there are differences among the atypicals (Zyprexa use, on average, produces 25 pounds of weight gain in a year while Risperdal use produces, on average, 5 pounds of weight gain in a year), Trial Tr. vol. X, 2433:10-2435:14, Mar. 18, 2011; and

    - testified (without contradiction) that, in calendar years 2003 and 2004, the comparative weight gain of Risperdal and Zyprexa was "pretty well understood" and it was consistent with his analysis as to all of the literature (subsequent studies also have shown the same finding), *id.* at 2447:12-2448:1.

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Janssen cannot be penalized for "willfully" trying to "differentiate" its product from a competitor's when, in fact, there are substantial differences.

### 2. Substantial Civil Penalties Are Not Warranted Because Janssen's Conduct Did Not Violate any Specific South Carolina Statute And Its Conduct Was Not "Prohibited" But Permitted And In Fact Mandated As To The Risperdal Package Insert

The Court refused to instruct the jury that it could find "willfulness" only if SCUTPA or another statute expressly prohibited the precise practice and only if the practice was not "common practice" in the industry. *See Hanley Nursery Co., Inc. v. Forrest*, 298 S.C. 520, 525, 381 S.E.2d 906, 909 (1989) ("[Defendant's] conduct is not prohibited and there is evidence it is in accord with the common practice of the trade. Applying the statutory definition, we hold the record supports the trial judge's finding the violation was not willful."); *Nest Egg*, 290 S.C. 124, 348 S.E.2d 381 (finding conduct was willful because pyramid schemes are expressly proscribed by S.C. Code Ann. § 39-5-30). *See generally Gentry v. Yonce*, 337 S.C. 1, 12, 522 S.E.2d 137, 143 (1999) ("Advertising a jackpot over the statutory $125 limit [set forth in S.C. Code Ann. § 12-21-2791] is offensive and has a tendency to deceive a person into thinking that a jackpot over $125 is legal."). Even if "willfulness" might be otherwise established, whether the practice is "prohibited" or "common" surely is relevant to the determination of appropriate penalties.

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The State presented no evidence that the Risperdal package insert was ever "prohibited" by the FDA or anyone else. Similarly, the State presented no evidence that medical communications such as the November 2003 mailing are "prohibited." In fact, the only evidence was to the contrary. *See, e.g.*, Trial Tr. vol. VIII, 1886:17-1887:5, Mar. 16, 2011 (Chester testimony); Defs.' Trial Ex. 6294 (Eli Lilly "Dear Doctor" Letter). Use of the FDA-approved package insert, of course, is not only "common practice," but is mandated. And communications with physicians are commonplace. Although the jury found

"willfulness," that finding, and the evidence upon which it was based, do not support an award of substantial penalties.

### K. Decisions From Other Courts Confirm That The Amount Of Civil Penalties Requested By The State Is Not Warranted

Although there is limited South Carolina law on the determination of an award of civil penalties, decisions from other courts provide ample guidance as to the relevant considerations for this Court, when deciding the appropriate penalty – between zero and the $5,000 maximum – for each SCUTPA violation. As discussed below, those other penalty cases consistently identify a number of important factors. A careful consideration of these factors is essential to ensure that any award is not unreasonable or arbitrary under the specific circumstances of this case.

As demonstrated by a long line of consumer protection act cases, a proper application of the factors leads to a civil penalty award that is, at most, a small fraction of the maximum allowed by statute. For example:

- Award of $100,000 for misleading and deceptive rental contract amounted to *20 cents per violation*, *People v. Dollar Rent-A-Car Sys., Inc.*, 259 Cal.Rptr. 191 (Cal. Ct. App. 1989);
- Award of $1,750,000 for 16,100,820 FTCA violations worked out to *11 cents per violation*, *United States v. Reader's Digest Ass'n*, 662 F.2d 955 (3d Cir. 1981);
- $550,000 penalty for unfair debt collection practices equaled *$1 per violation*, *United States v. Nat'l Fin. Servs., Inc.*, 98 F.3d 131 (4th Cir. 1996);
- Telephone companies' fine of $733,000 for consumer protection act violations amounted to *$100 per violation*, *Commw. v. AmCan Enters., Inc.*, 47 Mass. App. Ct. 330, 712 N.E.2d 1205 (1999);
- Award of $591,400 for defendant's usurious loans amounted to *$100 per violation* of the Maryland Consumer Protection Act, *B&S Mktg. Enters., LLC v. Consumer Prot. Div.*, 153 Md. App. 130, 835 A.2d 215 (Md. Ct. Spec. App. 2003); and

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- Award of $150,000 for defendant's solicitations and sales of coupon books in violation of California Unfair Practices Act equaled *$1 per violation*, *People v. Toomey*, 203 Cal. Rptr. 642, 656 (Cal. Ct. App. 1984).

While SCUTPA does not provide explicit guidance as to how the amount of the civil penalty should be determined, South Carolina case law rejects the formulaic approach – number of violations times maximum allowable penalty – for which the State advocates. *See Nest Egg*, 290 S.C. at 124, 348 S.E.2d at 381; *Midlands*, 313 S.C. 210, 437 S.E.2d at 120; *C & L Corp.*, 280 S.C. at 519, 313 S.E.2d at 334. Similarly, courts determining the amount of civil penalties, if any, to be imposed pursuant to the Federal Trade Commission Act ("FTCA") and state consumer protection laws engage in a careful, deliberate analysis of the facts of each case, often applying the five-factor analysis identified in *United States v. Reader's Digest Ass'n*, 662 F.2d 955 (3d Cir. 1981). Those factors are:

(1) The good faith or bad faith of the defendant;

(2) Injury to the public;

(3) The desire to eliminate the benefits derived by a violation;

(4) The necessity of vindicating the authority of the agency involved; and

(5) The defendant's ability to pay.

*Id.* at 967.

In *Reader's Digest*, the defendant conducted a direct-mail solicitation campaign that involved the mass mailing of sweepstakes entry forms that promised money or merchandise to a small percentage of people that returned the sweepstakes forms. *Id.* at 958. The entry forms often contained simulated checks, and other simulated items of value that, in fact, had no monetary value. *Id.* As a result, the FTC entered a consent order that prohibited a number of the defendant's marketing practices, including the use of simulated items of value in their sweepstakes campaign. *Id.* Nonetheless, the defendant continued its mass mailing campaign and sent more than 16 million sweepstakes letters, each of which violated

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the terms of the consent order. *Id.* at 959-60. Under the FTCA, each violation of the consent order could be punished by a civil penalty up to $10,000 per violation. *Id.* at 959. Despite finding more than 16 million violations, the district court utilized the five-factor analysis outlined above and imposed a civil penalty of only $1.75 million, which amounted to less than $0.11 per violation. *Id.* at 965-66. In affirming the lower court's decision, the Court of Appeals held that the court did not abuse its discretion because it "carefully considered the relevant factors prior to assessing the . . . penalty." *Id.* at 969.

After applying these same factors, courts regularly impose penalty amounts substantially below the maximum penalty available under the statute at issue. For example, in *National Financial Services, Inc.*, the Fourth Circuit Court of Appeals affirmed the District Court's holding that the defendants violated the Fair Debt Collection Practices Act ("FDCPA").[3] 98 F.3d at 133. The defendants sent collection notices to consumers that improperly threatened legal action on their accounts and contained false threats to sue. *Id.* at 134-35. Each one of the millions of collection notices constituted a separate violation of the statute, punishable by a civil penalty of up to $10,000. *Id.* at 141. Nonetheless, the Court of Appeals affirmed the district court's five-factor civil penalty analysis and its imposition of only $550,000 in penalties, which amounted to substantially less than $1 per statutory violation. *Id.*

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Furthermore, in *AmCan Enterprises, Inc.*, 47 Mass. App. Ct. at 331-32, 712 N.E.2d at 1207, the Appeals Court of Massachusetts held that the defendants had violated the Massachusetts Consumer Protection Act by sending misleading and deceptive

[3] "The FDCPA provides for enforcement as though it were an FTC rule. Thus, FDCPA violations can be punished under the [FTCA], which provides that the Government may impose civil penalties of up to $10,000 per each violation." 98 F.3d 131, 139 (4th Cir. 1996) (citations omitted).

advertisements to consumers. The defendants used the phrase "New England Yellow Pages" and the "walking fingers" logo to solicit advertising space in a telephone directory that was not connected to any telephone company. *Id.* Under the statute, the court could impose a penalty of up to $5,000 for each violation. The Appeals Court, however, affirmed the trial court's five-factor analysis and imposition of a substantially smaller penalty – $100 per violation. *Id.* at 340, 712 N.E.2d at 1212.

As discussed below, the five factors in *Reader's Digest Ass'n* support an even lower penalty award in this case.

1. **Whether Janssen Acted In Good Faith**

The evidence in the record supports a finding by this Court that Janssen acted in good faith with respect to both the November 2003 mailing and the Risperdal package insert.

a. **November 2003 Mailing**

The November 2003 mailing was a voluntary communication by Janssen in which it disclosed to healthcare providers the new class warning on diabetes, even before it was asked to do so by the FDA, and provided complete and truthful information about the then-available peer-reviewed scientific literature. Janssen's good faith regarding the November 2003 mailing is exemplified by the rigorous review undertaken prior to the mailing. Specifically, the mailing was sent only after it had undergone a comprehensive review by Janssen's Promotional Review Committee ("PRC"), which included members from a number of different disciplines (e.g., medicine, marketing, regulatory, and legal). The mailing was authorized only after unanimous agreement by the PRC members. Trial Tr. vol. VIII, 1859:4-1864:14, 1882:11-1883:13, 1886:17-1894:3, Mar. 16, 2011 (Chester testimony as to PRC and review and approval of November 2003 mailing); Defs.' Trial Ex. 6366 (sign-off sheet for November 2003 mailing).

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Janssen also clearly had a good faith basis for its position as to the November 2003 mailing because Janssen used the exact same articles in its September 2003 letter to the FDA requesting certain changes to the label as it used in the November 2003 mailing. *Compare* Defs.' Trial Ex. 351 *with* Defs.' Trial Ex. 3140; *see also* Trial Tr. vol. VIII, 1877:5-1882:7, 1936:23-1937:12, Mar. 18, 2011 (Chester testimony identifying articles sent to the FDA and in the November 2003 mailing). After that submission, the FDA *agreed* to the deletion of the sentence for the Janssen label that indicated that there were no differences in diabetes-related risks between Risperdal and other atypicals. Trial Tr. vol. VIII, 1938:4-1941:12, Mar. 18, 2011 (Chester testimony). Under those circumstances, it was hardly bad faith for Janssen to use that same information as the basis of its mailing to physicians.

Moreover, it is significant to the good faith factor under *Reader's Digest Ass'n* that DDMAC chose to convey its concerns about the November 2003 mailing to Janssen via a warning letter, not through a formal agency enforcement action. Pursuant to the FDA Regulatory Procedure Manual in effect at the time, DDMAC issued a warning letter if it *did not* believe that Janssen acted "willfully" or "intentionally" in disseminating "false misleading" materials. Defs.' Trial Ex. 4337; Trial Tr. vol. IX, 2083:11-2086:6, Mar. 17, 2011 (Bradshaw testimony as to when warning letters are, and are not, appropriate). If DDMAC believed that Janssen disseminated the information to healthcare providers in bad faith, the Manual indicates that DDMAC would have instituted a formal enforcement action. Significantly, when asked by DDMAC to send a clarifying communication to the healthcare providers, Janssen, despite its continuing disagreement with DDMAC about the underlying scientific research, fully cooperated with its regulator and sent an approved follow-up letter to the healthcare providers. DDMAC then closed the matter without further action.

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Janssen's November 2003 mailing was disseminated *before* any official at the FDA indicated that such communications would be problematic, and Janssen sent a clarifying

letter at DDMAC's request *before* any enforcement action was required. Thus, the circumstances here are materially different from those cited in *Reader's Digest*, where the defendant sent out millions of promotional mailings *after* a consent decree had been entered and *after* receiving notification from the FTC that the agency considered the promotional campaign to violate its order. *Reader's Digest Ass'n*, 662 F.2d at 958-59.

**b. Package Insert**

The trial testimony also reflects Janssen's good faith regarding the Risperdal package insert. On more than one occasion, for example, Janssen proposed revisions of the package insert to provide updated information as to the risks which the State alleged were "inadequately" disclosed. *See* Trial Tr. vol. IV, 899:12- 901:2, Mar. 10. 2011 (Plunkett testimony that Janssen changed label as to cerebrovascular events on its own prior to any request from the FDA); Trial Tr. vol. VII, 1519:10-1520:2, Mar. 15, 2011 (Mahmoud testimony that after 2000, Janssen went to the FDA and said label needed to be changed); Trial Tr. vol. VIII, 1780:16-1781:8, Mar. 16, 2011 (Caers testimony that in 2002, Janssen went to the FDA to request a label change as to the issue of hyperglycemia). Moreover, Janssen had no reason to believe that the FDA-approved package insert was ever "inadequate." Even when it proposed modifications of the package insert, the FDA did not suggest that the package insert was previously inadequate or had been used inappropriately. And the FDA has never taken any "enforcement" action, formal or informal, with respect to the package insert. *See* Trial Tr. vol. IV, 928:12-19, Mar. 10, 2011.

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**2. Whether There Is Any Evidence Of Injury To The Public**

Again, at trial, the State presented no evidence that the November 2003 Risperdal letter or the Risperdal label caused any injury to the public. On the contrary, the State disavowed any obligation to show that Janssen's communications actually deceived anyone, that any prescribing physicians in South Carolina relied to their or their patients'

detriment on the communications, or that any member of the public, including any of the thousands of mental health patients in South Carolina, was at any time harmed by the use of Risperdal.

The State took the position from the beginning of the trial that this case is not about whether Risperdal is a good drug or a bad drug. Trial Tr. vol. II, 236:19-21, Mar. 8, 2011; Trial Tr. vol. XI, 2728:1-7, Mar. 21, 2011. The State, however, cannot deny, at this stage of the proceeding, that the absence of any showing of injury to the public, coupled with the affirmative evidence proffered by Janssen, is relevant in assessing the appropriate amount of any civil penalty.

Indeed, there is no doubt that the availability of Risperdal has significantly benefited – and continues to this day to benefit – South Carolina residents. The State's expert, Dr. Wirshing, conceded that for certain patients Risperdal, like other atypical antipsychotics, is a "Godsend," "a miracle medicine," and "the closest thing to magic." Trial Tr., vol. III, 529:16-530:25, 531:13-533:15, Mar. 9, 2011. Dr. Wirshing further conceded that for certain patients Risperdal "is probably the best drug in the available pharmacopeia." *Id.* at 532:24-17. Finally, the benefits of Risperdal are not limited to a particular population or age group but include the elderly and children. *Id.* at 561:7-563:3, 563:17-565:3, 568:3-569:6 (Wirshing testimony about use of Risperdal for the elderly and children); *see also* Trial Tr. vol. VII, 1512:1-11, Mar. 15, 2011 (Mahmoud testimony that Risperdal is the "first and only" atypical antipsychotic to receive FDA approval for the treatment of certain conditions of autism); Trial Tr. vol. VIII, 1734:19-1736:12, Mar. 16, 2011 (Mahmoud testimony that Risperdal received autism indication because Janssen "had a drug which we had evidence could help children for which there was no treatment"). Given the absence of any evidence of bodily injury to any South Carolina resident, and the admitted substantial benefits of the

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use of Risperdal by South Carolina residents for serious mental health issues, the State has no claim to any substantial penalty.

### 3. Whether Janssen Benefited From The Alleged Violations

The State has offered no evidence that Janssen benefited from the November 2003 Risperdal mailing or from the "inadequacy" of the Risperdal package insert. In fact, the evidence is that Janssen's South Carolina market share was not affected by either the November 2003 mailing or the July 2004 corrective letter. *See* Defs.' Trial Ex. 7337. Because there is no evidence that Janssen benefited from the alleged violations – as opposed to benefiting from the sale of a good, effective medicine – again, a substantial penalty award is not justified.

Even in consumer protection act cases where the defendant has clearly benefitted from the deceptive trade practice, the courts have declined to impose the maximum civil penalty. For example, in *B&S Marketing Enterprises, LLC*, 153 Md. App. at 136-37, 835 A.2d at 219, the Maryland Court of Special Appeals affirmed the lower court's holding that the defendant violated the Maryland Consumer Protection Act by providing customers with usurious loans disguised as "sale-leasebacks." Under the defendant's loan program, interest rates on customer loans were as high as 730%. *Id.* at 137, 935 A.2d at 219. The lower court found that the defendant had engaged in 5,914 deceptive loan transactions, each of which constituted a separate violation of the Consumer Protection Statute. *Id.* at 148, 835 A.2d at 226. Under the statute, the court could impose a maximum civil penalty in the amount of $1,000 per violation. Nonetheless, the court imposed a penalty of only $100 per violation, even after finding that the defendants had acted in bad faith. *Id.* at 170, 835 A.2d at 239. This penalty amount was affirmed by the Court of Special Appeals. *Id.* at 171.

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### 4. Whether Civil Penalties Will Vindicate The Authority Of The Administrative Agency Involved

The FDA has its own exclusive mechanisms for enforcing the FDCA. 21 U.S.C. § 337(a). Significantly, while it was fully aware of the relevant facts surrounding Janssen's November 2003 mailing and had the power to do so, the FDA determined that no punitive action was necessary – and requested no corrective action other than the mailing of the "corrective" letter setting forth the FDA's position. Janssen's actions satisfied DDMAC, such that it closed the Risperdal matter shortly after the "corrective" letter was sent, and there is no evidence that Janssen's subsequent medical communications – or its promotion of Risperdal – were anything but respectful of the FDA's authority and mindful of its concerns. There is, accordingly, no evidence that imposition of a penalty in this case is necessary to vindicate the FDA's authority or to advance any legitimate public interest.

In contrast, many of the consumer protection act cases have involved violations of consent decrees, after the initiation by the agency of an enforcement action. In *People v. Bestline Products, Inc.*, 132 Cal. Rptr. 767, 794-95 (Cal. App. 1976), the trial court found that the defendants committed at least 3,000 violations of a consent decree that prohibited them from engaging in deceptive marketing practices in the course of their pyramid-style marketing program. For each violation of the consent decree, the court could have assessed a maximum civil penalty of $2,500. *Id.* at 795. Nevertheless, the California Court of Appeals affirmed the trial court's decision to impose a civil penalty that amounted to only $334 per violation. *Id.* at 795-96.

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Likewise, in *Toomey*, the court found that the defendant had committed 150,000 violations of California's Unfair Practices Act by making various misrepresentations to customers during telephone solicitations for the sale of coupon booklets. 203 Cal. Rptr. at 656. Each violation of the statute could be punished by a civil penalty of up to $2,500. *Id.*

at 657. Nonetheless, the Court of Appeals held that the trial court "did not assess civil penalties disproportionate to [defendant's] wealth or otherwise abuse its discretion" in assessing a penalty of only $1 per violation. *Id.* at 657-59.

There also is no need to vindicate the authority of the South Carolina Attorney General who, in pursuing this action, sought to assume a role similar to that of the FTC. Despite the length of this litigation, the Attorney General never sought injunctive relief to "protect the public interest" against Janssen's alleged unfair or deceptive trade practices. Nor has the Attorney General ever warned the State Department of Mental Health, or any other state agency, or the public, about the supposed inadequacies of the Risperdal package insert or made any effort to "correct" any misimpressions caused by Janssen's medical communications. Indeed, to this day, Risperdal and its generic equivalent are still prescribed – extensively and without any restriction – to South Carolina patients. Thus, unlike the instances where an agency's authority needs to be vindicated as a result of a defendant's violation of a court order, there can be no "vindication of authority" argument here.

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**5. Janssen's Ability To Pay**

It is anticipated that the State will rely heavily on the apparent ability of Janssen to pay a penalty as a factor supporting a large award. However, in circumstances such as those here, where there is no evidence of any detrimental reliance by the target audience (physicians), no evidence of actual harm to the affected consumers (patients), no evidence of benefit to the defendant (increased Risperdal market share), and no need to vindicate the enforcement actions of a public agency (the FDA), the ability to pay is typically treated as a non-dispositive factor. *United States v. Cornerstone Wealth Corp.*, 549 F. Supp. 2d 811, 824 (N.D. Tex. 2008) ("'[A]bility to pay' is not a determinative factor in assessing an [FTCA] civil penalty."); *United States v. Boston Sci. Corp.*, 253 F. Supp. 2d 85, 101 (D. Mass. 2003)

(disposing of ability-to-pay factor by noting simply that "BSC [the defendant] does not raise an issue of inability to pay"). And as the South Carolina Supreme Court has recognized, "[A] defendant's right to [due process] should not be diminished simply because the defendant is a deep pocket corporation." *Atkinson v. Orkin Exterminating Co.*, 361 S.C. 156, 165, 604 S.E.2d 385, 390 (2004) (citing *BMW of N. Am. v. Gore*, 517 U.S. 559, 574 (1996)).

* * *

In sum, the South Carolina precedent and persuasive authority from other jurisdictions concerning the award of civil penalties compel the conclusion that the State's anticipated requested relief is inappropriate. The conduct here simply was not the sort of egregious conduct that might justify the imposition of severe civil penalties.

### L. The State's Requested Relief – A Very Large Financial Penalty – Would Be Constitutionally Defective

#### 1. Due Process

The federal and state due process clauses, U.S. Const. amend. XIV; S.C. Const. art. I, § 3, limit a state's ability to impose a civil penalty. *See, e.g., Cooper Indus., Inc. v. Leatherman Tool Group, Inc.*, 532 U.S. 424, 433 (2001) ("Despite the broad discretion that States possess with respect to the imposition of criminal penalties and punitive damages, the Due Process Claim of the Fourteenth Amendment to the Federal Constitution imposes substantive limits on that discretion."); *see also, e.g., Mitchell v. Fortis Ins. Co.*, 385 S.C. 570, 584, 686 S.E.2d 176, 183 (2009) (same). The U.S. Supreme Court has been clear that "grossly excessive or arbitrary punishments" violate a defendant's due process rights. *State Farm Mut. Auto. Ins. Co. v. Campbell*, 538 U.S. 408, 416-17 (2003).

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An excessive penalty "furthers no legitimate purpose and constitutes an arbitrary deprivation of property." *Id.* at 417. As the Supreme Court has explained: "Elementary

notions of fairness enshrined in our constitutional jurisprudence dictate that a person receive fair notice not only of the conduct that will subject him to punishment, but also of the severity of the penalty that a State may impose." *Gore*, 517 U.S. at 574; *see also Sw. Tel. & Tel. Co. v. Danaher*, 238 U.S. 482, 490-91 (1915) (holding that "to inflict upon the company penalties aggregating $6,300 was so plainly arbitrary and oppressive as to be nothing short of a taking of its property without due process of law" where, among other things, "[t]here was no intentional wrongdoing, no departure from any prescribed or known standard of action, and no reckless conduct").

The South Carolina Supreme Court also has recognized that excessive awards violate a defendant's right to constitutional due process. *See, e.g., Mitchell*, 385 S.C. at 592, 686 S.E.2d at 187 ("[A] ratio of 13.9 to 1, based upon the $15 million punitive damages award and $1,081,189.40 in potential harm, is grossly excessive."), *cert. denied*, 130 S. Ct. 1896 (2010). In *Atkinson*, 361 S.C. at 171, 604 S.E.2d at 393, the South Carolina Supreme Court reversed a punitive damages award, reasoning that it was excessive and violated the defendant's due process rights. The Supreme Court explained, "Although the amount of compensatory damages in the present case was particularly low, [defendant's] acts were not so egregious as to warrant a 127 to 1 ratio. Therefore, we hold that the [plaintiffs] have failed to rebut the presumption that the three-digit, punitive-compensatory damages ratio in this case is unconstitutional." *Id.*, 604 S.E.2d at 393. Accordingly, an award here of substantial civil penalties, without any proof of actual harm or loss or any showing that Defendants' conduct was sufficiently reprehensible to justify imposition of a penalty of such magnitude, would violate basic principles of due process.

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2. **Excessive Fines**

Any civil penalty a court imposes also must comport with the federal and state excessive fines clauses. *See* U.S. Const. amend. VIII; S.C. Const. art. I, § 15; *see also*

*United States v. Bajakajian*, 524 U.S. 321, 328 (1998) ("The Excessive Fines Clause thus 'limits the government's power to extract payments, whether in cash or in kind, 'as punishment for some offense.'" (citation omitted)); *Singletary v. Wilson*, 191 S.C. 153, 153, 3 S.E.2d 802, 804 (1939) ("It is generally the case that in enacting penal statutes the Legislature fixes and designates a maximum penalty, but when it is not done, the power to impose a fine is limited by the constitutional provision that excessive fines shall not be imposed. . . . It necessarily follows that the discretion of the trial Court in its determination of the amount of the penalty, where the maximum amount of the fine is not fixed by the statute, must be subject to be reviewed on appeal to this Court, if clearly abused, under Article I, Section 19 [now Section 15] of the Constitution, which not only forbids the infliction of cruel and unusual punishment, but forbids the imposition of excessive fines."). Although *Singletary* involved a statute with no maximum penalty, the South Carolina Supreme Court stated explicitly that the excessive fines clause applied not only to the exercise of discretion by the courts when the legislature had set no bounds, but also in other circumstances. *Id.*, 191 S.C. at 158 ("We regard this constitutional restriction as an admonition . . . intended to embrace *the Legislature* and the judiciary." (emphasis added)).

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"The touchstone of the constitutional inquiry under the Excessive Fines Clause is the principle of proportionality: The amount of the forfeiture must bear some relationship to the gravity of the offense that it is designed to punish." *Bajakajian*, 524 U.S. at 334. A very large financial penalty in a case like this one, involving the supposed "inadequacy" of an FDA-approved product label – the sort of award the State seems likely to request – surely would be an unconstitutional "excessive fine." Indeed, in *In re Zyprexa Products Liability Litigation*, 671 F. Supp. 2d 397, 460 (E.D.N.Y. 2009), the court rejected the exact same expansive statutory penalty theory that the State is pursuing in this action, namely, the maximum statutory penalty for every prescription. The Zyprexa court first held that "proper

assessment of the claimed penalties would require individualized consideration of the circumstances of each prescription alleged to be in violation of the statute," which would be impracticable, if not impossible:

> Because the penalty is said to apply regardless of any costs or damages borne by the State, Mississippi requests a penalty to be assessed for each of almost a million estimated Zyprexa prescriptions in Mississippi. The statutory language indicates that the enforcing court is invested with discretion to determine the appropriate amount of the penalty with respect to each violation, whether the maximum of $10,000 or some smaller amount. The statute does not specify what factors are to inform the court's determination, but in the present case the court may wish to consider a number of issues as they bear on each Zyprexa prescription, including but not limited to: whether the prescription was for an on-label or off-label use; whether the prescription was medically necessary; whether the patient received any benefit from Zyprexa; whether and the extent to which the patient experienced any of Zyprexa's potential metabolic side effects; the information about Zyprexa available to the medical community at the time the prescription was written; and the times of the various alleged instances of misconduct by Lilly, and whether and to what extent each instance may have impacted the prescription in question.
>
> . . . .
>
> Regardless of the lack of individualized evidence, imposition of civil penalties on a per-violation basis would entail separate examination of each of hundreds of thousands of claimed violations for purposes of determining the appropriate fine. Such an inquiry is impractical and beyond the resources of any court.

*Id.* at 458-59.

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More important for purposes of this argument, the *Zyprexa* court held that the statutory claims for substantial civil penalties implicated *constitutional* considerations. *Id.* at 463 ("Under this constitutional fairness and equity standard, Mississippi's requests for statutory penalties on a per-violation basis, in addition to actual damages sought, would result in a multibillion dollar cumulative penalty grossly disproportionate to both the injury Mississippi has suffered and the seriousness of Lilly's alleged misconduct."). This same

constitutional problem arises in this case. The State's improper request for a large financial penalty without a single dollar of actual loss or a single instance of personal injury implicates serious constitutional considerations under both federal and state law. On this basis as well, an award of very substantial civil penalties would be improper.

3. **First Amendment**

The First Amendment to the United States Constitution also prevents the Court from imposing the oppressive civil penalties likely to be sought by the State. Even under the intermediate scrutiny test protecting commercial speech, regulation of (1) speech about a lawful commercial activity that is not misleading must (2) directly and materially advance a substantial state interest and (3) be no more restrictive than reasonably necessary. *Cent. Hudson Gas & Electric Corp. v. Pub. Serv. Comm'n*, 447 U.S. 557, 564 (1980) ("*Central Hudson*"). Therefore, to satisfy the requirements of the First Amendment, the State must show that imposition of civil penalties is no more restrictive than reasonably necessary to directly and materially advance a substantial state interest.

The first element of the *Central Hudson* test is sometimes paraphrased as stating that misleading commercial speech is not entitled to First Amendment protection. A finding that the subject speech had the *capacity* or the *tendency* to mislead – i.e., that it is "potentially misleading" – does not satisfy the threshold recognized by *Central Hudson* for withholding First Amendment protection. As the Fifth Circuit recently summarized the governing law:

> Advertising that "is inherently likely to deceive or where the record indicates that a particular form or method . . . of advertising has in fact been deceptive" receives no protection and the State may prohibit it entirely. *In re R.M.J.*, 455 U.S. 191, 202 (1982). Advertising that is potentially misleading – because it "may be presented in a way that is not deceptive" – may be regulated if it satisfies one of two standards. *See id.* at 203; *see also Zauderer v. Office of Disciplinary Counsel of the Sup. Ct. of Ohio*, 471 U.S. 626, 651 (1985). A regulation that

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> restricts potentially misleading commercial speech will pass constitutional muster if "the regulation directly advances a substantial government interest" and "is not more extensive than is necessary to serve that interest." *Central Hudson*, 447 U.S. at 566. A regulation that imposes a disclosure obligation on a potentially misleading form of advertising will survive First Amendment review if the required disclosure is "reasonably related to the State's interest in preventing deception of consumers." *Zauderer*, 471 U.S. at 651.

*Pub. Citizen Inc. v. La. Attorney Disciplinary Bd.*, 632 F.3d 212, 218 (5th Cir. 2011).

The jury's verdict in this case did not distinguish between "unfair" or "deceptive" conduct. At most, the verdict established that unspecified statements in the November 2003 mailing or the package insert had the *capacity* to mislead, not that any statement "has in fact been deceptive." This is especially true given the State's repeated assertion that it need not show "actual deception." *See, e.g.*, Trial Tr. vol. VII, 1362:1-5, Mar. 15, 2011 (argument by Mr. Cowan, counsel for the State, that: "The State proved tendency to deceive, which is all that the burden requires, as opposed to actual deception, which is what they argue, again, in their brief, or likely to deceive, which is not the language of the South Carolina standard."). Such a minimal showing requires that any government action with respect to the statement, including the imposition of penalties, satisfy the other elements of the *Central Hudson* test, i.e., that the remedy the State seeks is no more restrictive than reasonably necessary to directly and materially advance a substantial state interest. *See, e.g.*, *Peel v. Attorney Registration & Disciplinary Comm'n of Ill.*, 496 U.S. 91, 100-01, 106-07 (1990) (finding that bar of commercial speech violates First Amendment where "[t]here is no contention that any potential client or person was actually misled or deceived by petitioner's stationery. Neither the Commission nor the State Supreme Court made any factual finding of actual deception or misunderstanding . . . ."). Thus, "[a] governmental body seeking to sustain a restriction on commercial speech must demonstrate that the harms it recites are real and that its restrictions will in fact alleviate them to a material

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degree." *Video Gaming Consultants, Inc. v. S.C. Dep't of Revenue*, 342 S.C. 34, 42, 535 S.E.2d 642, 646 (2000) (citation omitted).

Accordingly, the Court may impose a civil penalty only if it finds such a penalty directly and materially advances a substantial state interest, and that other forms of regulation less restrictive than punishment, such as requiring disclaimers or other clarifying speech, would be insufficient to satisfy the State's interests. *See Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 371 (2002) ("[I]f the Government could achieve its interests in a manner that does not restrict speech, or that restricts less speech, the Government must do so."). As the State has made no showing – and can make no showing – that only an award of millions of dollars in penalties is necessary, its requested relief fails to satisfy the applicable constitutional standards.

## III. CONCLUSION

The present case is far removed from the typical consumer protection actions from South Carolina and elsewhere. This case has at its origins the cumulative work of doctors and scientists who have used their years of training and experience to develop successfully a medication that by all accounts safely and effectively treats thousands upon thousands of mentally ill citizens in South Carolina and throughout the United States. In many of the cases, courts have resorted to the remedy of civil penalties only because their orders and injunctions have been willfully and repeatedly violated. There was nothing like that here. Yet, the State has sought to extract from Janssen a civil penalty that exceeds beyond any reasonable measure the awards in these other consumer protection cases. And it has sought this extraordinary punishment without proof that a single doctor in South Carolina was actually deceived or a single South Carolina citizen was actually harmed by Janssen's medication. But, as the South Carolina Supreme Court has cautioned, "The state's interests in awarding punitive damages must remain consistent with the principle of penal

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theory that 'the punishment should fit the crime.'" Mitchell, 385 S.C. at 584, 686 S.E.2d at 183 (citation omitted).

This Court should reject the State's invitation to abandon all principles of fairness and due process, and it should award a minimum civil penalty, if any is to be awarded at all.

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# EXHIBIT A

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA<br>Ex rel. Henry McMaster, in his Capacity as Attorney General of the State of South Carolina,<br><br>PLAINTIFF,<br><br>v.<br><br>JANSSEN PHARMACEUTICA, INC., JANSSEN, LP, and JOHNSON & JOHNSON,<br><br>DEFENDANTS. | IN THE COURT OF COMMON PLEAS<br><br>FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>Civil Action No.: 2007-CP-42-1438<br><br>PLAINTIFF STATE OF SOUTH CAROLINA'S ANSWERS TO DEFENDANTS' FIRST SET OF INTERROGATORIES |

TO: STEVEN W. HAMM, ATTORNEYS FOR DEFENDANTS

Pursuant to Rule 33 of the South Carolina Rules of Civil Procedure, the Plaintiff State of South Carolina (the "State"), by and through the undersigned attorneys, hereby answers the Interrogatories propounded by Defendants as follows:

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## GENERAL OBJECTIONS

The State makes the following general objections, which are incorporated into its responses below and are in addition to its specific objections to individual discovery requests.

1. The State objects to discovery seeking medical records and/or detailed medical information pertaining to individual patients participating in the State's medical assistance programs. The State is not seeking damages for individual patients and does not intend to prove its case by presenting evidence regarding specific patients. Discovery of the identity and records of individual patients would be extraordinarily intrusive and expose highly personal and private information. Such invasion of the privacy of individual patients would not lead to the discovery or

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relevant or admissible evidence in this case.

2. The State objects to the discovery requests to the extent they seek privileged information and/or information beyond the scope of permissible discovery. The State further objects to the discovery requests to the extent they are vague and ambiguous, unduly burdensome, not reasonably calculated to lead to the discovery of admissible evidence, propounded solely for the purposes of harassment and constitute an impermissible "fishing expedition."

3. The State neither admits the existence of any facts set forth in any request or assumed by any request. The State does not concede the relevance of any request or any subject matter to which a request refers.

4. The State objects to these interrogatories to the extent the number of interrogatories exceeds the number allowed under Rule 33 of the South Carolina Rules of Civil Procedure. Any answer by the State to excess interrogatories does not concede the propriety of that interrogatory.

## ANSWERS TO INTERROGATORIES

**INTERROGATORY NO. 1:** Please identify all persons who are employed by Plaintiff who otherwise are representatives or agents of Plaintiff from whose files You produced documents responsive to Janssen Pharmaceutica Inc. and Janssen, L.P.'s First Set of Requests for Production of Documents Directed to Plaintiff.

**ANSWER:**

The State further objects to this request as premature because the gathering of responsive material is ongoing. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information from the state agencies listed below and will supplement this response as necessary: (a) the South Carolina Department of Health and Human Services; (b) the South Carolina Department of Mental Health; and (c) the South Carolina State

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Employees Health Plan.

INTERROGATORY NO. 2: Please identify all employees, agents, representatives, or attorneys of the State of South Carolina, the Attorney General for the State of South Carolina, the SCDHHS, the SCDMH, and the SHP who were consulted by counsel for Plaintiff concerning the initiation of this Action, including the drafting and filing of the Complaint in this Action.

ANSWER:

The State further objects to this request to the extent it seeks privileged and confidential information, including information protected by the attorney-client privilege and the attorney work-product privilege. Subject to and without waiving the foregoing general and specific objections, counsel consulted with the Attorney General's office concerning the initiation of this Action, including the drafting and filing of the Complaint. All other consultation with employees of the State would be privileged.

INTERROGATORY NO. 3: Please identify each specific healthcare professional who has prescribed Risperdal® for an off-label use or dosage, a non-medically accepted indication, or a non-medically necessary use for a South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program, and state the date(s) of each prescription.

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ANSWER:

The State further objects to this request as unduly burdensome, propounded for the purpose of harassment, not reasonably calculated to lead to the discovery of admissible evidence, and properly subject of medical and expert testimony.

INTERROGATORY NO. 4: Please state which of the healthcare professionals identified in Your response to Interrogatory No. 3 have made a statement to You that their act of prescribing Risperdal® for an off label use or dosage, a non-medically accepted indication, or a non-medically

necessary use was in any way influenced by any action, occurring after December 31, 1993, attributable to Janssen.

ANSWER:

Please see Answer to Interrogatory No. 3 above.

INTERROGATORY NO. 5: Please identify and set forth any statements or complaints, oral or written, that You have made to the Food and Drug Administration regarding Risperdal® or any other atypical antipsychotic medication of the same class as Risperdal®.

ANSWER:

Subject to and without waiving the foregoing general, the State has made no complaints to the Food and Drug Administration regarding Risperdal® or any other atypical antipsychotic medication of the same class as Risperdal®.

INTERROGATORY NO. 6: Please identify and set forth any statements or complaints, oral or written, made by a healthcare professional to You and/or the Food and Drug Administration regarding any statement made or any document disseminated by any Janssen employee, agent, representative in the course of detailing, marketing, or otherwise promoting Risperdal®.

ANSWER:

The State further objects to this request as vague, ambiguous, unduly burdensome, propounded for the purpose of harassment, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, please see the Answer to Interrogatory No. 3 above.

INTERROGATORY NO. 7: Please identify and set forth any statements or complaints, oral or written, concerning Risperdal® made to You by any South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program who has taken Risperdal®, or who is

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the guardian of any South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program who has taken Risperdal®.

ANSWER:

The State further objects to this request as unduly burdensome, propounded for the purpose of harassment, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State responds as follows: No formal mechanism exists within the SHP or the SCDMH that tracks complaints regarding specific drugs. The State will supplement this response as to Medicaid participants.

INTERROGATORY NO. 8: Please state what policies, if any, the State of South Carolina has had in place, since 1993, regarding off-label uses of prescription medications, uses of prescription medications for indications that are not medically accepted, and uses of prescription medications that are not medically necessary.

a. If the State of South Carolina has not promulgated written policies regarding same, please state what the State of South Carolina's unwritten policy is and/or has been, or state why the State of South Carolina has no such policy.

ANSWER:

The State further objects to this request as vague and ambiguous and as not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State's policy is not to reimburse prescriptions written for off-label uses, prescriptions written for indications that are not medically accepted, and prescriptions written for medications that are not medically necessary. Further responsive information is available in the South Carolina Department of Health and Human Services Medicaid Provider Manual (updated December 1, 2007) (the "Provider Manual"), which is available on the SCDHHS webpage.

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**INTERROGATORY NO. 9:** Please state and describe the procedure or process by which healthcare professionals entered into provider agreements with the State of South Carolina under South Carolina's Medicaid Program during calendar years 1994-2007.

**ANSWER:**

The State further objects to this request as vague and ambiguous, unduly burdensome, propounded for the purpose of harassment, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State will produce the Provider Manual, which contains responsive information..

**INTERROGATORY NO. 10:** Please describe what You believe to be the risks or benefits of Risperdal®.

**ANSWER:**

The State further objects to this request as premature, vague and ambiguous, overly broad, and properly the subject of medical and scientific expert testimony.

**INTERROGATORY NO. 11:** Please identify and set forth any oral or written statements concerning Risperdal® that You contend were made by Janssen or any of its employees that were directed to any South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program, or any guardian of any South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program, who is not a healthcare professional.

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**ANSWER:**

The State further objects to this request as unduly burdensome and premature. At this stage of discovery, the State is unclear as to the extent of direct consumer marketing by Janssen or its employees and requires discovery responses from Defendants to fully respond to this request. The State will supplement this response as necessary.

INTERROGATORY NO. 12: Please identify and set forth any oral or written statements concerning Risperdal® made by any Janssen employee to any healthcare professional that You contend were fraudulent and/or misleading. As to each statement:

a. Identify the maker;
b. Identify the recipient(s);
c. State date(s) on which it was made; and
d. Identify the place where it was made.

ANSWER:

The State further objects to this request as unduly burdensome, overly broad, and premature. The State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 13: Please identify all epidemiological studies, clinical trials, or other scientific studies concerning Risperdal® that You contend Janssen misrepresented to, or concealed from, healthcare professionals and South Carolina Medicaid participants, SHP participants, or patients under the care of the SCDMH program.

ANSWER:

The State further objects to this request as premature, vague, and ambiguous, and the proper subject of medical and expert testimony.

INTERROGATORY NO. 14: Please (a) identify, separately for each South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program, all injuries allegedly suffered as a result of taking Risperdal®, (b) state the date she/he was diagnosed with the injury, (c) state Your basis for asserting that each such injury resulted from Risperdal®, (d) identify the dosage and period of time over which he/she took Risperdal®, and (e) state whether he/she ever took any antipsychotic medicines other than Risperdal® and, if so, identify the other antipsychotic

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medicines as well as the dosage and period of time over which he/she took such medicines.

ANSWER:

The State further objects to this request as unduly burdensome, unduly invasive of patient privacy, propounded for the purpose of harassment, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State will produce a list of patients, identified by number, who are or have taken Risperdal during the time period in question.

INTERROGATORY NO. 15: Please describe the process through which the State of South Carolina has authorized reimbursement for prescription medication through the South Carolina Medicaid Program since 1993.

ANSWER:

The State further objects to this request as vague and ambiguous. Subject to and without waiving the foregoing general and specific objections, the State will produce the Provider Manual, which contains responsive information.

INTERROGATORY NO. 16: Please describe the process through which the State of South Carolina has authorized the purchase of prescription medication through the SCDMH program since 1993.

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ANSWER:

The State further objects to this request as vague and ambiguous. Subject to and without waiving the foregoing general and specific objections, [DOES THE SCDMH HAVE A MANUAL; DOES MEDCO PROCESS THESE CLAIMS?].

INTERROGATORY NO. 17: Please describe the process through which the State of South Carolina has authorized reimbursement for prescription medication through the SHP program since

1993.

ANSWER:

Subject to and without waiving the foregoing general and specific objections, the State of South Carolina, since 1993, has authorized reimbursement for prescription medication through the SHP program for any FDA approved drug.

INTERROGATORY NO. 18: Please identify and describe any communications between the State of South Carolina and any federal agency, including the Food and Drug Administration and the Commission for Medicare and Medicaid Services, regarding reimbursement for Risperdal® through the South Carolina Medicaid Program.

ANSWER:

The State further objects to this request as vague, ambiguous, overly broad, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is searching for responsive information and will supplement its response as necessary.

INTERROGATORY NO. 19: Please identify each individual, including consultants or other independent contractors hired by the State of South Carolina, who participated in the decision to place Risperdal® on South Carolina's Medicaid formulary or Preferred Drug List, and for each such individual specify:

a. The individual's name, title, address, and telephone number;
b. Whether the individual is still a South Carolina official, consultant, employee, or agent;
c. A summary of the person's involvement in the review and approval process for Risperdal® on the formulary or Preferred Drug List; and
d. The individual's background and qualifications related to that individual's participation in the decision to place Risperdal® on the formulary or Preferred Drug List.
e. A description of any knowledge that individual has regarding Risperdal®, including information related to the placement of Risperdal® on (1) the

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Medicaid formulary and (2) the Preferred Drug List.

ANSWER:

The State further objects to this request as unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 20: Please identify each individual, including consultants or other independent contractors hired by the State of South Carolina, who participated in the decision to place Risperdal® on the SCDMH program's formulary or Preferred Drug List, and for each such individual specify:

a. The individual's name, title, address, and telephone number;
b. Whether the individual is still a South Carolina official, consultant, employee, or agent;
c. A summary of the person's involvement in the review and approval process for Risperdal® on the formulary or Preferred Drug List; and
d. The individual's background and qualifications related to that individual's participation in the decision to place Risperdal® on the formulary or Preferred Drug List.
e. A description of any knowledge that individual has regarding Risperdal®, including information related to the placement of Risperdal® on (1) the formulary and (2) the Preferred Drug List.

ANSWER:

The State further objects to this request as unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 21: Please identify each individual, including consultants or other independent contractors hired by the State of South Carolina, who participated in the decision to place Risperdal® on the SHP's formulary or Preferred Drug List, and for each such individual

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specify:

a. The individual's name, title, address, and telephone number;
b. Whether the individual is still a South Carolina official, consultant, employee, or agent;
c. A summary of the person's involvement in the review and approval process for Risperdal® on the formulary or Preferred Drug List; and
d. The individual's background and qualifications related to that individual's participation in the decision to place Risperdal® on the formulary or Preferred Drug List.
e. A description of any knowledge that individual has regarding Risperdal®, including information related to the placement of Risperdal® on (1) the formulary and (2) the Preferred Drug List.

ANSWER:

Subject to and without waiving the foregoing general and specific objections, the State will supplement this response.

INTERROGATORY NO. 22: Please identify all members of the South Carolina Board of Pharmacy during calendar years 1994-2007. In identifying these individuals, please provide:

a. The individual's name, title, address and telephone number;
b. The individual's background and qualifications related to that individual's position on the State Board of Pharmacy;
c. The dates during which the individual was involved with the State Board of Pharmacy; and
d. A description of any knowledge that individual has regarding Risperdal® including information related to the placement of Risperdal® on (1) the Medicaid formulary and (2) the Preferred Drug List.

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ANSWER:

The State further objects to this request as unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the following is a list of the current members of the South Carolina Board of Pharmacy:

**Dock Henry Rose , R.Ph.**
Board Position: Chair

Statutory Designation: Registered Pharmacist
Term Appoint Date: 6/30/2002
Term Expire Date: 6/30/2008

**Davis C. Hook, Jr., R.Ph.**
Board Position: Vice Chair
Statutory Designation: Registered Pharmacist
Term Appoint Date: 7/1/1997
Term Expire Date: 6/30/2009

**David M. Banks, R.Ph.**
Board Position: Member
Statutory Designation: Registered Pharmacist
Term Appoint Date: 4/1/2004

**James R. Bradham, R.Ph.**
Board Position: Member
Statutory Designation: Registered Pharmacist
Term Appoint Date: 3/23/2006
Term Expire Date: 6/30/2011

**Joseph D. Bushardt, R.Ph.**
Board Position: Member
Statutory Designation: Registered Pharmacist
Term Appoint Date: 3/19/2007
Term Expire Date: 6/30/2012

**Hubert "Hugh" F. Mobley, R.Ph.**
Board Position: Member
Statutory Designation: Registered Pharmacist
Term Appoint Date: 6/30/2007
Term Expire Date: 6/30/2013

**Leo Richardson, Ph.D.**
Board Position: Member
Statutory Designation: General Public
Term Appoint Date: 6/27/2000

**W. Allen Toole, R.Ph.**
Board Position: Member
Statutory Designation: Registered Pharmacist
Term Appoint Date: 5/27/2004
Term Expire Date: 6/30/2010

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INTERROGATORY NO. 23: Please describe the procedure by which the State of South

Carolina reviews or administers claims under the Medicaid Program, and identify all persons or entities involved in the review or administration of claims involving Risperdal®. In identifying these individuals and/or entities, please provide:

a. The entity's or individual's name, title, address, and telephone number;
b. The individual's background and qualifications related to that individual's involvement with the review or administration process;
c. The dates during which the individual or entity was involved with the review or administration process; and
d. A description of any knowledge that individual or entity has regarding Risperdal® and any claims involving Risperdal®.

ANSWER:

The State further objects to this request as vague and ambiguous, unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is producing the Provider Manual, which contains responsive information.

INTERROGATORY NO. 24: Please describe the procedure by which the State of South Carolina reviews or administers claims under the SHP program, and identify all persons or entities involved in the review or administration of claims involving Risperdal®. In identifying these individuals and/or entities, please provide:

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a. The entity's or individual's name, title, address, and telephone number;
b. The individual's background and qualifications related to involvement with the review or administration process;
c. The dates during which the individual or entity was involved with the claims review or administration process; and
d. A description of any knowledge that individual or entity has regarding Risperdal® and any claims involving Risperdal®.

ANSWER:

The State further objects to this request as vague and ambiguous, unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, , the State is producing the Provider Manual,

which contains responsive information.

INTERROGATORY NO. 25: Please describe the procedure by which the State of South Carolina authorizes the purchase of prescription medications for patients under the SCDMH program and identify all persons or entities involved in authorizing the purchase of Risperdal® under the SCDMH program. In identifying these individuals and/or entities, please provide:

a. The entity's or individual's name, title, address, and telephone number;
b. The individual's background and qualifications related to involvement in authorizing the purchase of Risperdal®;
c. The dates during which the individual or entity was involved in authorizing the purchase of Risperdal®; and
d. A description of any knowledge that individual or entity has regarding Risperdal® and any purchases of Risperdal®.

ANSWER:

The State further objects to this request as vague and ambiguous, unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, , the State is producing the Provider Manual, which contains responsive information.

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INTERROGATORY NO. 26: Please set forth and explain the procedure and criteria used in evaluating the safety of antipsychotic medicines that have been placed on (1) South Carolina's Medicaid formulary and (2) South Carolina's Preferred Drug List, including the State of South Carolina's consideration of any P&T Committee's recommendations. Specifically, in identifying the procedure and criteria, include a description of how the State of South Carolina evaluated the safety of Risperdal® when considering whether Risperdal® should be placed on the State of South Carolina's Preferred Drug List.

ANSWER:

The State further objects to this request as vague and ambiguous, unduly burdensome and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without

waiving the foregoing general and specific objections, the Statedoes not perform any independent specific safety evaluation for any drugs including antipsychotic medicines.

INTERROGATORY NO. 27: Please state the amount of funds You spent on behalf of South Carolina Medicaid participants for prescriptions of Risperdal® filled in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

Subject to and without waiving the foregoing objections, the State is producing responsive information.

INTERROGATORY NO. 28: Please state the amount of funds You spent on behalf of SHP participants for prescriptions of Risperdal® filled in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

Subject to and without waiving the foregoing objections, the State possesses and is producing data indicating the amount of funds the State spent on behalf of SHP participants for prescriptions of Risperdal®.

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INTERROGATORY NO. 29: Please state the amount of funds You spent on behalf of patients under the care of the SCDMH program for prescriptions of Risperdal® filled in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

Subject to and without waiving the foregoing objections, the State is producing responsive information.

INTERROGATORY NO. 30: Please state the amount that You have received from Janssen for Medicaid-related rebates for Risperdal® prescriptions filled in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

The State further objects to this request as seeking information equally available to Defendants as to the State. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 31: Please state the amount of funds that the Centers for Medicare and Medicaid Services paid You for prescriptions of Risperdal® filled in each of the following calendar years for South Carolina Medicaid participants: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 32: Please identify all prescriptions for Risperdal®, written for a "non-medically necessary" use or a "non-medically accepted" indication, filled for South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

The State further objects to this request as premature, unduly burdensome, overly broad, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and

specific objections, the State is producing pharmacy data regarding Risperdal prescriptions filled for South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program.

INTERROGATORY NO. 33: With regard to the prescriptions identified in Your response to Interrogatory No. 32, please (a) identify those that were not written as a result of Janssen's allegedly improper efforts to facilitate and promote prescriptions of Risperdal® for "non-medically necessary" uses or "non-medically accepted" indications, and (b) state Your basis for identifying each prescription as one that was written for a "non-medically necessary" use or "non-medically accepted" indication.

ANSWER:

The State further objects to this request as premature, undly burdensome, overly broad, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is producing pharmacy data regarding Risperdal prescriptions filled for South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program.

INTERROGATORY NO. 34: Please state the amount of discount and/or rebate payments that You have received from Janssen under any South Carolina program other than Medicaid for Risperdal® prescriptions filled in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

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ANSWER:

The State further objects to this request as seeking information equally available to Defendants as to Plaintiff, and as not reasonably calculated to lead to the discovery of admissible evidence. The State requires discovery responses from Defendants to fully respond to this request.

Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 35: Please set forth the amount of Medicaid funds You spent to pay for Risperdal® prescriptions, written for non-medically accepted indications or non-medically necessary uses, filled for South Carolina Medicaid participants in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 36: How much of the Medicaid funds set forth in Your response to Interrogatory No. 35 did You spend as a result of Janssen's "protracted and willful course of corporate misconduct and misrepresentation," as alleged in Paragraph 13 of the Complaint?

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 37: Please set forth the amount of funds You spent to pay for Risperdal® prescriptions, written for non-medically accepted indications or non-medically necessary uses, filled for SHP participants in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

The State further objects to this request as premature and properly the subject of expert

testimony.

INTERROGATORY NO. 38: How much of the funds set forth in Your response to Interrogatory No. 37 did You spend as a result of Janssen's "protracted and willful course of corporate misconduct and misrepresentation," as alleged in Paragraph 13 of the Complaint?

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony

INTERROGATORY NO. 39: Please set forth the amount of funds You spent to pay for Risperdal® prescriptions, written for non-medically accepted indications or non-medically necessary uses, filled for patients under the care of the SCDMH program in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony.

INTERROGATORY NO. 40: How much of the funds set forth in Your response Interrogatory No. 39 did You spend as a result of Janssen's "protracted and willful course corporate misconduct and misrepresentation," as alleged in Paragraph 13 of the Complaint?

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony.

INTERROGATORY NO. 41: Please state the amount of funds that You contend You would have saved if, instead of Risperdal®, a first generation antipsychotic medicine had been prescribed

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for all South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program who took Risperdal® in each of the following calendar years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007. For each calendar year, please:

a. Identify the amount that You contend You would have saved in treatment costs associated with the injuries, diseases, or potentially life threatening medical conditions allegedly caused by taking Risperdal®; and
b. Identify the amount that You contend You would have saved in reimbursements for prescriptions filled for South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program.

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 42: Please identify each and every South Carolina state hospital and mental health facility where SCIMAP has been implemented and as to each state the date on which SCIMAP first was implemented.

ANSWER:

The State further objects to this request as vague and ambiguous and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement when necessary.

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INTERROGATORY NO. 43: Please identify each and every South Carolina correctional facility where SCIMAP has been implemented, and as to each state the date on which SCIMAP first was implemented.

ANSWER:

The State further objects to this request as not reasonably calculated to lead to the discovery of admissible evidence. At this point in the litigation the State is not alleging any damages based on reimbursement expenses at South Carolina correctional facilities.

INTERROGATORY NO. 44: Please describe in detail the process by which You developed or created SCIMAP as an algorithm or protocol for the treatment of or schizophrenia in South Carolina state hospitals, mental health facilities, and correctional facilities.

ANSWER:

The State further objects to this request as unduly burdensome, vague and ambiguous and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 45: Please identify all current and former South Carolina employees who participated in the creation or development of SCIMAP, and state what role each played in the creation or development of SCIMAP.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 46: Please state the date on which a formulary or Preferred Drug List first was established for the medicines covered under the South Carolina Medicaid Program.

RESPONSE:

The State further objects to this request as vague and ambiguous and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will

supplement as necessary.

INTERROGATORY NO. 47: Please identify every member of the SCDHHS P&T Committee and every member of any other P&T Committee who reviewed, assessed or otherwise evaluated SCIMAP prior to its implementation.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 48: Please identify the members of the SCDHHS P&T Committee during each of the following years: 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, and 2007.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 49: Please list the criteria employed by the SCDHHS or the P&T Committee in considering whether to place Risperdal® on any formulary.

ANSWER:

The State further objects to this request as vague and ambiguous. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 50: Please list the criteria employed by the SCDMH in considering whether to place Risperdal® on any formulary.

ANSWER:

The State further objects to this request as vague and ambiguous. Subject to and without

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waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 51: Please list the criteria employed by the SHP in considering whether to place Risperdal® on any formulary.

ANSWER:

Subject to and without waiving the foregoing general and specific objections, SHP did not make the decision to place Risperdal® on any formulary. The State retains Medco to maintain the formulary.

INTERROGATORY NO. 52: Please state the date when the SCDHHS P&T Committee first developed guidelines to monitor and evaluate possible side effects of antipsychotic medications.

ANSWER:

The State further objects to this request as vague and ambiguous Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 53: Please state and explain in detail all restrictions imposed by the SCDMH, the SHP, the SCDHHS, or the P&T Committee on the prescription of Risperdal® in South Carolina state hospitals, mental health facilities, correctional facilities, and other healthcare facilities since its initial inclusion as a covered drug on the South Carolina formulary.

ANSWER:

The State further objects to this request as vague and ambiguous and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

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**INTERROGATORY NO. 54:** With respect to the allegations in Paragraph 77 of the Complaint that "[t]he defective condition of Risperdal directly and proximately caused South Carolina residents to suffer various Risperdal-induced diseases, injuries and sicknesses" please:

a. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
b. Identify all other persons with knowledge about these allegations;
c. Identify all South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program who You contend have suffered Risperdal®-induced diseases, injuries or sicknesses after taking Risperdal® together with their healthcare providers;
d. Identify each disease, injury or sickness that You contend was caused, in whole or in part, by Risperdal®; and
e. Identify all documents that support or otherwise relate to these allegations.

**ANSWER:**

The State further objects to this request as unduly burdensome and invasive of patient privacy, propounded for the purpose of harassment, premature, properly the subject of expert testimony, and not reasonably calculated to lead to the discovery of admissible evidence. The State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

**INTERROGATORY NO. 55:** Please identify each individual pediatric injury that You consider to be Risperdal®-related and the treatment of which required expenditures by Yo

**ANSWER:**

The State further objects to this request as properly the subject of expert testimony.

**INTERROGATORY NO. 56:** With respect to the allegations in Paragraph 90 of the Complaint that Janssen "knowingly caused false claims for payment to the State's Medicaid program by intentionally promoting non-medically accepted indications and non-medically necessary uses of Risperdal to prescribing physicians," please:

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a. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
b. Identify all other persons with knowledge about these allegations;
c. Please identify each specific Janssen employee, agent, or representative who You contend illegally promoted Risperdal® for non-medically accepted indications and non-medically necessary uses in South Carolina and state the dates of each allegedly illegal act; and
d. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as unduly burdensome, premature, and properly the subject of expert testimony. The State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 57: Please identify each specific healthcare professional that You contend was illegally detailed or otherwise solicited by Janssen employees, agents, or representatives to prescribe Risperdal® for an off-label use or dosage, a non-medically accepted indication, or a non-medically necessary use for a South Carolina Medicaid participant, SCDMH participant, or patient under the care of the SCDMH program.

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ANSWER:

The State further objects to this request as unduly burdensome, overly broad, properly the subject of expert testimony, seeking information equally available to Defendants as to Plaintiff and not reasonably calculated to lead to the discovery of admissible evidence. The State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 58: Please identify and describe the place, time, and manner in

which each specific healthcare professional identified in Your response to Interrogatory No. 57 was illegally detailed or otherwise solicited by Janssen employees, agents, or representatives to prescribe Risperdal® for an off-label use or dosage, a non-medically accepted indication, or a non-medically necessary use for a South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program.

ANSWER:

The State further objects to this request as seeking information equally available to Defendants as to Plaintiff and not reasonably calculated to lead to the discovery of admissible evidence. The State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 59: With respect to the allegations in Paragraphs 21 and 90 of the Complaint that Janssen "knowingly" caused prescriptions for non-medically accepted indications and non-medically necessary uses of Risperdal® to be submitted to Medicaid for reimbursement, please:

a. Identify the person or persons most knowledgeable about these allegations;
b. Identify all other persons with knowledge about these allegations;
c. Identify each Janssen employee, agent, or representative who You contend promoted Risperdal® for non-medically accepted indications and non-medically necessary uses with knowledge that such indications were not medically accepted and such uses were not medically necessary;
d. State Your basis for alleging that each such Janssen employee, agent, or representative "knew" that the allegedly promoted uses and indications were not medically accepted and were not medically necessary; and
e. Identify all documents that support or otherwise relate to these allegations.

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ANSWER:

The State further objects to this request as unduly burdensome, premature, and properly the subject of expert testimony. The State requires discovery responses from Defendants to fully

respond to this request. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 60: When do You contend that Janssen first learned of Your beliefs regarding the "medically accepted indications" and "medically necessary uses" of Risperdal®?

ANSWER:

The State further objects to this request as vague and ambiguous, the proper subject of expert testimony, and not reasonably calculated to lead to the discovery of admissible evidence.

INTERROGATORY NO. 61: Please describe how Janssen first made aware of Your beliefs regarding the "medically accepted indications" and "medically necessary uses" of Risperdal®.

ANSWER:

The State further objects to this request as vague and ambiguous, the proper subject of expert testimony, and not reasonably calculated to lead to the discovery of admissible evidence.

INTERROGATORY NO. 62: With respect to the allegations in Paragraph 95 of the Complaint that Janssen "fraudulently represented that Risperdal is safer and more effective than less expensive, first generation antipsychotics," please:

a. Identify all employees, agents, or representatives of Janssen who You contend intentionally misrepresented that Risperdal® is safer than less expensive, first generation antipsychotics;
b. Identify the healthcare professionals to whom these allegedly false representations were directed; and
c. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as premature and the proper subject of expert testimony,. The State requires discovery responses from Defendants to fully respond to this request.

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Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 63: Please identify each antipsychotic medicine that You contend is less expensive, equally effective, and safer than Risperdal®.

ANSWER:

The State further objects to this request as premature, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 64: Do You contend that You are entitled to reimbursement for all expenditures made by the State of South Carolina for Risperdal® prescriptions because, for every such prescription, a first-generation antipsychotic should have been prescribed instead? If Your answer is anything other than an unqualified "yes," please identify and describe any Risperdal® prescriptions for which You do not seek reimbursement.

ANSWER:

The State further objects to this request as unduly burdensome, premature, vague and ambiguous, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 65: With respect to the allegations in Paragraph 43 of the Complaint that "Medical literature dating as far back as the 1950s ... demonstrated that Risperdal, like older antipsychotic medications, had the potential to cause diabetes, diabetes-related injuries (e.g. weight gain and hyperglycemia), cardiovascular and cerebrovascular complications, and other severe adverse effects," please:

a. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
b. Identify all other persons with knowledge about these allegations;
c. Identify each piece of "medical literature" from the 1950's to the present that You contend demonstrates that antipsychotic drugs have the potential to cause diabetes, diabetes-related injuries (e.g., weight gain and hyperglycemia), cardiovascular and cardiovascular complications, and other severe adverse effects; and
d. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as the proper subject of expert testimony. Further, the State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 66: Do You contend that You are entitled to reimbursement for any expenditures made by the State of South Carolina for Risperdal® prescriptions filled prior to March 3, 2002, under the Medicaid, SCDMH, and SHP programs, for off-label or non-FDA-approved uses? If Your answer is anything other than an unqualified "no," identify each use of Risperdal® that You contend was not medically necessary and not medically accepted and for which You seek reimbursement of expenditures made prior to March 3, 2002.

ANSWER:

The State further objects to this request as unduly burdensome, premature, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 67: Do You contend that You are entitled to reimbursement for any expenditures made by the State of South Carolina for Risperdal® prescriptions filled after March 3, 2002, under the Medicaid, SCDMH, and SHP programs, for off-label or non-FDA-

approved uses? If Your answer is anything other than an unqualified "no," identify each off-label use of Risperdal® that You contend was not medically necessary and not medically accepted and for which You seek reimbursement of expenditures made after March 3, 2002.

ANSWER:

The State further objects to this request as unduly burdensome, premature, and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 68: Do You contend that healthcare professionals, who prescribed Risperdal® consistent with its initial FDA-approved indication, should have stopped writing prescriptions for Risperdal® for purposes other than the treatment of schizophrenia, after March 3, 2002?

ANSWER:

The State further objects to this request as properly the subject of expert testimony and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 69: Please identify any off-label uses of Risperdal® that You contend are medically accepted or medically necessary.

ANSWER:

The State further objects to this request as properly the subject of expert testimony. Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 70: With respect to the allegations in Paragraph 30 of the Complaint that "[n]either the Compendia cited above nor the FDA-approved labeling support any use of Risperdal by children or adults with depression, anxiety, ADD, ADHD, sleep disorders, anger management, mood enhancement or mood stabilization," please:

a. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
b. Identify all other persons with knowledge about these allegations;.
c. State and describe the uses of Risperdal® that You contend are supported by the Compendia; and
d. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as properly the subject of expert testimony. Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 71: Do You contend that the United States Pharmacopeia-Drug Information citation for Risperdal® supports the use of Risperdal® for the treatment of the manifestations of psychotic disorders? If Your answer is anything other than an unqualified "yes," what use(s) do You contend that the United States Pharmacopeia-Drug Information citation for Risperdal® supports?

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 72: Do You contend that the treatment of the manifestations of psychotic disorders is not a "medically accepted indication" for Risperdal® as the term is defined in Paragraph 29 of the Complaint? Please state the basis of Your contention.

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ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 73: Do You contend that there are medically accepted indications for Risperdal® that are not medically necessary uses? If Your answer is anything other than an unqualified "no," please identify all medically accepted indications for Risperdal® that You contend are not medically necessary uses.

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 74: Please state those aspects of Janssen's labeling concerning Risperdal® that You contend were inadequate because they failed to provide adequate warnings to healthcare professionals and South Carolina Medicaid participants, SHP participants, and patients under the care of the SCDMH program.

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ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 75: With respect to the allegation in Paragraph 64 of the Complaint that "[t]here is no valid scientific evidence to support Defendants' contention that

Risperdal is safe and effective for treatment of any non-medically accepted indication, including any use in children," please:

a. State Your basis for this contention;
b. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
c. Identify all other persons with knowledge about these allegations; and
d. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as properly the subject of expert testimony. Also, the State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 76: With respect to the allegation in Paragraph 64 of the Complaint that "[t]here is no valid scientific evidence concerning the therapeutic equivalence of Risperdal for any non-medically accepted indication, including any use in children," please:

a. State Your basis for this contention;
b. Identify the South Carolina employee, agent or representative most knowledgeable about these allegations;
c. Identify all other persons with knowledge about these allegations; and
d. Identify all documents that support or otherwise relate to these allegations.

ANSWER:

The State further objects to this request as properly the subject of expert testimony. Further, the State requires discovery responses from Defendants to fully respond to this request. Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 77: Please identify each and every healthcare provider who has stated, suggested or otherwise reported to You that Janssen misrepresented to them (or any other prescriber) that Risperdal® is safer than less expensive first generation antipsychotic medicines.

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ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 78: Please identify all inquiries You made of Janssen during calendar years 1994-2007 regarding Risperdal's® safety profile and its known risks and side effects.

ANSWER:

The State further objects to this request as seeking information equally available to Defendants as to Plaintiff. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 79: Please identify all inquiries You made of Janssen during calendar years 1994-2007 regarding or relating to off-label uses or dosages, non-medically accepted indications, and non-medically necessary uses of Risperdal®.

ANSWER:

The State further objects to this request as seeking information equally available to Defendants as to Plaintiff. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

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INTERROGATORY NO. 80: Please identify all communications from You to healthcare professionals advising or announcing that the South Carolina Medicaid Program will not pay for any prescription of Risperdal® written for an off-label use.

ANSWER:

Subject to and without waiving the foregoing general and specific objections, the State is

gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 81: Please identify all communications from You to healthcare professionals advising or announcing that the SHP program will not pay for any prescription of Risperdal® written for an off-label use.

ANSWER:

The State is unaware of the existence of any responsive communications.

INTERROGATORY NO. 82: Please identify all communications from You to healthcare professionals advising or announcing that the SCDMH program will not pay for any prescription of Risperdal® written for an off-label use.

ANSWER:

The State is unaware of the existence of any responsive communications.

INTERROGATORY NO. 83: Please identify all employees, agents, consultants, independent contractors, representatives, or academic detailers of the State of South Carolina who have advised, educated, or detailed health care professionals regarding the risks, costs, and benefits of antipsychotic medicines, and for each please:

a. Identify the individual's name, title, address and telephone number;
b. State whether the individual is still an employee, agent, consultant or independent contractor of the State of South Carolina; and
c. Identify all healthcare professionals who have been advised, educated, or detailed by each such employee, agent, independent contractor, representative, or academic detailer regarding Risperdal®.

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ANSWER:

The State further objects to this request as unduly burdensome, vague and ambiguous, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 84: Please state whether You have conducted any audit of any healthcare professional as a result of suspected or confirmed submissions of fraudulent claims arising out of prescriptions for Risperdal® filled during calendar years 1994-2007. If so, as to each audit, state:

a. Date(s) conducted;
b. Healthcare professional(s) involved;
c. Number of false claims identified;
d. Date(s) any false claims were submitted, and their amounts;
e. Amount paid to healthcare professional(s) as a result of the false claims submitted; and
f. Whether the healthcare professional(s) involved was prosecuted, and whether You recovered any portion of the funds paid pursuant to the false claim(s) submitted.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 85: Please state whether any audit of any healthcare professional has revealed or uncovered the submission of fraudulent claims arising out of prescriptions of Risperdal® filled during calendar years 1994-2007. If so, as to each audit, state:

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a. Date(s) conducted;
b. Healthcare professional(s) involved;
c. Number of false claims identified;
d. Date(s) any false claims were submitted, and their amounts;
e. Amount paid to healthcare professional(s) as a result of the false claims submitted; and
f. Whether the healthcare professional(s) involved was prosecuted, and whether You recovered any portion of the funds paid pursuant to the false claim(s) submitted.

ANSWER:

Subject to and without waiving the foregoing objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 86: Please identify each specific healthcare professional,

employed by South Carolina, who has prescribed Risperdal® for an off-label use or dosage, a non-medically accepted indication, or a non-medically necessary use for a South Carolina Medicaid participant, SHP participant, or patient under the care of the SCDMH program, and please identify:

a. Each South Carolina Medicaid participant, SHP participant, and patient under the care of the SCDMH program for whom such prescriptions were written;
b. The date(s) any such prescriptions; and
c. All documents relating to such prescriptions.

ANSWER:

The State further objects to this request as unduly burdensome, invasive of patient privacy, propounded for the purpose of harassment, premature, properly the subject of expert testimony, and not reasonably calculated to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 87: Please describe the process or procedure by which the private attorneys or law firms who purport to represent the State of South Carolina in this Action were selected, engaged, or hired to represent the State of South Carolina in this Action, and please:

a. Identify all invitations to qualify, submissions in response to invitations to qualify, contracts, appointment letters, engagement letters, and other documents relating to the selection, engagement, or use of private counsel to represent South Carolina in this Action;
b. Describe the compensation of the private attorneys who represent South Carolina in this Action;
c. Identify all of Your communications with or about any of the private attorneys or any of their law firms before they were engaged as counsel for South Carolina in this Action; and
d. Identify each instance in which private counsel has been selected, engaged, or used to represent South Carolina in any other litigation, and state whether such private counsel's compensation was contingent on success.

ANSWER:

The State further objects to this request to the extent it seeks information protected by the

attorney-client and/or attorney work product privilege. The State further objects to this request as propounded for the purpose of harassment, and not reasonably calculated to lead to the discovery of admissible evidence

INTERROGATORY NO. 88: Provide the full name, current address and telephone number of every person known to you or your attorney who has any knowledge regarding the facts and circumstances concerning the products, incidents, injuries or damages alleged in your Complaint. Please state whether or not any statements have been obtained from any of these witnesses and identify who has possession of such statements.

ANSWER:

Subject to and without waiving the foregoing general objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 89: Please state the general area of testimony expected to be elicited from each of the witnesses named in response to the preceding Interrogatory.

ANSWER:

The State further objects to this request as unduly burdensome, propounded for the purpose of harassment, and premature. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response necessary.

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INTERROGATORY NO. 90: Provide the full name, current address, place of employment and qualifications of each and every expert witness Plaintiff intends to call at the trial of this litigation. As to each person named in response to this Interrogatory, please state:

a. The subject matter on which each expert is expected to testify;
b. the facts and opinions to which each expert is expected to testify; and
c. a summary of the basis for each opinion expected to be elicited from each expert. If the work product of any expert for consultation purposes only,

forms any part of the basis of any opinion of an expert whom you may call, then please identify such consulting expert in your answer to this Interrogatory.

ANSWER:

The State further objects to this request as premature. The State has not yet designated expert witnesses in this case. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 91: Set forth a list of photographs, sketches or other prepared documents in your possession that relate to your claims in this case.

ANSWER:

The State further objects to this request to the extent it seeks information protected by the attorney-client and/or attorney work product privilege. The State further objects to this request as unduly burdensome and premature. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 92: Set forth an itemized statement of all damages, exclusive of pain and suffering, claimed to have been sustained by you and set forth the basis for the calculation of each element of damage. Also identify who paid any such expense and to whom payment was made.

ANSWER:

The State further objects to this request as premature and properly the subject of expert testimony. Subject to and without waiving the foregoing general and specific objections, the State is gathering responsive information and will supplement its response as necessary.

INTERROGATORY NO. 93: Are you or your attorney aware of the existence of any written

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or recorded statement made by Janssen or any of its present or former agents, employees, servants or representatives? If so, please state:

a. the name of each person making the statement;
b. the name, employer, occupation and last known address of the person or persons taking the statement; and
c. the name and last known address of the person or persons now in possession of the original statement or a copy of it.

ANSWER:

Subject to and without waiving the foregoing general objections, the State is gathering responsive information and will supplement its response as necessary.

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Spartanburg, South Carolina

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# EXHIBIT B

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA ex. rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina,<br><br>PLAINTIFF,<br><br>v.<br><br>ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, LP and JOHNSON & JOHNSON, INC.,<br><br>DEFENDANTS. | IN THE COURT OF COMMON PLEAS<br><br>FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>Civil Action No.: 2007-CP-42-1438<br><br>PLAINTIFF STATE OF SOUTH CAROLINA'S ANSWERS TO DEFENDANT ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC.'S SIXTH SET OF INTERROGATORIES TO PLAINTIFF |

TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR DEFENDANTS

Pursuant to Rule 33 of the South Carolina Rules of Civil Procedure, the Plaintiff State of South Carolina ex. rel. Henry McMaster, in his capacity as Attorney General of the State of South Carolina (the "State"), by and through the undersigned attorneys, hereby answers the Sixth Set of Interrogatories propounded by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. as follows:

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## GENERAL OBJECTIONS

The State makes the following general objections, which are incorporated into its responses below and are in addition to its specific objections to individual discovery requests.

1. The State objects to discovery seeking medical records and/or detailed medical information pertaining to individual patients participating in the State's medical assistance

programs. The State is not seeking damages for individual patients and does not intend to prove its case by presenting evidence regarding specific patients. Discovery of the identity and records of individual patients would be extraordinarily intrusive and expose highly personal and private information. Such invasion of the privacy of individual patients would not lead to the discovery or relevant or admissible evidence in this case.

2. The State objects to the discovery requests to the extent they seek privileged information and/or information beyond the scope of permissible discovery. The State further objects to the discovery requests to the extent they are vague and ambiguous, unduly burdensome, not reasonably calculated to lead to the discovery of admissible evidence, propounded solely for the purposes of harassment and constitute an impermissible "fishing expedition."

3. The State neither admits the existence of any facts set forth in any request or assumed by any request. The State does not concede the relevance of any request or any subject matter to which a request refers.

4. The State objects to these interrogatories to the extent the number of interrogatories exceeds the number allowed under Rule 33 of the South Carolina Rules of Civil Procedure. Any answer by the State to excess interrogatories does not concede the propriety of that interrogatory.

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ANSWERS AND OBJECTIONS TO SIXTH SET OF INTERROGATORIES

1. With regard to paragraph 60 of the Second Amended Complaint in this case, state all facts upon which you rely in asserting that "[each Risperdal prescription written constitutes a separate and distinct violation of SCUTPA."

ANSWER: Each Risperdal prescription filled by South Carolina consumers resulted in the

dissemination of a Risperdal package insert. Each Risperdal package insert constitutes a separate violation of SCUTPA because it tends to deceive recipients about Risperdal's association with diabetes-related and hyperprolactinemia risks in addition to alpha toxicity in the elderly.

2. With regard to paragraph 60 of the Second Amended Complaint in this case, state all legal support upon which you rely in asserting that "[each Risperdal prescription written constitutes a separate and distinct violation of SCUTPA."

ANSWER: The South Carolina Unfair Trade Practices Act declares unlawful "unfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce," and provides, in pertinent part, that any person who is willfully using or has willfully used a method, act or practice declared unlawful shall be liable for civil penalties. Defendants have repeatedly and willfully engaged in the following conduct, *inter alia*, with respect to their labeling of Risperdal which constitutes a deceptive trade practice and a violation of SCUTPA: making false and misleading misrepresentations of fact regarding Risperdal's risk profile; misrepresenting and concealing material facts regarding Risperdal that are readily ascertainable by Defendants; misrepresenting that Risperdal is safer and more effective than less expensive first generation antipsychotics; misrepresenting Risperdal as being of a particular standard, quality or grade when it is not; and, intentionally creating a likelihood of confusion or misunderstanding as to whether Risperdal is safe, efficacious, and/or FDA approved. Each Risperdal prescription filled was accompanied by a package insert containing the foregoing misrepresentations and omissions. Therefore, each Risperdal prescription filled constitutes a separate and distinct violation of SCUTPA.

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3. Do you contend that each Risperdal package insert distributed to South Carolina healthcare professionals constitutes a separate violation of SCUTPA? Is so, state the basis for

your contention.

ANSWER: Yes, each Risperdal package insert constitutes a separate violation of SCUTPA because it tends to deceive recipients about Risperdal's association with diabetes-related and hyperprolactinemia risks in addition to alpha toxicity in the elderly.

4. Identify the number of Janssen-manufactured Risperdal package inserts which you contend constitute a violation of SCUTPA.

ANSWER: The State contends that each Risperdal package insert disseminated in South Carolina constitutes a separate violation of SCUTPA. (*See* Answer to Interrogatory 5.) However, because this Answer is dependent on certain of Defendants' prescription data which the State has requested in discovery, the State cannot fully respond to this Interrogatory until Defendants have made the requested production.

5. Identify the number of Risperdal prescriptions you contend were dispensed to South Carolina patients.

ANSWER: The State further objects to this Interrogatory as seeking information readily available to Defendants in multiple forms. Upon information and belief, the number of Risperdal prescriptions is available through IMS Health, Inc. The State refers Defendants to Supplemental Response to Request for Production No. 2 in Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc.'s Supplemental Responses to Plaintiff's Tenth Set of Requests for Production of Documents and to Supplemental Response to Interrogatory No. 1 of Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc.'s Supplemental Responses to Plaintiff's Third Set of Interrogatories. In further response, because this Answer is dependent on certain of Defendants' prescription data which the State has requested in discovery, the State cannot fully respond to this Interrogatory until Defendants have made the requested production.

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6. Do you contend the number of Risperdal package inserts distributed to physicians in South Carolina is equivalent to the number of Risperdal prescriptions actually filled on behalf of South Carolina patients? If so, state the basis for your contention.

ANSWER: No.

7. Identify all facts which you contend demonstrate that the number of Risperdal package inserts distributed to healthcare professionals in South Carolina is equivalent to the number of Risperdal prescriptions actually filled in South Carolina.

ANSWER: The State does not contend that the number of Risperdal package inserts distributed to healthcare professionals in South Carolina is equivalent to the number of Risperdal prescriptions actually filled in South Carolina.

8. Do you contend that each Risperdal prescription filled by a South Carolina pharmacy on behalf of a South Carolina patient is accompanied by an FDA-approved, Janssen-generated Risperdal package insert? If so, state the basis for your contention.

ANSWER: Yes, 21 C.F.R. § 208, *et seq.* requires that Defendants distribute and dispense "FDA-approved patient labeling conforming to the specifications set forth [therein]," (a "Medication Guide"), and holds Defendants "responsible for ensuring that Medication Guides are available for distribution to patients" with each container of drug product.

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9. Do you contend that South Carolina pharmacies are required to distribute an FDA-approved, Janssen-generated Risperdal package insert to patients with each filled Risperdal prescription? If so, state the basis for your contention.

ANSWER: Yes, 21 C.F.R. § 208, *et seq.* requires that Defendants distribute and dispense "FDA-approved patient labeling conforming to the specifications set forth [therein]," (a

"Medication Guide"), and holds Defendants "responsible for ensuring that Medication Guides are available for distribution to patients" with each container of drug product.

10. If you contend that every Risperdal prescription filled in South Carolina was accompanied by the FDA-approved, Janssen-generated package insert, identify the witness most knowledge about this contention and the facts supporting same.

ANSWER: No witness is required to testify about this contention. Pursuant to South Carolina Rule of Evidence 201, the Court may take judicial notice of any adjudicative fact of "such common knowledge that it is readily accepted by the general public without qualification or contention, or its accuracy may be ascertained by reference to readily available sources of indisputable reliability." *Bowers v. Bowers*, 349 S.C. 85, 94 (S.C. Ct. App. 2002). The Court may, therefore, take judicial notice of the fact that each Risperdal prescription filled in South Carolina was accompanied by Defendants' package insert consistent with 21 C.F.R. § 208, *et seq.* Upon taking judicial notice of this fact, the Court will "admit into evidence and consider, without proof of the facts, matters of common and general knowledge," and therefore the State further objects to this Interrogatory to the extent that it requires that the State proffer facts and evidence to support the same. *South Carolina Dept. of Social Servs. V. Janice C.*, 381 S.C. 221, 227 (S.C. Ct. App. 2009).

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Respectfully submitted,

STATE OF SOUTH CAROLINA
OFFICE OF THE ATTORNEY GENERAL
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Office of Attorney General
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Attorneys for the State of South Carolina

November 23rd 2010

Spartanburg, South Carolina

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# EXHIBIT C

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA<br>Ex rel. Henry McMaster, in his Capacity as Attorney General of the State of South Carolina,<br><br>PLAINTIFF,<br><br>v.<br><br>ORTHO-MCNEIL-JANSSEN, PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, LP and JOHNSON & JOHNSON, INC.<br><br>DEFENDANTS. | IN THE COURT OF COMMON PLEAS<br><br>FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>PLAINTIFF STATE OF SOUTH CAROLINA'S SUPPLEMENTAL ANSWERS TO DEFENDANTS' FIFTH SET OF INTERROGATORIES<br><br>Civil Action No.: 2007-CP-42-1438 |

TO: STEVE PUGH AND KENNETH MURPHY, ATTORNEYS FOR DEFENDANTS

Pursuant to Rule 33 of the South Carolina Rules of Civil Procedure, the Plaintiff State of South Carolina (the "State"), by and through the undersigned attorneys, hereby supplements its answers to the Interrogatories propounded by Defendants as follows:

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## GENERAL OBJECTIONS

The State makes the following general objections, which are incorporated into its responses below and are in addition to its specific objections to individual discovery requests.

1. The State objects to discovery seeking medical records and/or detailed medical information pertaining to individual patients participating in the State's medical assistance programs. The State is not seeking damages for individual patients and does not intend to prove its case by presenting evidence regarding specific patients. Discovery of the identity and records of individual patients would be extraordinarily intrusive and expose highly personal and private information. Such invasion of the privacy of individual patients would not lead to the discovery or relevant or admissible evidence in this case.

2. The State objects to the discovery requests to the extent they seek privileged information and/or information beyond the scope of permissible discovery. The State further objects to the discovery requests to the extent they are vague and ambiguous, unduly burdensome, not reasonably calculated to lead to the discovery of admissible evidence, propounded solely for the purposes of harassment and constitute an impermissible "fishing expedition."

3. The State neither admits the existence of any facts set forth in any request or assumed by any request. The State does not concede the relevance of any request or any subject matter to which a request refers.

4. The State objects to these interrogatories to the extent the number of interrogatories exceeds the number allowed under Rule 33 of the South Carolina Rules of Civil Procedure. Any answer by the State to excess interrogatories does not concede the propriety of that interrogatory.

## ANSWERS TO FIFTH SET OF INTERROGATORIES

1. Do you contend that Janssen failed to inform the FDA of certain side effect and/or risk information concerning Risperdal® of which Janssen had superior knowledge? If so, identity (i) precisely what information Janssen had; (ii) when Janssen became aware of such information; and (iii) when, you contend, Janssen should have informed the FDA of same.

ANSWER: Yes, the State contends that Janssen failed to inform the FDA of certain side effect and/or risk information concerning Risperdal of which Janssen had superior knowledge. Janssen failed to disclose its superior knowledge regarding the risks associated with diabetes mellitus, weight gain, hyperglycemia, extra pyramidal symptoms, tardive dyskenesia, hyperprolactinemia, propensity for weight gain, cerebrovascular events. Janssen has been aware of these risks since before marketing Risperdal. The State further incorporates herein the opinions contained in the State's experts' reports.

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2. With regard to paragraph 26 of the Second Amended Complaint in this case, state the date you contend it became "clear" that Risperdal® was linked to the development of diabetes.

ANSWER: The State contends that it became clear to Janssen prior to marketing to Risperdal that Risperdal was linked to the development of diabetes.

3. With regard to paragraph 26 of the Second Amended Complaint in this case, identify each instance in which, you contend, Janssen resisted "changes to its U.S. label."

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that Janssen has continuously resisted "changes to its U.S. label." Janssen failed to disclose certain information in the original label that was known to Janssen based on pre-marketing studies and its collection of adverse event data. Janssen further contends that Risperdal has a better side effect profile than other antipsychotic medications, which Janssen knows is false and misleading.

4. With regard to paragraph 30 of the Second Amended Complaint in this case, state all facts upon which you rely in asserting that Janssen "selected individuals who had previously taken traditional antipsychotics to be in the placebo groups, knowing that their prior antipsychotic use would cause them to continue to suffer EPS even while on placebos during the study."

ANSWER: The State further objects to this interrogatory as vague, ambiguous, and as seeking information that is already in the possession, custody, or control of Defendants.

5. Do you contend that Janssen failed to warn prescribing physicians adequately of the Tardive Dyskinesia risk associated with Risperdal®?

ANSWER: The State does not contend that "Janssen failed to warn prescribing physicians adequately of the Tardive Dyskinesia risk associated with Risperdal®."

6. With regard to the allegations set forth in paragraph 37 of the Second Amended Complaint, state the date or year in which, you contend, Janssen first alerted prescribing physicians to the risk of increased mortality associated with the use of Risperdal® in elderly demented patients.

ANSWER: The warning regarding the risk of increased mortality associated with the use of Risperdal® in elderly demented patients first appeared in the Risperdal labeling in or about 2005. The State contends that the warning continues to be inadequate.

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7. With regard to the allegations set forth in paragraph 42 of the Second Amended Complaint, identify and describe the means and methods by which "Defendants continue to make false and misleading statements in their promotion of Risperdal through their labeling and otherwise."

ANSWER: The State contends that "Defendants continue to make false and misleading statements in their promotion of Risperdal through their labeling and otherwise" through the continued dissemination of the Risperdal package insert.

8. With regard to the allegations set forth in paragraph 46 of the Second Amended Complaint, do you contend that Janssen's dissemination of its November 2003 Dear HealthCare Provider letter constitutes a violation of the SCUTPA? If so, specify how you contend that Janssen knew or should have known that the contents of its November 2003 letter were false, misleading, or likely to cause confusion in the minds of South Carolina prescribing physicians?

ANSWER: Yes, the State contends that "Janssen's dissemination of its November 2003 Dear HealthCare Provider letter constitutes a violation of the SCUTPA." The State contends that Janssen knew or should have known that the contents of the its November 2003 letter were false, misleading, or likely to cause confusion based on RIS Study 113, ERI, and the collection of adverse event reports in Janssen's possession. Based on this information Janssen knew or should have known that the risk of diabetes, weight gain and/or other side effects was greater than what

Janssen characterized in the November 2003 Dear Doctor Letter.

9. With regard to the allegations set forth in paragraph 54 of the Second Amended Complaint, identify all statements, representations and promotional schemes by Defendant Janssen that, you contend, were unfair, deceptive, false, incomplete, misleading, and untrue. As to each (i) state the date(s) publicized or made; (ii) identify the addressee(s)/recipient(s) of same; (iii) identify the means or method by which the statement(s), representation(s) or promotional scheme(s) was/were communicated.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that Janssen made "unfair, deceptive, false, incomplete, misleading, and untrue" statements in each version of the Risperdal package insert and the November 2003 Dear Doctor Letter.

10. With regard to the allegations set forth in paragraph 57(a) of the Second Amended Complaint, identify each instance in which, you contend, Janssen made a false and misleading misrepresentation of fact regarding Risperdal®'s risk profile. As to each instance, (i) identify the date on which the misrepresentation was made; (ii) identify the recipients/addressee(s) of the misrepresentation; and (iii) the method or means by which the misrepresentation was communicated.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that "Janssen made a false and misleading misrepresentation of fact regarding Risperdal®'s risk profile" each instance a Risperdal package insert or the November 2003 Dear Doctor Letter was disseminated in South Carolina.

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11. With regard to the allegations set forth in paragraph 57(c) of the Second Amended Complaint, identify each instance in which, you contend, Janssen misrepresented that Risperdal® is safer and more effective than less expensive first generation "typical" antipsychotics.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that "Janssen misrepresented that Risperdal® is safer and more effective than less expensive first generation 'typical' antipsychotics" each instance that Janssen disseminated the Risperdal package insert.

12. With regard to the allegations set forth in paragraph 57(e) of the Second Amended Complaint, identify each instance in which, you contend, Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is safe.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not

reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that "Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is safe" each instance that Janssen disseminated the November 2003 Dear Doctor Letter and the Risperdal package insert.

13. With regard to the allegations set forth in paragraph 57(e) of the Second Amended Complaint, identify each instance in which, you contend, Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is efficacious.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that "Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is efficacious" each instance that Janssen disseminated the November 2003 Dear Doctor Letter and the Risperdal package insert.

14. With regard to the allegations set forth in paragraph 57(e) of the Second Amended Complaint, identify each instance in which, you contend, Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is FDA-approved.

ANSWER: The State does not contend that "Janssen intentionally created a likelihood of confusion or misunderstanding as to whether Risperdal® is FDA-approved."

15. Identify all alleged false and deceptive promotional activity by Janssen of which, you contend, the FDA is and has been unaware.

ANSWER: The State objects to this interrogatory as seeking irrelevant information as it seeks information related to Janssen's "promotional activities." To the extent that the package insert and/or the November 2003 Dear Doctor Letter may be characterized as "promotional activities" then the State incorporates by reference the factual allegations in the Amended Complaint and the State's responses to these and previous discovery requests.

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16. Do you contend that any clinical trial, upon which the FDA relied in granting Janssen approval to market Risperdal, was tainted, flawed or otherwise inadequate for purposes of the FDA's approval process?

If so, (i) identify each such clinical trial; (ii) explain the basis for your contention that the clinical trial(s) was/were tainted, flawed or otherwise inadequate for purposes of the FDA's approval process.

ANSWER: The State does not contend that the Phase III clinical trials suffered from any flaw making them inadequate for purposes of the FDA's approval process.

17. Do you contend that each Risperdal prescription filled since 1994 constitutes a separate and distinct violation of the South Carolina Unfair Trade Practices Act? If so, set forth the factual and legal basis for that contention.

ANSWER: Yes, the State contends that each Risperdal prescription filled since 1994 constitutes a separate and distinct violation of the South Carolina Unfair Trade Practices Act. The State incorporates the factual allegations in the Complaint and the opinions of the State's experts already produced to Janssen.

18. Do you contend that Janssen failed to provide the FDA any information or data in Janssen's possession, regarding Risperdal, that would have adversely impacted the FDA's decision whether to approve Risperdal as safe and effective for either the management of the manifestations of psychiatric disorders, or the treatment of schizophrenia?

If so, identify any and all such information and data you contend Janssen failed and/or refused to provide to the FDA.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence. The State has no knowledge as to whether information was withheld from the FDA that would have adversely impacted the FDA's decision to approve Risperdal for marketing.

19. Identify any and all statements made by the SCORxE academic detailing program that inform physicians of any false, misleading and/or deceptive statements in Janssen's promotional and/or labeling materials regarding Risperdal.

ANSWER: The State objects to this request as overbroad, vague, unduly burdensome. Further, the State has already produced documents responsive to this request. The documents speak for themselves, and the State need not summarize these documents in this interrogatory response.

20. Identify every current and/or former FDA employee whom you have interviewed, deposed or conferred with regarding Risperdal or any other atypical antipsychotic medicine.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence, and as seeking information that is protected by the attorney-client privilege and the attorney work product doctrine. Subject to and without waiving the foregoing objections, the State has not deposed any current or former FDA employee concerning Risperdal or any other atypical antipsychotic.

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21. Identify every South Carolina healthcare professional that you have interviewed, deposed or conferred with regarding Risperdal.

ANSWER: The State objects to this interrogatory as overbroad, unduly burdensome, and as seeking information that is protected from disclosure by the attorney-client privilege. Further, this interrogatory seeks information that is already in the possession of Janssen as Janssen participated in the depositions of South Carolina healthcare professionals that were deposed in this case.

22. State the date on which you first became aware of the facts that led you to file this

lawsuit.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence, and as seeking information that is protected by the attorney-client privilege and the attorney work product doctrine. Subject to and without waiving the foregoing objections, the State first became aware of the facts that led to the filing of this lawsuit at or about the time the complaint was filed.

23. Identify and explain the means by which you first came to believe that you had a viable claim against Janssen under the South Carolina Unfair Trade Practices Act.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence, and as seeking information that is protected by the attorney-client privilege and the attorney work product doctrine. Subject to and without waiving the foregoing objections, the State learned it had a viable claim against Janssen through consultation with its attorneys.

24. State all facts which led you to believe that you had a viable claim against Janssen under the South Carolina Unfair Trade Practices Act.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing objections, the State incorporates herein the factual allegations contained in the Complaint.

25. Identify every FDA-promulgated rule, regulation or statue whose alleged breach by Janssen supports your claim under the South Carolina Unfair Trade Practices Act.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and as not reasonably likely to lead to the discovery of admissible evidence. Subject to and without waiving the foregoing objections, the State does not contend that Janssen's breach of any FDA-promulgated rule, regulation, or statute provides for the basis for Janssen's violation of the South Carolina Unfair Trade Practices Act. The State contends that the basis for its claims is Janssen's violation of South Carolina Unfair Trade Practices Act.

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26. Identify all Risperdal-related "labeling" materials disseminated by Janssen in the State of South Carolina that, you contend, were likely to deceive South Carolina prescribing physicians.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State contends that all variations of the Risperdal package insert disseminated by Janssen in the State of South Carolina were likely to deceive South Carolina prescribing physicians

27. Identify all preclinical studies of Risperdal that "demonstrated that Risperdal has the potential to cause diabetes, diabetes-related injuries (e.g. weight gain and hyperglycemia), cardiovascular and cerebrovascular complications, and other severe adverse effects," as alleged in paragraph 24 of the Second Amended Complaint.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. The State further objects to the term "preclinical studies" as undefined and therefore vague and ambiguous. The State interprets "preclinical studies" to mean pre-marketing studies. Subject to and without waving the foregoing objections, the State contends that the following list of pre-marketing studies of Risperdal demonstrated that Risperdal has the potential to cause diabetes, diabetes-related injuries (e.g. weight gain and hyperglycemia), cardiovascular and cerebrovascular complications, and other severe adverse effects," as alleged in paragraph 24 of the Second Amended Complaint: Phase III Studies numbered 201, 204, and 024.

28. Identify all means and media by which, you contend, Janssen made false and misleading misrepresentations of fact regarding Risperdal's risk profile.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State answers as follows: The State contends that "Janssen made false and misleading misrepresentations of fact regarding Risperdal's risk profile" in the November 2003 Dear Doctor Letter and the Risperdal package insert.

29. Identify all means and media by which, you contend, Janssen misrepresented material facts regarding Risperdal.

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ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State answers as follows: The State contends that "Janssen misrepresented material facts regarding Risperdal" in the November 2003 Dear Doctor Letter and the Risperdal package insert.

30. Identify all means and media by which, you contend, Janssen misrepresented that Risperdal is safer and more effective than less expensive first generation "typical" antipsychotics.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State answers as follows: The State contends that "Janssen misrepresented that Risperdal is safer and more effective than less expensive first generation 'typical' antipsychotics" in the November 2003 Dear Doctor Letter and the Risperdal package insert.

31. Identify all means and media by which, you contend, Janssen misrepresented

Risperdal as being of a particular standard, quality or grade when it is not.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State answers as follows: The State contends that "Janssen misrepresented Risperdal as being of a particular standard, quality or grade when it is not" in the November 2003 Dear Doctor Letter and the Risperdal package insert.

32. Identify all means and media by which, you contend, Janssen created a likelihood of confusion or misunderstanding as to whether Risperdal is safe, efficacious, and/or FDA approved.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and more properly within the scope of expert testimony. Subject to and without waving the foregoing objections, the State answers as follows: The State does contend that Janssen created a likelihood of confusion or misunderstanding as to whether Risperdal is safe and/or efficacious in the November 2003 Dear Doctor Letter and the Risperdal package insert. The State does not contend that Risperdal is not approved by the FDA for certain indications.

33. Identify all false, misleading or deceptive representations regarding Risperdal that Janssen has made to South Carolina prescribing physicians via advertisements and promotions.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, as not reasonably likely to lead to the discovery of admissible evidence, and as seeking information not relevant to any claims brought by the State or any defenses raised by the Defendants. Subject to and without waving the foregoing objections, the State answers as follows: The State does not contend that the November 2003 Dear Doctor Letter or the package insert constitute advertisements or promotions. The State does contend that the November 2003 Dear Doctor Letter and the Risperdal package insert contain false and deceptive representations.

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34. Identify all documents that support your contention that Janssen has been aware "since the inception of Risperdal marketing" - that Risperdal poses a risk of increased mortality in elderly patients with dementia.

ANSWER: The State objects to this interrogatory as properly the subject matter of expert testimony. Subject to and without waving the foregoing objections, the State incorporates herein the opinions of the experts previously produced by the State.

35. Identify each person whom you intend to call as a fact witness at time of trial. For each such person, please state the general area of testimony expected to be elicited from each witness identified. Additionally, please state whether or not any statements have been obtained from any of these witnesses and identify who has possession of such statements.

ANSWER: The State objects to this interrogatory as overbroad, vague, ambiguous, and

premature. Subject to and without waving the foregoing objections, the State answers as follows: The State reserves its right to call at trial any employee of Defendants, whether or not they were deposed in this litigation. The State further reserves the right to call as a witness at trial any employee of the State that was deposed in this litigation. Further, the State will provide a witness list prior to the time of trial.

36. Provide the full name, current address, place of employment and qualifications of each and every expert witness you intend to call at the trial of this case. As to each person named in response to this Interrogatory, please state:

a. The subject matter on which each expert is expected to testify;

b. The facts and opinions to which each expert is expected to testify;

c. A summary of the basis for each opinion expected to be elicited from each expert.

If the work product of any expert for consultation purposes only, forms any party of the basis of any opinion of an expert whom you may call, then please identify such consulting expert in your answer to this Interrogatory.

ANSWER: The State objects to this request as overbroad, vague, ambiguous, and as properly within the scope of expert testimony. The State has identified and served expert reports for the following individuals:

- John Abramson, MD
- Laura M. Plunkett, Ph.D., DABT
- Lon S. Schneider, MD (with exhibits)
- William C. Wirshing, MD

Information responsive to this interrogatory is located within the respective expert reports. No work product of any expert hired for consultation purposes only forms the basis of any opinion of any expert whom the state intends to call at trial. The State also intends to call W. David Patterson, Ph.D. Dr. Patterson is the Chief of Health and Demographics within the Office of Research and Statistics, SC Budget and Control Board. He may be contacted through counsel for the State. Dr. Patterson will offer testimony regarding the number of Risperdal prescriptions filled within the state of South Carolina during the relevant time period.

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37. Identify the fact witness or expert witness most knowledgeable about the allegations set forth in paragraph 30 of the Second Amended Complaint; particularly the allegation that "...Defendants selected individuals who had previously taken traditional antipsychotics to be in placebo groups, knowing that their prior antipsychotic use would cause them to continue to suffer EPS even while on placebos during the study."

ANSWER: Dr. William Wirshing.

38. Identify all facts upon which you rely in support of your claim that Janssen's

alleged violations of the South Carolina Unfair Trade Practices Act were "willful," as that term is defined in said Act and cases construing it.

ANSWER: The State will rely on internal Janssen documents to support its claims that Janssen willfully violated the South Carolina Unfair Trade Practices Act. The State contends that the following non-exclusive list of documents support the State's claim that Janssen willfully violated the South Carolina Unfair Trade Practices Act: JJRE 06128553, JJRE 06128300, JJRE 02481419, JJRE 13059226-13059232, JJRE 09071897-09071900, and JJRIS 00694006-00694010.

39. Identify all information that, you contend, Janssen failed to include in the Risperdal product label or package insert.

ANSWER: The State contends that Janssen failed to include an adequate warning against weight gain, diabetes, hyperglycemia, hyperlipidemia, cerebrovascular events in the elderly, and hyperprolactinemia.

40. Identify all information included in the Risperdal product label or package insert that, you contend, is deceptive, false and/or misleading.

ANSWER: The State contends that Janssen failed to include adequate warnings in the product label and package insert regarding risks associated with Risperdal. The State contends that this failure by Janssen is deceptive, false, and misleading. The State further contends that Janssen's characterization of adverse events in the package insert and product labeling as infrequent or rare is deceptive, false, and misleading.

41. Identify each Risperdal-related clinical trial result, clinical trial report or clinical trial conclusion that, you contend, Janssen failed to provide to the FDA.

ANSWER: On information and belief, the State contends that certain studies including RIS Study 113 and ERI were never disclosed to the FDA.

42. Identify each Risperdal-related clinical trial result, clinical trial report or clinical trial conclusion that, you contend, Janssen failed to disclose or publish to South Carolina prescribing physicians.

ANSWER: The State contends as follows: the package insert for Risperdal includes reference to clinical trials on which FDA approval is based. The package insert does not include a comprehensive recitation of the results from those studies. No study was disclosed in its entirety. All studies not used in the NDA or SNDA for Risperdal were undisclosed.

43. Identify all documents that refer, reflect or relate to any analysis of Risperdal-related risk(s) or side effects that, you contend, Janssen failed to provide to the FDA.

ANSWER: On information and belief, the State contends that Janssen failed to disclose the results of certain pre-marketing studies to the FDA, including the results of RIS Trial 113, ERI,

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and adverse event reports as they accumulated over time.

44. Do you contend that South Carolina prescribing physicians were unaware of Risperdal's actual side effect and risk profile due to Janssen's alleged failure to include specific information in the Risperdal product label or package insert? If so, upon what do you base this contention? Also, identify each South Carolina physician whom you have confirmed was unaware and, therefore, was misinformed or misled by the Risperdal product label or package insert.

ANSWER: The State objects to this interrogatory as not reasonably likely to lead to the discovery of admissible evidence. What certain physicians may have known is irrelevant to the issues raised by the State's complaint.

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Spartanburg, South Carolina

Date: July 23, 2010

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA ex. rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina,<br><br>PLAINTIFF,<br><br>v.<br><br>ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.<br><br>DEFENDANTS. | IN THE COURT OF COMMON PLEAS<br><br>FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>Civil Action No.: 2007-CP-42-1438<br><br>PLAINTIFF THE STATE OF SOUTH CAROLINA'S RESPONSE IN OPPOSITION TO DEFENDANT'S MOTION FOR JUDGMENT NOTWITHSTANDING THE VERDICT OR, IN THE ALTERNATIVE, FOR A NEW TRIAL |

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TO: STEVEN J. PUGH AND KENNETH A. MURPHY, ATTORNEYS FOR DEFENDANTS

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson,[1] in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby responds in opposition to the Motion for Judgment Notwithstanding the Verdict or, in the Alternative, for a New Trial ("Motion") and Memorandum of Law in Support ("Memorandum") filed by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. f/k/a Janssen Pharmaceutica, Inc., and/or Janssen, L.P. ("Defendant" or "Janssen"). In support of its response, the State relies on its accompanying memorandum of law and the exhibits attached thereto, which are incorporated by reference as if repeated in full herein.

[1] Pursuant to South Carolina Rule of Civil Procedure 25(d)(1), the Honorable Alan Wilson has been substituted for the Honorable Henry McMaster as Attorney General for the State of South Carolina.

In an effort to overturn the jury's unanimous verdict that Defendant willfully violated the South Carolina Unfair Trade Practices Act ("SCUTPA") by disseminating its Risperdal label, or "package insert," and its November 10, 2003 "Dear Doctor" Letter ("2003 Dear Doctor Letter") in the State of South Carolina, Defendant raises a host of meritless arguments. For the following reasons, as well as those set forth in the accompanying memorandum of law, the Court should deny Defendant's request for a judgment notwithstanding the jury's verdict or, alternatively, for a new trial.

***First***, the State's SCUTPA claim based on the Risperdal package insert is legally sufficient, in that Defendant's unfair and deceptive labeling practices are not exempt under S.C. Code Ann. § 39-5-40 as actions or transactions permitted under laws administered by a regulatory body or officer acting under statutory authority of the United States.

***Second***, the State's SCUTPA claim is not preempted by federal law. The State's case was not a "fraud on the FDA" case barred under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001). Nor was the State's case in any way expressly preempted.

***Third***, Defendant incorrectly asserts that the jury should have been instructed on a "clear and convincing evidence," "actual malice" standard applicable to defamation cases involving the media. Defendant's argument is contrary to the United States Supreme Court's prior opinions involving First Amendment challenges in the prescription drug and consumer products context.

***Fourth***, the State introduced overwhelming evidence in support of its *unfair* trade practices claim under SCUTPA.

***Fifth***, the State introduced overwhelming evidence in support of its *deceptive* trade practices claim under SCUTPA.

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*Sixth*, the State introduced overwhelming evidence for the jury to find that the alleged deceptive or unfair trade practices adversely affected the public interest.

*Seventh*, the State introduced overwhelming evidence for the jury to find that Defendant "willfully" violated SCUTPA.

*Eighth*, the State's SCUTPA claim is not barred by the applicable statute of limitations.

*Ninth*, the Court did not abuse its discretion in its evidentiary rulings. Specifically, the Court did not err in:

1. allowing the State to try its case and not limit its SCUTPA claims to the conduct Defendant incorrectly asserts the State consistently identified in discovery as the basis of Defendant's SCUTPA violations;

2. admitting various categories of evidence relevant to, *inter alia*, whether Defendant acted willfully in committing its SCUTPA violations, including but not limited to, documents and testimony related to (i) letters from the FDA's Division of Drug Marketing, Advertising, and Communications ("DDMAC"); (ii) the number of Risperdal prescriptions filled in South Carolina from 1994 through 2007; (iii) Defendants' profits, sales, revenues, and business plans; (iv) e-mails sent by Scott Reines; (v) off-label and otherwise improper, deceptive, and unfair promotional and marketing activities; and (vi) nondisclosures to the FDA;

3. excluding inadmissible evidence, including post-2004 evidence regarding the diabetes-related risks and side effects of Risperdal and other atypical antipsychotics, the testimony and documents relating to the Dr. William Wecker's "survey," the testimony of twenty South Carolina doctors, and the testimony of Dr. Gerard Jebaily;

4. precluding Defendant from introducing the testimony of Dr. Eugene Barrett;

5. precluding Defendant from introducing evidence regarding the SCORxE Program;

6. precluding Defendant from introducing Dr. Wecker's testimony regarding the incidence rates of side effects of Risperdal versus other antipsychotic medications and whether certain peer-reviewed medical literature and drug studies supported the statements made in Defendant's 2003 Dear Doctor Letter; and

7. precluding Defendant from introducing certain testimony of Sheldon Bradshaw.

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*Tenth*, the State's opening and closing statements were well within the bounds of permissible jury argument.

*Finally*, the jury instructions were more than adequate and not flawed, and the verdict sheet was sufficiently specific and not confusing.

WHEREFORE, for all the reasons stated herein and in the accompanying memorandum of law, which is incorporated herein by reference as though set forth fully herein, the Court should deny Defendant's Motion in its entirety.

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Respectfully submitted,

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April 15, 2011
Spartanburg, South Carolina

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| STATE OF SOUTH CAROLINA<br><br>COUNTY OF SPARTANBURG<br><br>STATE OF SOUTH CAROLINA ex. rel. Alan Wilson, in his capacity as Attorney General of the State of South Carolina;<br><br>PLAINTIFF,<br><br>v.<br><br>ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., f/k/a JANSSEN PHARMACEUTICA, INC., and/or JANSSEN, L.P., AND JOHNSON & JOHNSON, INC.<br><br>DEFENDANTS. | IN THE COURT OF COMMON PLEAS<br><br>FOR THE SEVENTH JUDICIAL CIRCUIT<br><br>Civil Action No.: 2007-CP-42-1438<br><br>PLAINTIFF THE STATE OF SOUTH CAROLINA'S MEMORANDUM OF LAW IN SUPPORT OF ITS RESPONSE IN OPPOSITION TO DEFENDANT'S MOTION FOR JUDGMENT NOTWITHSTANDING THE VERDICT OR, IN THE ALTERNATIVE, FOR A NEW TRIAL |

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HOPE BLACKLEY

TO: STEVEN J. PUGH, KENNETH A. MURPHY, EDWARD M. POSNER, AND THOMAS F. CAMPION, ATTORNEYS FOR DEFENDANTS

Plaintiff, the State of South Carolina, *ex rel.* Alan Wilson, in his capacity as Attorney General of the State of South Carolina (hereinafter, "the State"), by and through the undersigned counsel, hereby submits its Memorandum of Law in Support of Its Response in Opposition to the Motion for Judgment Notwithstanding the Verdict, or in the Alternative, For a New Trial (the "Motion") and accompanying Memorandum of Law (the "Memorandum") filed by Defendant Ortho-McNeil-Janssen Pharmaceuticals, Inc. (hereinafter "Janssen" or "Defendant"), and would respectfully show the Court as follows:

## I.
## SUMMARY OF THE RESPONSE

On Tuesday, March 22, 2011, after a two-week trial and following a full day of deliberation, the jury unanimously found that Defendant had willfully committed deceptive or

unfair acts in violation of the South Carolina Trade Practices Act ("SCUTPA"). With its eyes squarely on an eventual appeal from this Court, Defendant predictably conjures up every argument it can muster, colorable or not, and whether previously rejected by this Court or not, in an attempt to overturn the jury's uniform verdict in this case.

The Court should not be swayed by Defendant's meritless arguments for the following reasons, as well as those described in detail *infra*:

- Defendant again contends (unsuccessfully) that because its FDA-approved Risperdal label was purportedly "permitted" under federal law, purposefully *ignoring application of the relevant "changes being effective" ("CBE") regulations for updating prescription drug labeling*, its conduct relative to the Risperdal label falls within SCUTPA's "safe harbor" exception for legally "permitted" conduct;

- Defendant fails to meet its burden on its novel "primary jurisdiction" argument, in which it contends that this South Carolina State Court must defer to the federal Food & Drug Administration ("FDA") as the exclusive and final arbiter of all things related to prescription drugs (which, of course, is not the law);

- Defendant's "no duty to warn consumers" argument again misses the broad side of the State's claim and evidence; there is no "duty to warn" element that is a component of the State's burden of proof in this case;

- Defendant's carefully parsed excerpts of State witnesses' testimony do not show, in Defendant's federal preemption argument, that the State relied exclusively on the April 2004 Warning Letter or any other so-called "FDA evidence" in support of the jury's verdict that the November 2003 Dear Doctor Letter violated SCUTPA; indeed the record reveals precisely the opposite;

- Defendant's other federal preemption arguments—based on a contrived "express preemption" provision that Defendant cites but apparently the United States Supreme Court was unable to identify in its recent *Wyeth v. Levine* opinion, as well as based on a *Buckman* "fraud on the FDA" challenge—fare no better; the jury reasonably found that Defendant withheld important safety information about Risperdal from South Carolina prescribers and patients in violation of SCUTPA, notwithstanding any nondisclosure to the FDA;

- Defendant's limited First Amendment challenge to the jury verdict—that it should be overturned because the jury was not instructed on a "clear and convincing evidence," "actual malice" standard that is applicable to defamation cases involving the media (and that is all the authority Defendant cites)—is devoid of *any* on-point support from any jurisdiction in this country; indeed, the argument

runs counter to the United States Supreme Court's prior opinions involving First Amendment challenges in the prescription drug and consumer products context;

- notwithstanding Defendant's repeated departures from SCUTPA standards well-established in the South Carolina case law and in SCUTPA itself, the State adduced sufficient evidence of all elements of its SCUTPA claim;
- the Court's entry of directed verdict on the State's motion as to the statute of limitations was appropriate; and
- the Court's jury instructions and attendant verdict form were entirely supported by South Carolina precedent.

The Court should deny Defendant's Motion.

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## II.
## ARGUMENT & AUTHORITIES

### A. Standard

"When ruling on motions for . . . judgment notwithstanding the verdict, the trial court must view the evidence and its reasonable inferences in the light most favorable to the party opposing the motions." *Hessenthaler v. Tri-County Sister Help, Inc.*, 616 5 S.E.2d 694, 697 (S.C. 2005) (citing *Jinks v. Richland County*, 585 S.E.2d 281, 283 (S.C. 2003)). "The trial court must deny the motions when the evidence yields more than one inference or its inference is in doubt." *Id.* On review, the appellate courts will reverse the trial court's ruling only when there is no evidence to support it. *Id.*

With respect to motions for new trial, "a trial judge's order . . . denying a new trial will be upheld unless the order is 'wholly unsupported by the evidence, or the conclusion reached was controlled by an error of law.'" *Norton v. Norfolk S. Ry. Co.*, 567 S.E.2d 851, 854 (S.C. 2002) (citing *Folkens v. Hunt*, 387 S.E.2d 265, 265 (S.C. 1990)). "[R]eview [of the order denying a motion for new trial] is limited to consideration of whether evidence exists to support the trial court's order." *Norton*, 567 S.E.2d at 854 (citing *Folkens*, 387 S.E.2d at 267)).

Regarding both motions described above, the credibility of any witness testimony and the weight to be assigned to it is for the trier of fact, not the judge, to determine. *Collins v. Frasier*, 662 S.E.2d 464, 466 (S.C. Ct. App. 2008) (citing *Parsons v. Georgetown Steel*, 456 S.E.2d 366, 368 (S.C. 1995)). Further, if there is any testimony tending to prove allegations of the complaint, the motions must be refused. *Proctor v. Dep't of Health & Envtl. Control*, 696 S.E.2d 496, 504 (S.C. Ct. App. 2006). "This rule is especially strong in South Carolina where the 'scintilla of evidence rule' is applied." *Id.*

**B. The State's SCUTPA Claim Based On The Risperdal Package Insert Is Legally Sufficient.**

***1. Defendants Ignore Established Precedent of the United States Supreme Court, the South Carolina Supreme Court, and this Court in Maintaining That S.C. Code Ann. § 39-5-40 Establishes a "Safe Harbor" for Their Unfair and Deceptive Conduct in the Labeling of Risperdal.***

Defendants brazenly ask this Court (again) to ignore established precedent of the United States Supreme Court and the South Carolina Supreme Court—as well as to overrule this Court's multiple orders and rulings—in arguing that their unfair and deceptive labeling practices are exempt from SCUTPA as actions or transactions *permitted* under laws administered by a regulatory body or officer acting under statutory authority of the United States. *See* S.C. Code Ann. § 39-5-40(a). In doing so, Defendants improperly rely on the FDA's August 22, 2008 amendment and accompanying preamble to the applicable regulations enacted *after* the period for which the State is seeking civil penalties under SCUTPA. (*See* Def.'s Mem. at 7.)

The South Carolina Legislature has specifically required that such actions or transactions be "permitted" under law in order to qualify for SCUTPA's narrow exemption, and it is inarguable that Defendant's misconduct does not fall within that category. Moreover, this Court excluded from evidence on relevance and unfair prejudice grounds the very regulation on which Defendant relies, implicitly basing its ruling not only on the fact that the revision was adopted

outside the relevant time period, but also in consideration of the United States Supreme Court's treatment of this lesser standard in *Wyeth v. Levine*.[1] (*See* Trial Tr. at 1046-1051, a true and correct copy of which is attached hereto as Exhibit A; *see also id.* at 2047, 2060-2075.)

Defendant, however, attempts to impose contrived and inapposite limitations on well-established SCUTPA enforcement powers under South Carolina law through Defendant's unsubstantiated argument that Risperdal's deceptive labeling was authorized by the FDA. Defendant further argues that Risperdal's labeling evades SCUTPA's reach because the State has not proven that Defendant had "newly acquired information" or "evidence of a *causal* association [that] satisfies the standard for inclusion in the labeling under § 201.57(c)" sufficient to *permit* Defendant's submission of a unilateral CBE label change. (Def.'s Mem. at 9 (citing 73 Fed. Reg. 49603, 49604, 49605-06 (Aug. 22, 2008); 21 C.F.R. § 201.57(c) (6)(i) (2008) (emphasis added)).) Yet, Defendant fails to explain satisfactorily how Risperdal's labeling would qualify as "permitted" for purposes of SCUTPA's "safe harbor" exception in light of its willful refusal to strengthen Risperdal's warning section in the labeling, as they were required to do by the FDA, "*as soon as* there [was] reasonable *evidence of an association* of a serious hazard" with Risperdal (under the standard applicable to this case)—not *until* a "*causal* association" was recognized. 21 C.F.R. § 201.57(e) (2006) (emphases added); *id.* ("a *causal* relationship need *not* have been proved" to implicate the requirements of this section) (emphasis added); (Def.'s Mem. at 9 (quoting 21 C.F.R. § 201.57(c)(6)(i) (2008) (emphasis added)).)

More specifically, Risperdal's labeling contained false and misleading information, and omitted true information regarding the "association of . . . serious hazards with" Risperdal, since the time of the drug's launch in the United States. *Id.* (*See* discussion, *infra* at II.G. & II.H.)

[1] *See* discussion, *infra* at II.K.4.f.

Because the false and misleading labeling was unfair and had the tendency to deceive, Defendant's conduct is actionable under SCUTPA. *See* S.C. Code Ann. § 39-5-20. Defendant's conduct with respect to the representations in the labeling was "willful" under the statute because it is merely necessary to show that Defendant knew or should have known that the labeling was unfair or deceptive. S.C. Code Ann. §§ 39-5-20, 39-5-110(c). Contrary to Defendant's assertions, the FDA's revision to the applicable regulations is not retroactive, and, thus, Defendant was required to comply with then-existing labeling requirements. Even assuming the 2008 CBE regulations Defendant urges upon the Court were applicable, *Wyeth v. Levine* forecloses Defendant's argument thereon. 555 U.S. 555, ___; 129 S. Ct. 1187 (2009).

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In *Levine*, the Court emphasized that, despite recent amendments to the FDCA and to FDA regulations, "it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times," and "is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." 129 S. Ct. at 1197-98. "Indeed, the 'complex and extensive' regulatory history and background relevant to this case . . . undercut the FDA's recent pronouncements of pre-emption [in the amendment and preamble on which Defendant relies here]; as they reveal the longstanding coexistence of state and federal law and the FDA's traditional recognition of state-law remedies." *Id.* at 1203. As in the case of Wyeth's Phenergan label, this "traditional recognition of state-law remedies" was in place each time the agency reviewed Defendant's Risperdal label. *See id.* Defendant, thus, had the opportunity to strengthen the warnings in Risperdal's labeling *at any time* that it determined there was reasonable evidence of an association between Risperdal consumption and a serious hazard but

continuously failed to take advantage of that regulatory self-help provision. *See* 21 C.F.R. § 201.57(e) (2006).

Therefore, it is unquestionable that *Levine* rejected the argument that because the prescription drug labeling at issue was FDA-approved and regulated, a drug manufacturer could not comply with state law. Accordingly, this Court has already determined "***as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA.***" *State of South Carolina v. Eli Lilly & Co.*, No. 2007-CP-42-1855, slip op. at 27-28 (S.C. Ct. Com. Pleas Sept. 22, 2009) (emphasis added), a true and correct copy of which is attached hereto as Exhibit B. In *Lilly*, this Court rejected that defendant's virtually identical arguments "[b]ased on [defendant's] ability to make unilateral amendments to its labeling and the further facts concerning [its] marketing and labeling methods which have been demonstrated to this Court as being in controversy." Slip op. 22-23 (Ex. B). The fact that the FDA had intermediately "approved" Zyprexa's labeling, therefore, did not absolve Lilly from its duty to update the labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *See* 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); *accord, Levine*, 129 S. Ct. at 1197.

Defeated with respect to the above authority, Defendant further advocates the application of the now-discarded "general activity" test once applicable to S.C. Code Ann. § 39-5-40, arguing that Risperdal's labeling is exempted under SCUTPA for that reason. Defendant also posits (circularly) that *all* unfair or deceptive acts and practices under SCUTPA might be subject to the regulated activity exemption because "every SCUTPA defendant is necessarily accused of committing an 'unfair' or 'deceptive' act," and such acts are never "permitted" by regulatory

agencies or other statutes. If that interpretation were true, Defendant argues, "there would be no reason for the exemption at all." (Def.'s Mem. at 6-7.) In support, Defendant cites the South Carolina Supreme Court decision *abandoning* the "general activity" test and the case cited in reliance therein, without more. (*See* Def.'s Mem. at 6 (citing *Ward v. Dick Dyer & Assoc., Inc.*, 403 S.E.2d 310, 312 (S.C. 1991) (quoting *Skinner v. Steele*, 730 S.W.2d 335, 337 (Tenn. Ct. App. 1987))).)

In *Ward*, the Supreme Court held that claims are no longer barred if the "general activity" that is the subject of the claim is administered by another regulatory body such as the FDA. 403 S.E.2d at 312 (considering that interpretation of the exemption through a general activity test "would not fulfill the intent of the Legislature in prohibiting unfair trade practices through SCUTPA). "This conclusion is buttressed by the fact that § 39-5-160 of the Act provides that 'the powers and remedies provided by this article shall be cumulative and supplementary to all powers and remedies otherwise provided by law.'" *Id.* (quoting S.C. Code. Ann. § 39-5-160). Defendant's argument, however, discounts the baseline objectives of the statutory exemption articulated in *Ward*, which include "avoid[ing] conflict between laws, [but] not . . . [excluding] from the Act's coverage every activity that is authorized or regulated by another statute or agency." *Id.* (quoting *Skinner*, 730 S.W.2d at 337).

Moreover, none of the cases Defendant cites for the proposition "that the FDA's specific approval of the Risperdal package insert bars claims of deceptive or misleading conduct" are controlling or supportive of a blanket exemption for FDA-approved drug labeling. (Def.'s Mem. at 7.) Rather, the referenced opinions demonstrate only that advertisements that merely replicate FDA-approved labeling are not actionable under New York consumer protection law, *see, e.g.*, *Mylan Pharms., Inc. v. P&G*, 443 F. Supp. 2d 453, 460 (S.D.N.Y. 2006) and *Cytyc Corp. v.*

*Neuromedical Sys.*, 12 F. Supp. 2d 296, 301 (S.D.N.Y. 1998), and, similarly, that other promotional claims separate from a product's labeling could fall within a consumer protection statute's safe harbor, *see, e.g., Prohias v. AstraZeneca Pharm.*, 958 So.2d 1054 (Fla. App. 2007).

In *Prohias v. Pfizer*, in particular, the court held that some promotional claims about the ability of the drug Lipitor to reduce the risk of coronary heart disease did not fall within the "safe harbor" provisions of the consumer fraud acts of Florida and Massachusetts, and that other promotional claims were exempted under those provisions. 490 F. Supp. 2d 1228, 1232-35 (S.D. Fla. 2007). The issue before the *Prohias* court was whether the relevant promotional claims were supported by the FDA-approved label for Lipitor. *Id.* The court did not address the question of whether an FDA-approved drug label can ever be actionable under those statutes because *Prohias* did not involve allegations that the drug label at issue contained willful misstatements or omissions. In fact, the plaintiffs effectively conceded that the promotional claims that were supported by the FDA-approved label fell within the statutes' "safe harbor" provisions, presumably because the plaintiffs sought advertising requirements that paralleled and were not stronger than the FDA-approved label. *See id.* at 1233, 1235.

*American Home Products Corp. v. Johnson & Johnson*, 672 F. Supp. 135 (S.D.N.Y. 1987) is equally distinguishable because the *American Home* court considered unfair competition claims which, as the court emphasized, are separate and distinct from consumer protection claims for unfair trade practices. *Id.* at 143-144. Articulating that distinction, the court explained that a manufacturer is "supported by a powerful trade association, has substantial input into and influence over the regulatory process," and thus competitors require less protections; but, on the other hand, consumers require more protection because they "played no role in, nor even had any knowledge of, the proceedings which led to the regulatory agency's approval of the

product and its label." *Id.* Therefore, the court stated, it would be manifestly unfair if the consumer "should be denied recovery merely because the manufacturer's trade association, through aggressive lobbying, had succeeded in persuading the regulatory agency that the hazard was not sufficiently well established to require a label warning." *Id.*

Lastly, rejecting a virtually identical argument in *Lilly*, the Court ruled as follows:

> It is clear that when dealing with false information contained in an application document submitted directly to a state regulatory agency for the purpose of having that agency act upon that application, that such matters would be within the regulatory jurisdiction of that agency. The issues involved in this case revolve around . . . ***consumer protection issues which are precisely the issues concerning which the South Carolina Legislature enacted SCUTPA.*** Ward abandoned the "general activities" test, and subsequently adopted the language of a Tennessee case stating:
>
> > . . . The purpose of the exemption is to insure that a business is not subjected to a lawsuit under the Act when it does something required by law, or does something that would otherwise be a violation of the Act, but which is allowed under other statutes or regulations. It is intended to avoid conflict between laws, not to exclude from the Act's coverage every activity that is authorized or regulated by another statute or agency. Virtually every activity is regulated to some degree. The defendant's interpretation of the exemption would deprive consumers of a meaningful remedy in many situations. We find this reasoning persuasive and applicable to our statutory exemption . . .
>
> Ward v. Dick Dyer and Associates, Inc., 304 S.C. 152, 156, 403 S.E.2d 310, 312 (S.C. 1991).
>
> The FDA does not allow or authorize the illegal or deceptive activities that the Plaintiff alleges to have occurred in this case. . . .

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> *This Court does not interpret the SCUTPA to create a "safe harbor" for the alleged activities of [defendant] in the marketing and labeling of [its drug].* The exemption of § 39-5-40(a) does not bar this claim.

Slip op. at 24-26 (emphases added).

Relying on the foregoing, the Court correctly denied Defendant's motion for directed verdict concerning the exemption and reiterated that "[t]he allegations and evidence presented . . . do establish a cause of action that is not covered by the regulatory safe harbor in that some of the actions which have been described in the evidence are not permitted by state law, by federal law or federal regulation[,]" which "include[s] withholding of pertinent information[.]" (Trial Tr. at 1803-1804 (Ex. A).) Thus, this Court has not ignored in the past, and should not ignore in this case, that even if the abandoned "general activity" test were reinstated, the State's SCUTPA claim would nevertheless be viable because the activity that is the subject of the claim—i.e., concealing and misrepresenting Risperdal safety information in the drug's labeling—is not authorized, or "*permitted*," by the FDA. S.C. Code Ann. § 39-5-40(a) (emphasis added).

Defendant's "safe harbor" contentions are plainly unmeritorious and do not comport with controlling decisions by this Court and others. Consistent with that controlling precedent, the Court should deny Defendant's Motion.

**C. Defendant's Novel "Primary Jurisdiction" and "Failure to Exhaust Administrative Remedies" Contentions Must Be Rejected As Based on False Legal Premises.**

Together with its argument that the State's claim is preempted by federal law (discussed in § II.E, *infra*), Defendant's Motion again attempts to morph the State's SCUTPA claim and the attendant jury verdict into an attempt to enforce the Food, Drug and Cosmetic Act ("FDCA"), albeit with a slightly different spin. Here, without express mention of the FDCA, Defendant now asserts that the FDA has "primary jurisdiction" over prescription drug labeling, and therefore the State may not enforce SCUTPA violations arising from unfairness or deception in "prescription

drug package inserts." (Def.'s Mem. at 12.) Defendant also half-heartedly devotes a paragraph of its Motion to the argument that the State must have exhausted the "administrative remedy" of filing a "citizen petition" over any concerns about Risperdal's label, as opposed to the Attorney General's pursuing his statutory duties under South Carolina law and, in particular, SCUTPA. (Def.'s Mem. at 13-14). Neither argument signals any impropriety in the jury verdict.[2]

First, there is no dispute that the FDA oversees, reviews, and approves prescription drug labeling. But, there is "no merit" in the argument that Congress had entrusted the FDA *exclusively* "to make drug labeling decisions that strike a balance between competing objectives." *Levine*, 129 S. Ct. at 1199. "The most glaring problem with this argument," the Supreme Court recognized, "is that all evidence of Congress' purpose is to the contrary." *Id.* The High Court concluded there was "powerful evidence that *Congress did not intend FDA oversight to be the exclusive means of ensuring drug safety and effectiveness.*" *Id.* (emphasis added). Further, the Court determined that "the FDA [itself] long maintained that *state law offers an additional, and important, layer of consumer protection that complements FDA regulation.*" 129 S. Ct. at 1202.[3]

Had the State brought an action to enforce the FDCA, then Defendant's arguments and case law concerning "misbranding" actions might carry some weight. But the State instead pursued its own "state-law remedies," which the Supreme Court observed that Congress "may also have recognized" as "further[ing] consumer protection by motivating manufacturers to

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2 "The party seeking to impose the primary jurisdiction doctrine bears the burden of demonstrating its application." *In re Budeprion XL Mktg. & Sales Litig.*, No. 09-md-2107, 2010 U.S. Dist. LEXIS 51980, at *40 (E.D. Pa. May 26, 2010).

3 Defendant infers in presenting this argument that by "approving and permitting the exact language used" in a prescription drug label, thus purportedly deciding that such language "is neither false nor misleading" (Def.'s Mem. at 12), that the FDA's blessing of particular language in the label a final and unassailable determination by the agency. Nothing could be further from the truth, as *Wyeth v. Levine* makes clear and as further discussed *infra* at § II.B.

produce safe and effective drugs and to give adequate warnings." *Id.* at 1199-1200.

In any event, the primary jurisdiction doctrine is inapplicable here because resolution of the State's claim does not require the expertise of the FDA. "The doctrine of primary jurisdiction 'applies where a claim is originally cognizable in the courts, and comes into play whenever enforcement of the claim requires the resolution of issues which, under a regulatory scheme, have been placed within the special competence of an administrative body.'" *Alpharma, Inc. v. Pennfield Oil Co.*, 411 F.3d 934, 938 (8th Cir. 2005) (quoting *Atlantis Exp., Inc. v. Standard Transp. Services, Inc.*, 955 F.2d 529, 532 (8th Cir. 1992)). "The doctrine is to be 'invoked sparingly, as it often results in added expense and delay.'" *Id.* (quoting *Red Lake Band of Chippewa Indians v. Barlow*, 846 F.2d 474, 477 (8th Cir. 1988)).

To support its argument, Janssen relies on *Wyeth v. Sun Pharmaceutical Industries*, No. 09-11726, 2010 U.S. Dist. LEXIS 18180, 2010 WL 746394 (E.D. Mich. Mar. 2, 2010). In *Sun*, the plaintiff, a manufacturer of the name brand prescription drug, sued under the Lanham Act and Michigan's Consumer Protection Act alleging that, although the FDA had approved the defendants' generic product as containing the active ingredient in plaintiff's product, in reality the defendants' generic product contained a different active ingredient. *Id.* at *6. The court believed that the plaintiff requested a finding either: (1) that the FDA erred or was misled in approving the defendants' generic drug application, or (2) the defendants received FDA approval to market sesquihydrate, yet instead sold a non-approved product with monohydrate as the active ingredient. *Id.* at *10. In dismissing the plaintiff's complaint, the court concluded that the FDA's approval of the defendants' generic drug application was a matter for the FDA. *Id.* at *10-11. Regarding the allegations that the defendants' product included a different active ingredient than approved by the FDA, the court stated that in order to adjudicate the plaintiff's

claims, the Court would be required to interpret FDA regulations regarding the equivalency of polymorphs and predict the FDA's ruling on the issue, which is a matter better left to the expertise of the FDA. *Id.* at *16.

Unlike *Sun*, the State is not asking this Court to invade the purview of the FDA by questioning the approval of a generic drug or making a determination of the equivalency of active ingredients. Rather, the State claims Janssen violated the SCUTPA by failing to disclose material information about Risperdal's true risk profile. *See Alpharma*, 411 F.3d at 939 ("The question of whether [defendant's drug] *has been* approved as safe and effective is much different from the question of whether [defendant's drug] *should be* approved as safe and effective, *and it is only the latter that requires the FDA's scientific expertise.*") (emphasis added). Thus, the State's "charges will not require this Court or a jury to decide what is in Defendant['s] medication. Instead, this case involves an inquiry that frequently falls upon judges and juries: whether a defendant gave an appropriate warning when it sold its product to the public." *See In re Budeprion XL Mktg. & Sales Litig.*, No. 09-md-2107, 2010 U.S. Dist. LEXIS 51980, at *43 (E.D. Pa. May 26, 2010) (holding the primary jurisdiction doctrine is not implicated in suit where plaintiffs claim that defendants failed to warn them about differences between their generic medication and the name brand medication); *accord Ackerman v. Coca-Cola Co.*, No. CV-09-0395, 2010 U.S. Dist. LEXIS 73156, at *54 (E.D.N.Y. July 21, 2010) ("The question whether defendants have violated FDA regulations and marketed a product that could mislead a reasonable consumer is one courts are well-equipped to handle, *and is not an appropriate basis for invoking the primary jurisdiction doctrine.*") (emphasis added).

Lastly, the doctrine of exhaustion of administrative remedies requires that where an administrative remedy is provided by statute, relief must be sought by exhausting this remedy

before the courts will act. *Columbia v. Abbott*, 269 S.C. 504, 509 (S.C. 1977): "FDA regulations require that, before filing suit in court, a party requesting that the FDA take or refrain from taking an action must first use the citizen petition process set forth in 21 C.F.R. § 10.25." *Farm-To-Consumer Legal Def. Fund v. Sebelius*, 734 F. Supp. 2d 668, 701 (N.D. Iowa 2010); 21 C.F.R. § 10.45.[4] Therefore, in order for the exhaustion of administrative remedies doctrine to be applicable to a given case, the suit must be requesting that the FDA take or refrain from taking an action. Because the State does not ask the FDA to take or refrain from taking any action, the exhaustion of administrative remedies should not be implicated.

**D. No Common Law "Duty to Warn" Was Implicated in this Case.**

Defendant asserts—in essence—that because prescription drug "package inserts" i.e., labeling that accompanies a prescription drug—is directed at physicians rather than consumers, there can be no SCUTPA violation based on that labeling. Defendant's contentions are mistaken for at least three reasons.

*First*, Defendant's argument addresses claims the State did not make. To be perfectly clear, Defendant seeks (as it did unsuccessfully at the summary judgment stage) to interject into the State's SCUTPA claim an element that does not exist and does not apply, so that Defendant may take advantage of a widely recognized (but entirely inapposite) learned intermediary *exception* to that inapplicable, non-existent element of proof.

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[4] A request that the Commissioner take or refrain from taking any form of administrative action must first be the subject of a final administrative decision based on a petition submitted under § 10.25(a) or, where applicable, a hearing under § 16.1(b) before any legal action is filed in a court complaining of the action or failure to act. If a court action is filed complaining of the action or failure to act before the submission of the decision on a petition under § 10.25(a) or, where applicable, a hearing under § 16.1(b), the Commissioner shall request dismissal of the court action or referral to the agency for an initial administrative determination on the grounds of a failure to exhaust administrative remedies, the lack of final agency action as required by 5 U.S.C. 701 et seq., and the lack of an actual controversy as required by 28 U.S.C. 2201.

21 C.F.R. § 10.45.

Defendant argues that because the "package insert is not written for consumers, it cannot, as a matter of law, be considered 'unfair' or 'deceptive' as to consumers." (Def.'s Mem. at 16.) Defendant's legal premise for that contention is that "as a matter of law, a pharmaceutical manufacturer has *no duty* to advise consumers of a prescription medicine as to the risks of a particular drug." (*Id.* at 15 (emphasis added).)

But the State is not bringing common law negligence, failure to warn, or other fraud claims; thus any existence or absence of common law "duty" to consumers is irrelevant. That is because SCUTPA "creates *new substantive rights* by making unlawful conduct that was *not actionable under the common law*." *State v. C & L Corp.*, 313 S.E.2d 334, 338 (S.C. Ct. App. 1984) (emphasis added). No "duty" prerequisite may be found in SCUTPA's express language, and none has been determined to exist by any court. As the South Carolina cases make abundantly clear that, unlike a common law fraud or negligence claim, there exists no requirement that the State prove that any prescriber or consumer was actually deceived, or that anyone relied upon deceptive information disseminated by Defendant about Risperdal. *See Id.* ("[T]here is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive."); *Dowd v. Imperial Chrysler-Plymouth, Inc.*, 381 S.E.2d 212, 213-214 (S.C. Ct. App. 1989) ("To recover for fraud, the familiar [sic] nine elements must be proved 'by clear, cogent, and convincing evidence.' No such proof is required to recover under [SCUTPA]."). Indeed, Defendant certainly cannot (and does not) argue that it has "no duty" under South Carolina law to avoid "unfair" and "deceptive" conduct in labeling Risperdal—it is SCUTPA that creates *that* very duty in this case.

Further, there can be no disagreement that the *purpose* of prescription drug labeling, whether directed at physicians or consumers, is to provide the essential "information needed for

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the safe and effective use of the drug" *ultimately by the consumer*. 21 C.F.R. § 215.56(1)(1); *see* 21 C.F.R. § 201.57(a)(10) (labeling must contain "information . . . critical to the *safe use* of the drug" by the consumer "and measures that can be taken to prevent or mitigate harm" to the consumer) (emphasis added).

In any event, the overriding concern of SCUTPA is not which person in particular (consumer or otherwise) received or was affected by a deceptive representation about a product, but instead focuses on unfairness or deception "in the conduct of any trade or commerce . . ." *that affects the public interest generally*. S.C. Code Ann. § 39-5-20(a) (2009); *see Bessinger v. Food Lion, Inc.*, 305 F. Supp. 2d 574, 582 (D.S.C. 2003) ("[SCUTPA] is not available to redress a private wrong where the public interest is unaffected."); *Noack Enters., Inc. v. Country Corner Interiors of Hilton Head Island, Inc.*, 351 S.E.2d 347, 349 (S.C. Ct. App. 1986) ("The legislature's intent [was] to limit the application of the [SC]UTPA to only those unfair or deceptive acts or practices in the conduct of trade or commerce *that affect the public interest* . . ") (emphasis added). Indeed, momentarily setting aside the *deceptiveness* of Defendant's conduct, all the State was required to show to recover penalties under section 39-5-110 is that Defendant willfully committed *unfair* trade practices that affected the public interest. *See* S.C. Code Ann. §§ 39-5-20; 39-5-110 (2009). "An unfair trade practice has been defined as a practice which is offensive to public policy or which is immoral, unethical, or oppressive." *Wright v. Craft*, 640 S.E.2d 486, 500 (S.C. Ct. App. 2006) (emphasis added); *see Bessinger*, 305 F. Supp. 2d at 582 (construing SCUTPA—per section 39-5-20(b)—in accordance with the Federal Trade Commission Act, under which courts have determined that a practice is *unfair* when it "offends established public policy and when the practice is immoral, unethical, oppressive, unscrupulous, or substantially injurious to consumers"); *accord Dowd*, 381 S.E.2d at 214 (holding that, in order

to impact the public interest, unfair or deceptive acts or practices in the conduct of trade or commerce must simply have "the *potential* for repetition") (emphasis added) (citations omitted).[5]

This Court, of course, has previously recognized and upheld the critical public interests underlying these SCUTPA actions in *Lilly*:

> I am surprised by the fact that most of the members of the public who are involved in this case are economically disadvantaged individuals who suffer from such debilitating conditions as schizophrenia, bi-polar mania, [and] [A]lzheimer[']s, [are] children, and [suffer from] dementia. They were in these [Medicaid] programs because they could not pay for or arrange their own care. In other words, they were unable to care for themselves.
>
> *When looking at the purpose of SCUTPA, one comes to the conclusion that the legislature intended [to] cast a wide net for causes of action in order to prevent and discourage deceit and fraud perpetrated on both the public at large and the business community of this state. It is clear that the legislature speaks in broad terms as to the activities that it seeks to make actionable and allows various avenues of enforcement of its prohibitions. Once a deceptive or unfair act in the commerce of this state is identified as affecting the public interest as a whole, and as such, the act is capable of repetition; then it would seem that the legislature seeks broad enforcement of the act.*
>
> In reviewing the above issues I found that the discussion in City of Charleston, S.C. v. Hotels.com, LP, 520 F.Supp.2d 757 (D.S.C. 2007) is relevant concerning the broad enforcement of SCUTPA. In that case the City of Charleston brought action against Hotels.com under the SCUTPA for charging consumers, on a national basis, a hospitality tax which it represented to be for a City tax. Instead of remitting the funds to the City (which it was under no apparent obligation to do in the first place) Hotels.com kept the funds and thus collected [them] as additional profit. Charleston was not a party to the transactions, had no right to collect the tax, and had no contractual connection with

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[5] "The potential for repetition may be demonstrated in either of two ways: (1) by showing the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) by showing the company's procedures create a potential for repetition of the unfair and deceptive acts." *Id.* at 502. Of course, "[those] two ways are not the only means for showing the potential for repetition or public impact, and each case must be evaluated on its own merits[.]" *Id.* A "plaintiff need not allege or prove anything further in relation to the public interest[.]" *Crary v. Djebelli*, 496 S.E.2d 21, 23 (S.C. 1998).

> Hotels[.com]. In determining the legislative intent of SCUTPA and whether it would apply to this relationship, Judge Duffy held that the [d]efendants are clearly involved in trade and commercial activity of the type that legislators intended to regulate by enacting SCUTPA. He took this action in spite of the lack of a close connection between the city and the defendant and the fact that the victims could have protected themselves. *It appears he looked to the nature of the wrong and its relationship to public policy and considerations in find[ing] the City could proceed. In reviewing SCUTPA as a whole it is clear to me that the legislature intended to provide many avenues for the enforcement of its prohibitions.*

Slip op. at 27-28 (Ex. B).

In light of the Court's observations and the standards set forth above, Defendant's contention regarding any targeted audience of prescription drug labeling is simply immaterial to the State's SCUTPA claim.

In addition, Janssen is arguably correct in its assertion that South Carolina law requires strict construction of penal statutes. Indeed, the Court explicitly instructed the jury that the SCUTPA was to be strictly construed against the State. (Trial Tr. XII, 2763, Mar. 22, 2011) ("However, because of the nature of this action, the statutes that you are using in this case should be strictly interpreted by you according to their terms. And any ambiguities or interpretations of the statutes that you are required to make should be resolved against the State, and so they're strictly interpreted, these statutes, that I'm going to talk to you about.") Moreover, such an instruction delivered by the Court is presumed to have been heeded by the jury. *See Conner v. City of Forest Acres*, 363 S.C. 460, 471 (S.C. 2005) (juries are presumed to heed the instructions of the trial court); *Arnold v. State*, 309 S.C. 157, 166 (S.C. 1992) (same). Therefore, Janssen's citations to South Carolina case law suggesting strict construction of penal statutes is, at a minimum, curious. (Def.'s Mem. at 16.)

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### E. Neither Express Preemption Nor Implied Conflict Preemption Preclude the Jury Verdict.

As noted in the State's discussion regarding the FDA's purported "primary jurisdiction over prescription drug labeling (§ II.C, *supra*), Defendant continues to misconstrue the State's statutory claim under South Carolina law as instead an impermissible private action brought to enforce the FDCA. Viewing the State's claim and jury verdict through that misconstruction, Defendant asserts that the State's SCUTPA claim is either impliedly or expressly preempted by federal law. Defendant argues that selectively excerpted testimony from the State's witnesses demonstrates that the SCUTPA claim as to the November 2003 Dear Doctor Letter was "based entirely on Janssen's supposed violations of federal law." (Def.'s Mem. at 17.) But, that simply ignores the totality of the State's evidence, as well as the Court's admonition to the jury regarding its consideration of federal regulatory violations.

Defendant next argues that it is entitled to judgment notwithstanding the verdict as to the Risperdal label because (1) *Wyeth v. Levine* does not apply to this case, or if it does apply, the State adduced insufficient evidence to satisfy *Levine*'s purported preemption "exception"; (2) to the extent the State based its claim on the failure to disclose Trial 113 and ERI to the FDA, that claim is preempted under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001); and (3) to the extent the State claims that "off-label promotion" is a SCUTPA violation, that claim is expressly preempted by the FDCA. Defendant's contentions are meritless.

#### *1. The State's Claim as to the November 2003 Dear Doctor Letter Is Not Based on Defendant's Federal Law Violations, Is Not an FDCA Claim, and Is Not Preempted.*

Defendant's contention that the State's claim based on the November 2003 Letter hinged entirely on federal law violations is grossly mistaken. At trial, the State first introduced the testimony of Dr. William Wirshing, who the Court admitted without objection from Defendant,

as the State's psychiatrist, antipsychotic drug, and clinical trials expert. In addition to the testimony the State elicited from Dr. Wirshing regarding the April 2004 Warning Letter (the only testimony of Dr. Wirshing cited by Defendant in its Memorandum (at 17-18)), Dr. Wirshing—who was actually an original recipient of the November 2003 Letter himself (Trial Tr. at 454 (Ex. A))—testified that Defendant's representations in the Letter *based on his own qualifications and experience*[6] were "patently untrue." (*Id.* at 459 (Ex. A).) Wholly undermining Defendant's argument that Dr. Wirshing premised his opinion "entirely" on the FDA's April 2004 Warning Letter, the State elicited those expert opinions from Dr. Wirshing *even before the April 2004 Warning Letter was ever introduced into evidence at trial*:

> Q. Next sentence [in the November 2003 Letter reads], "Although confirmatory research is still needed, a body of evidence from published peer-reviewed epidemiology research suggests that Risperdal is not associated with an increased risk of diabetes when compared to untreated patients or patients treated with conventional antipsychotics." Do you see that, Doctor?
>
> A. I do.
>
> Q. What's the implication of that sentence?
>
> A. That – the implication is that risperidone is actually devoid of a diabetic risk potential.
>
> Q. And, again, talking about the truth is the truth, is that a true message?
>
> A. No, no, as – we've talked about that risperidone's unequivocally associated with an increased weight gain and it's axiomatic that if you cause an increase in weight gain, you will cause an increase in diabetic risk in the population that you've

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[6] As noted, Dr. Wirshing was admitted (without trial objection from Defendant) as an expert witness in the areas of psychiatry and treatment of the mentally ill. (Trial Tr. at 337 (prescribes Risperdal); at 339, 343-45 (performed many clinical trials himself, including on Risperdal); at 347-48 (experience diagnosing and treating diabetes); at 413 (weight gain and diabetes are serious health problems associated with Risperdal); at 414 (weight gain leading cause of type II diabetes); at 428 (Trial 113 results showed no difference in weight gain, Risperdal vs. Zyprexa; inconsistent with Risperdal marketing message at time); at 433-34 (Trial 113 showed indistinguishable rates of diabetes, Risperdal vs. Zyprexa; also inconsistent with marketing message); at 438 (Trial 113 never published); at 439 (Trial 113 results valuable data) (Ex. A).)

caused the weight gain in, so that's a no. So this can't possibly be true.

Q. Is Janssen's implication that Risperdal's devoid of a diabetes risk true in light of Janssen's study 113?

A. It's not true, period. It certainly isn't true in that study 113. It's not true, period. Their core take-home message is compared to untreated patients. That's just patently untrue.

Q. And it says, "Evidence also suggests that Risperdal is associated with a lower risk of diabetes than some other studied atypical antipsychotics." And we've talked about trial 113, the head-to-head with them and Zyprexa. Based on 113, is that last sentence true, um, as it applies to Zyprexa?

A. Based on study 113 alone, no, that sentence is not true.[7]

(Trial Tr. at 458-59 (Ex. A).) Plainly, Defendant's mischaracterization of Dr. Wirshing's testimony, in a vain effort to establish its preemption defense, mirrors the jury's finding as to the truthfulness of the November 2003 Letter—i.e., both Defendant's position here and the Letter are *untruthful*.

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Defendant's preemption argument as to the November 2003 Letter fails on the above testimony alone. Dr. Wirshing's expert testimony clearly amounts to more than a scintilla evidence as to the deceptive, misleading, and unfair nature of the November 2003 Letter—"testimony tending to prove allegations of the complaint"—before the State ever introduced the April 2004 Warning Letter into evidence. *Proctor*, 696 S.E.2d at 504.

Additionally, Defendant's Motion improperly truncates Dr. Wirshing's actual testimony to further leave the false impression that his opinion as to the November 2003 Letter depended exclusively on the FDA's assessment of the Letter. Beyond the testimony Defendant's Motion cites (reproduced below in plain text), Dr. Wirshing also testified (in bold text):

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[7] The State *subsequently* introduced the April 2004 Warning Letter and asked Dr. Wirshing if the FDA's conclusions matched his own opinions described above. (Trial Tr. at 465-69 (Ex. A).)

Q. According to the FDA, is that letter true or not?

A. No, the FDA felt it was false and misleading.

**Q. According to you, Doctor, was that letter true or not?**

**A. No, it was not true then and it's not true now.**

(Trial Tr. at 488-89 (Ex. A).)

Likewise, Dr. Laura Plunkett, the State's pharmacologist, toxicologist, and FDA regulatory expert (Trial Tr. at 662 (Ex. A)), again permitted to testify without objection from Defendant, also testified that the November 2003 Letter was untrue, deceptive, and unfair in her expert opinion. Her testimony was independent of Defendant's numerous federal regulatory violations. Again, *before* Dr. Plunkett gave any testimony on the April 2004 Warning Letter, the following was elicited by the State:

Q. And we heard from Dr. Wirshing yesterday regarding his view of this letter. But based on the peer-reviewed epidemiological research, based on [the] ERI [study] and based on [Trial] 113, do you have an opinion as to whether the representations in this letter are true?

A. Yes, I do.

Q. What is your opinion?

A. That it is not an accurate representation. It's not true based on the information [Defendant] had, and especially when you consider the whole body of information they had.

Q. And just to be on the safe side, look back here at the references attached to this letter that Janssen uses to support its point. Do you see the ERI data anywhere on these references?

A. No.

Q. How about Study 113?

A. No.

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(Trial Tr. at 747-48 (Ex. A).) Therefore, again, it misrepresents the trial testimony for Defendant to cast Dr. Plunkett's trial testimony as entirely reliant upon the April 2004 Warning Letter. Dr. Plunkett obviously formed her own expert opinions in support of the jury's verdict, which the State elicited independently of any testimony about FDA conclusions. Dr. Plunkett also observed that Defendant's own regulatory expert designee, Dr. Janet Arrowsmith, had previously testified that "it was a mistake to have sent" the November 2003 Letter. (*Id.* at 774-75 (Ex. A).)

Next, unlike the State's experts, the State did not ask Defendant's sales representative, Angie Alderman, to offer any expert testimony as to the truth of Defendant's representation in the November 2003 Letter. Instead, Ms. Alderman made clear that she served as a mere messenger of company-approved and sponsored information about Risperdal, such as the November 2003 Letter, which Ms. Alderman personally distributed to South Carolina doctors. But, *even through her testimony*, the jury was reasonably entitled to infer that Defendant had not been truthful with South Carolina doctors in the November 2003 Letter—separate and apart from any FDA conclusions about the Letter:

> Q. [Y]ou showed [South Carolina doctors] the letter, and Janssen mailed them the letter, and if the letter was later found to be misleading, deceptive, then that would be a problem, wouldn't it?
>
> A. All I did was present the information that my company told me to do. . . . . I'm just doing what the company asked me to do.
>
> Q. All right. So you just do what the company asks you to do?
>
> A. I'm doing – I represent the company and they provide me with clinical information and approved materials and I provide that information to the doctors.
>
> Q. Okay. Well, let me ask you this. If they provide you with clinical materials, did they ever provide you with a study called 113?
>
> A. I'm not familiar with 113.

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Q. Okay. Have you ever heard of 113 in regards to the drug Risperdal?

A. When – can I see that, too?

Q. No, ma'am, I'm just asking if you have ever heard of it.

A. I have never heard of it.

(Trial Tr. at 1155-56 (Ex. A).) As with Drs. Wirshing's and Plunkett's testimony above, Ms. Alderman's testimony above was elicited before she was ever shown the April 2004 Warning Letter.

Notwithstanding Defendant's citations to the State's cross-examination of Defendant's witnesses, the above testimony overwhelmingly demonstrates that the State adduced sufficient evidence to support a jury verdict that the November 2003 Letter was deceptive and unfair under SCUTPA—wholly apart from any FDA determinations about the Letter.

Further, in instructing the jury, the Court (on two occasions) admonished:

> [T]his is an action under South Carolina law, the South Carolina Unfair Trade Practices Act. It's not an action that has been brought under federal law or federal regulations, and this is not an effort to enforce any federal laws or regulations.
>
> It's recognized that the actions of the Defendants are sometimes governed by those laws, but this action does not constitute an effort to enforce those federal laws.
>
> What must be shown in this case is a violation of the South Carolina Unfair Trade Practices. And there must be a showing that SCUTPA has been violated . . . by the actions of the Defendant in order for there to be a finding for the Plaintiff in this case.
>
> * * *
>
> [T]he violation of a federal law or regulation in and of itself does not constitute a violation of SCUTPA.
>
> There must be a showing that SCUTPA has been violated by the actions of the Defendant in order for there to be a finding for the Plaintiff.

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(Trial Tr. at 2763-64, 2812-13 (Ex. A).) As noted above, it is a "sound presumption" that "jurors are reasonable and generally follow the instructions they are given." *Arnold*, 420 S.E.2d at 838-39 (citing *Richardson v. Marsh*, 481 U.S. 200, 206 (1987) (observing that there is "an almost invariable assumption of the law that jurors follow their instructions"). The sound presumption here is that the jury followed the Court's instructions, among others, that the violation of a federal law or regulation did not constitute a SCUTPA violation.

It is readily apparent, then, that the State did not attempt to impose liability on alleged FDCA violations. The State offered independent, stand-alone proof of deceptive an unfair representations in the November 2003 Letter, as shown above. They jury was specifically cautioned not to "intertwine[]" the evidence of State law and federal law violations. (Def.'s Mem. at 22.) Therefore, the federal preemption basis on which Defendant seeks judgment notwithstanding the verdict as to the November 2003 Letter must fail.

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*2. Defendant Is Not Entitled to Judgment Notwithstanding the Verdict as to the Package Insert Because the Claim Is Not Preempted Under Any of Defendant's Theories.*

Defendant additionally contends that the State's SCUTPA claim based on Risperdal's labeling is preempted because (1) undefined "conflict preemption principles" (Def.'s Mem. at 23) supposedly apply here (though Defendant fails to explain how or why, or even what "conflict preemption principles" it refers to in its Motion); (2) *Wyeth v. Levine* purportedly provides no "exception" (Def.'s Mem. at 23) to those "conflict preemption principles" in this case; (3) even if the so-called *Levine* "exception" does apply here, the State has not satisfied its "[burden of] proof" under the "exception"; (4) to the extent that the State's claim was based on Defendant's failures to disclose the Trial 113 and ERI study results to the FDA, that claim constitutes a prohibited "fraud on the FDA" claim under *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001); and (5) to the extent that the State's claim is based on Defendant's off-label

promotion or other violations of federal law or regulations, that claim is expressly preempted by the FDCA. Each of those preemption arguments is also meritless.

First, *Levine* directly contradicts points (1)-(3). Turning first to arguments (1) and (2), Defendant attempts to persuade this Court to adopt the very position the United States Supreme Court rejected in *Levine*. Identical to Defendant's argument here, Wyeth argued that "the CBE regulation [was] not implicated in [*Levine*] because a 2008 amendment provides that a manufacturer may only change its label 'to reflect newly acquired information.'" 129 S. Ct. at 1196. (*See* Def.'s Mem. at 22-23 ("a narrow exception to principles of federal preemption" applies "when a plaintiff alleges that a pharmaceutical manufacturer had the sort of 'newly acquired' information that would trigger the manufacturer's obligation to update its label under the CBE regulations")). And, like Defendant, Wyeth argued that the plaintiff "had not pointed to any such [newly acquired] information" that would justify strengthening the warning of the drug at issue. 129 S. Ct. at 1196. (*See* Def.'s Mem. at 23 (the State "could not identify the specific 'newly acquired information' Janssen possessed that" would have triggered a CBE labeling revision)).[8]

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The United States Supreme Court decided, however, that the precise argument Defendant makes here "misapprehends both the federal drug regulatory scheme and [the defendant's] burden in establishing a pre-emption defense." 129 S. Ct. at 1196. With respect to burden, the Court observed that Wyeth had not even argued at trial that "newly acquired information" was a

[8] The State's argument here sets aside, for argument's sake only, the fact that this Court ruled that the 2008 amendment to the CBE regulation was irrelevant to this case, a fact that Defendant ignores in this portion of its Motion. (Trial Tr. at 1047-51 (relevance objection sustained) (Ex. A).) As the record reflects, the State made clear that its claim that Defendant violated SCUTPA extended only to 2007; thus, the 2008 regulation was not in effect during the relevant time period. (*Id.* at 1048, 1050 (Ex. A).) Defendant subsequently attempted to introduce the FDA's preamble to the 2008 amendment, but upon the State's objection, Defendant agreed to withdraw that proffer. (*Id.* at 2046-2048 (Ex. A).) When Defendant's regulatory expert subsequently "volunteered" testimony regarding the content of the 2008 CBE amendment, the Court struck that testimony. (*Id.* at 2058-2076.)

prerequisite to a CBE label change, much less offered any evidence in support of that position.[9] *Id.* at 1197. With respect to Wyeth's take on the FDA's regulatory scheme, *Levine* rejected "Wyeth's cramped reading of the CBE regulation" as "premised on a . . . fundamental misunderstanding" of that law. *Id.* at 1197-98. Wyeth, like Defendant here, "suggest[ed] that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling." *Id.* at 1197. "Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times." *Id.* at 1197-98. "[The drug manufacturer] is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market." *Id.* at 1198. The Court ultimately held that implied conflict preemption "is a demanding defense" and that on the record before that Court, "*Wyeth . . . failed to*" carry *its* burden on that defense. *Id.* at 1199 (emphasis added).

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Thus, Defendant's contention in argument (2) that the *State* somehow failed in *its* burden to establish a "*Wyeth* exception" to "conflict preemption principles," as Defendant characterizes it, entirely distorts Defendant's actual preemption burden and applicable law. It is plainly ***Defendant's burden*** to establish that the Motion's unspecified "conflict preemption principles" apply to this case and are established through sufficient proof. ***But, Defendant's Motion does not so much as identify the principles to which it refers.***[10] (Def.'s Mem. at 22-23.) And,

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[9] Though it was not her burden to produce such evidence, the Court noted that Levine had introduced the sum total of 20 adverse event reports dating back as far as 33 years before Levine suffered her injury. *Id.* Even based on that "sparse" evidence, the High Court concluded that Wyeth "could have analyzed the accumulating [adverse event reports over the 33 years] and added a stronger warning about . . . the drug." *Id.*

[10] Implied conflict preemption comes in two forms: impossibility preemption and frustration (or obstacle) preemption. *See, e.g., Pacific Gas & Elec. Co. v. State Energy Res. Conservation & Dev. Comm'n*, 461 U.S. 190, 203-04 (1983). Defendant does not indicate the form or forms on which it relies, adding to the murkiness of Defendant's argument. For purposes of the State's formulating a response, however, Defendant's (wrongheaded) argument that the State purportedly failed to adduce sufficient evidence to "fall[] within the '*Wyeth* exception'" to conflict preemption apparently relates to CBE label changes (Def.'s Mem. at 22-23), and appears to urge a finding of impossibility preemption. On the other hand, Defendant's bald assertion that "surely a 'penalties' action by a

reviewing the conflict preemption principles set forth in *Levine* (the most recent, authoritative, and on-point implied conflict preemption case), Defendant fails to remotely attempted to satisfy its burden in that regard.

More specifically, Defendant makes no showing that South Carolina's "traditional[]" and "historic police powers" governing deceptive and unfair trade practices in the State's trade and commerce were "superseded by . . . a clear and manifest purpose of Congress." 129 S. Ct. at 1194-95 (internal quotation marks and citation omitted). As the Supreme Court acknowledged, "respect for the States as 'independent sovereigns in our federal system' leads us to assume that '***Congress does not cavalierly pre-empt state-law causes of action.***'" 129 S. Ct. at 1195 n.3 (quoting *Medtronic, Inc. v. Lohr*, 518 U.S. 470, 485 (1996)) (emphasis added). Thus, Defendant fails to overcome the "presumption against preemption" applicable to implied conflict preemption. 129 S. Ct. at 1194-95 & n.3. Defendant also offers no proof that it was impossible to comply with both South Carolina and federal law, as it must to prove implied conflict preemption. As in *Levine*, the CBE regulation permitted Defendant "to unilaterally strengthen [Risperdal's] warning, and the mere fact that the FDA approved [Risperdal's] label does not establish that it would have prohibited such a change." *Id.* at 1199. Impossibility preemption applies only when it is a "physical impossibility" to comply with both the state and federal law. *Florida Lime & Avocado Growers, Inc. v. Paul*, 373 U.S. 132, 142-43 (1963). This occurs when federal law forbids what state law requires or vice versa. *Barnett Bank v. Nelson*, 517 U.S. 25, 31 (1996). Defendant does not attempt to show that it was physically impossible to comply with both federal and South Carolina law. Additionally, "absent clear evidence that the FDA would not have approved a change to [the drug's] label, [the Court] will not conclude that it was

state . . . threat[ens] . . . FDA regulation of drug labeling" (*id.* at 23) seems to argue frustration (or obstacle) preemption. To the extent the State is mistaken in those estimations, the State reserves the right to supplement this briefing, or further reply to Defendant's subsequent briefing, if any.

impossible for [the drug manufacturer] to comply with both federal and state requirements." *Levine*, 129 S. Ct. at 1198. But, there is no such clear evidence offered by Defendant here. Defendant fails to satisfy its burden to prove that the State's claim and the jury verdict are barred by federal implied conflict preemption.

With particular attention to Defendant's argument (3), *Levine* most certainly governs the Court's implied conflict preemption ruling here, notwithstanding Defendant's contrary argument. Opposite of Defendant's narrow reading of *Levine*, the United States Supreme Court recognized and upheld the presumption against preemption in "field[s] which the States have traditionally occupied," observing that "historic police powers of the States were not to be superseded by [federal law] unless that was the clear and manifest purpose of Congress." 129 S. Ct. at 1194-95.[11] And, *Levine* made clear that Congress has never enacted an *express* preemption provision for prescription drugs; indeed, there is an utter lack of evidence of "clear and manifest purpose of Congress" over the years that might overcome the presumption. 129 S. Ct. at 1194-96.

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Additionally, Defendant treats as self-evident its view that "surely a 'penalties' action by a state attorney general challenging the FDA's decisions as to the adequacy of a prescription drug label poses quite a different and much greater threat to the effectiveness and uniformity of FDA regulation of drug labeling" as compared to the personal injury products liability claim in *Levine*. (Def.'s Mem. at 23.) Defendant sets forth no legal or other basis, however, explaining why that view is so "surely" true. Instead, Defendant ignores *Levine*'s flat rejection of Wyeth's fundamental premise, identical to Defendant's here, that "[o]nce the FDA has approved a drug's

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[11] The Supreme Court observed it had already held that the presumption does apply to "state regulation of health and safety matters . . . ." *Id.* at 1195 n.3 (citing *Buckman*, 531 U.S. at 347-48); *see also Medtronic*, 518 U.S. at 475 ("Throughout our history the several States have exercised their police powers to protect the health and safety of their citizens."). Also, "[g]iven the long history of state common-law and statutory remedies against . . . unfair business practices, it is plain that this is an area traditionally regulated by the States." *California v. ARC America Corp.*, 490 U.S. 93, 101 (U.S. 1989).

label, ***a state-law verdict*** may not deem the label inadequate." *Levine*, 129 S. Ct. at 1199 (emphasis added). "The most glaring problem with this argument," stated the Court, "is that all evidence of Congress'[s] purposes is to the contrary." *Levine*, 129 S. Ct. at 1199. Congress's purpose in enacting the FDCA was "to bolster consumer protection against harmful products." *Levine*, 129 S. Ct. at 1199. Congress, having never enacted any federal consumer protection remedy for "unsafe or ineffective" drugs since first approving the FDCA in 1938, evidently "determined that widely available ***state rights of action . . . appropriate[ly]" protected consumers***. *Levine*, 129 S. Ct. at 1199. Congress, the Court observed, "may also have recognized that ***state-law remedies further consumer protection*** by motivating manufacturers to produce safe and effective drugs and to give adequate warnings." *Id.* at 1199-1200 (emphasis added). The Supreme Court concluded that "[i]f Congress thought state-law suits posed an obstacle to its objectives, it surely would have enacted an express pre-emption provision at some point during the FDCA's 70-year history." 129 S. Ct. at 1200. The Court further determined that the ***FDA itself "long maintained that state law offers an additional, and important, layer of consumer protection that compliments FDA regulation."***[12] *Id.* at 1202 (emphasis added). Nothing in the Court's analysis suggests that the above, expansive preemption tenets are restricted to personal injury "failure to warn" cases, as Defendant argues without support in its Motion, or that state attorney general enforcement of state deceptive and unfair practices laws somehow frustrate congressional purposes any more than state tort verdicts.[13] Thus, Defendant

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[12] "The FDA has limited resources to monitor the 11,000 drugs on the market" and lacks the capacity to effectively identify all the warnings that should be added based on the emergence of new risks. *Levine*, 129 S. Ct. at 1202 & n.11.

[13] It is important to note that none of the State's contentions address or touch upon, restrict, revise, or enjoin any Risperdal label currently in use. The State instead seeks to penalize deception and unfairness arising from misrepresentations, false statements, and half-truths contained in Risperdal's labeling that was previously in use.

has not met its burden to prove that the State's claim and the jury verdict are barred by federal implied conflict preemption.[14]

As to point (4), Defendant contends that at least a portion of the State's claim is barred by *Buckman* "fraud on the FDA" preemption. *Buckman*, an express preemption case,[15] is limited to state law claims for fraud *directed at the FDA*, and the State here disclaimed any such theories of recovery. As noted above, the jury was repeatedly instructed that the case "is not an effort to enforce any federal laws or regulations," and was also admonished that it may not consider "the violation of federal law or regulation [to be] in and of itself . . . a violation of SCUTPA." (Trial Tr. at 2764, 2812 (Ex. A).)[16] Indeed, proof of common law fraud (against the FDA or anyone else) is not at all implicated or required by SCUTPA, which "creates new substantive rights by making conduct unlawful that was not actionable under the common law." *McLeod*, 313 S.E.2d at 338. Moreover, *Buckman* recognized that *Medtronic* carved out "state-law causes of action that parallel federal safety requirements . . . ," *Buckman*, 531 U.S. at 353, which in turn accords

[14] In keeping with *Levine*, this Court ruled in *South Carolina v. Eli Lilly & Co.* that "[b]ased upon Lilly's ability to make unilateral amendments to its labeling [under 21 C.F.R. §§ 201.57(e) and 314.70(c)(6)(iii)(A), (C), as well as *Wyeth v. Levine*] . . . this Court finds as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA." *Lilly*, slip op. at 22-23 (Ex. B).

[15] Recall that the United States Supreme Court in *Levine* determined that Congress has never enacted an *express* preemption provision for prescription drugs. 129 S. Ct. at 1194-96. *Buckman* involved a medical device governed by an express preemption provision in the FDCA's Medical Device Amendments of 1976, applicable only to medical devices. 531 U.S. at 343-44, 348-50.

[16] The Court repeatedly and correctly ruled (*see, e.g.*, Trial Tr. at 86-87, 2522-2523, 2597-98, 2779), however, that evidence of conduct violating FDA regulations that governed Defendant's behavior was admissible on the issue of willfulness, a required element of the State's SCUTPA penalties claim. South Carolina law permits the jury to consider evidence of regulatory violations to support a finding of willful conduct. *See, e.g.*, *Ravan v. Greenville County*, 434 S.E.2d 296, 303 (S.C. Ct. App. 1993) (citing *Rhodes v. Lawrence*, 302 S.E.2d 343, 344 (S.C. 1983) and *Tant v. Dan River, Inc.*, 345 S.E.2d 495, 496 (1986)); *Cooper by Cooper v. County of Florence*, 412 S.E.2d 417, 419 (S.C. 1991). In addition, the evidence that the proposed instruction purports to address was admissible and may have been considered by the jury under S.C.R. Evid. 404(b) as evidence of motive, absence of mistake or accident, and intent. Such evidence was also admissible and may have been considered by the jury under S.C.R. Evid. 406 as evidence of habit or routine practice of the Defendant. Finally, the evidence was relevant to whether Defendant's SCUTPA violations were capable of repetition, thereby implicating the public interest.

with *Levine*'s recognition that state law consumer protection verdicts are complimentary to and in furtherance of federal regulation, *Levine*, 129 S. Ct. at 199-1200, 1202.

Finally, as to Defendant's point (5), the State's allegations and evidence regarding marketing for non-FDA-approved ("off-label") uses was not focused on FDCA violations, but on the deceptive and unfair representations in violation of SCUTPA that were made in marketing plans and materials, as contrasted with Janssen's actual knowledge of Risperdal's risks at the time. Evidence of Defendant's product knowledge juxtaposed with representations/ characterizations of Risperdal that are contrary to that knowledge is plainly relevant to the State's SCUTPA burden of willfulness, requiring a "knew or should have known" showing by the State as to the Defendant. *See* S.C. Code Ann. § 39-5-110(c). Further, there is no such "off-label promotion claim" to bar—i.e., the State did not seek to have the Court assess penalties for the number of times Defendants promoted Risperdal off-label. And, given the United States Supreme Court's acknowledgement that Congress has consistently "declined to enact [an express] preemption provision for prescription drugs," Defendant's reliance on *City of Cayce v. Norfolk S. Ry. Co.*, which hinges on the existence of a "federal statute *[that] contains an express provision regarding preemption*," is misplaced. (Def.'s Mem. at 24 (citing 706 S.E.2d 6, 9 (S.C. 2011) (emphasis added).)

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**F. Defendant's First Amendment Defense Cannot Overcome the Jury Verdict.**

Defendant's First Amendment defense hinges entirely on Defendant's summary classification of the November 2003 Letter and the Risperdal package insert/label as speech on "matters of public concern." (Def.'s Mem. at 24-25.) Defendant asserts no other basis for the Court to extend First Amendment protections to Defendant's so-called protected speech. Also, notably, Defendant does not assert that SCUTPA, in and of itself, violates the First Amendment, and in no way attempts to invalidate the relevant statutes or Act. Defendant merely argues that

the jury was required to be instructed that the November 2003 Letter and the Risperdal label "cannot be punished absent proof by clear and convincing evidence that they were made with actual malice." (Def.'s Mem. at 25 (citing *Gertz v. Robert Welch, Inc.*, 418 U.S. 323, 342, 348-50 (1974); *Erickson v. Jones Street Publishers, LLC*, 629 S.E.2d 653, 665-66 (2006)).)

But not one of Defendant's far-flung cases in its Motion answers the question of whether a promotional letter to doctors about Risperdal (the November 2003 Letter) and a commercial prescription drug label constitute "matters of public concern" or are entitled to First Amendment protections at all. (*See* Def.'s Mem. at 25 (citing, *inter alia*, *Snyder v. Phelps*, 131 S. Ct. 1207, 1213-14 (2011) (involving picketing by church members at dead soldier's funeral); *Illinois ex rel. Madigan v. Telemarketing Assocs., Inc.*, 538 U.S. 600, 606 (2003) (limiting free speech protections attributable to charitable solicitation, which otherwise enjoys full First Amendment protections, in certain fraud cases)).) Indeed, the *Snyder* opinion is expressly limited to the facts considered by the United States Supreme Court in that case—i.e., free speech protections extending to protests about matters of public concern at a funeral service. *Id. Telemarketing* is not a "public concern" case at all—the words "public concern" do not appear in the opinion. The *Telemarketing* Court held that charitable fundraisers may be subjected to state law fraud liability notwithstanding First Amendment protections provided that the fraud consists of misleading statements and not merely the nondisclosure of charitable donations fundraisers keep for themselves. 538 U.S. at 606. Additionally, *Connick v. Myers*, involving an employee who was terminated for unprotected private speech, addressed the "particularized balancing" attributable to punishing government employees for speech at work. 461 U.S. 138, 150 (1983). None of those cases will assist the Court in deciding the threshold matter of whether "public concern" First Amendment protections even apply here. Nor will they guide the Court in applying

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deciding whether an "actual malice" standard applies to Defendant's "speech" because none of those cases adopted an "actual malice" standard of proof.

Similarly, *Gertz*, *Erickson*, and *Parker v. Evening Post Publ'g Co.* are all striking in their inaptness. All are media-related defamation and/or libel cases discussing the extent to which the *New York Times* "actual malice" standard applies, if at all. *Gertz*, 418 U.S. at 346 ("We hold that, so long as they do not impose liability without fault, the States may define for themselves the appropriate standard of liability *for a publisher or broadcaster of defamatory falsehood injurious to a private individual.*") (emphasis added); *Erickson v. Jones St. Publrs., LLC*, 629 S.E.2d 653, 671 (S.C. 2006) (applying "actual malice" in libel case); *Parker*, 452 S.E.2d 640, 644-46 (S.C. Ct. App. 1994) (same). Defendant never explains how those media-related defamation cases fit the First Amendment questions before this Court.

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Lastly, Defendant cites two federal district court cases (from the District of Columbia and Brooklyn, New York) for the proposition that "[s]tatements on scientific and medical research are, as a matter of law, statements of public concern." (Def.'s Mem. at 25 (citing *McMillan v. Togus Reg'l Office, Dep't of Veteran Affairs*, 294 F. Supp. 2d 305, 317 (E.D.N.Y. 2003); *Bd. of Trs. of Leland Stanford Jr. Univ. v. Sullivan*, 773 F. Supp. 472, 474 (D.D.C. 1991). *McMillan* involved a private plaintiff decorated Vietnam War veteran's declaratory judgment action against the National Academy of Sciences and Institute of Medicine for allegedly failing to adequately review scientific evidence concerning the association between Vietnam soldiers' exposure to the herbicide Agent Orange and illnesses they suffered. 294 F. Supp. 2d at 305-306. Nothing in that case addressed the overlay of commercial, for-profit speech (or corporate decisions about "speech" in the form of promotional letters and drug labeling) potentially implicated here, much less the state's well-settled, constitutional interest in policing commercial speech. *See Zauderer*

*v. Office of Disciplinary Counsel of Supreme Ct.*, 471 U.S. 626, 638 (1985); *see Va. State Bd. of Pharm. v. Va. Citizens Consumer Council*, 425 U.S. 748, 772 n.24 (1976) (states may regulate commercial speech "to require that a commercial message appear in such a form, or include such additional information, warnings, and disclaimers, as are necessary to prevent its being deceptive"); *accord, 44 Liquormart v. R.I.*, 517 U.S. 484, 498-99 (1996) (citing *Ohralik v. Ohio State Bar Ass'n.*, 436 U.S. 447, 456 (1978) (commercial speech "occurs in an area traditionally subject to government regulation"). Defendant's reliance on *Sullivan*, on the other hand, is misplaced because that is a "prior restraint" First Amendment case, which distinctly "comes to . . . Court bearing a heavy presumption against its constitutional validity." 773 F. Supp. at 474. There is no prior restraint at issue here. Further, the *Sullivan* court recognized, "this case does not involve commercial speech," suggesting a different standard applies in commercial speech cases. *Id.* at 475 n.8. (*See* discussion below.)

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Thus, the State (and, apparently Defendant too) are unable to identify *any court* in *any jurisdiction* that has applied a broad "matter of public concern" First Amendment free speech guarantee, or a "clear and convincing" *New York Times* "actual malice" burden of proof, in *any action* concerning pharmaceutical companies' communications with prescribers in support of a for-profit prescription drug, such as the Letter and label here.[17]

Moreover, in an apparent effort to achieve a favorable result under a less unwieldy First Amendment standard arguably applicable to "matters of public concern," Defendant simply ignores any commercial attributes of the November 2003 Letter and the Risperdal label. That

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[17] "The statute clearly requires that in order to recover pursuant to [SCUTPA] one must prove . . . three elements by the greater weight or preponderance of the evidence." *Charleston Lumber Company, Inc. v. Miller Housing Corp.*, 458 S.E.2d 431, 438 (S.C. Ct. App. 1995), *rev'd on other grounds by Charleston Lumber Co., Inc. v. Miller Housing Corp.*, 525 S.E.2d 869 (S.C. 2000). Defendant improperly attempts to impose a heightened standard upon the State's civil action, to which a preponderance or greater weight of the evidence standard applies. *See, e.g., Welch v. Clifton Mfg. Co.*, 33 S.E. 739, 746 (1899). Moreover, Defendant cites no case in which such an elevated standard of proof has been applied in a SCUTPA action.

omission is fatal to Defendant's First Amendment defense. The United States Supreme Court routinely addresses First Amendment protections that may be due communications, including promotion and labeling, related to prescription drugs and other consumer products under a "commercial speech," not a "public concern" standard. *See, e.g., Thompson v. Western States Med. Ctr.*, 535 U.S. 357, 364-77 (2002) (applying commercial speech First Amendment protections set forth in *Central Hudson Gas & Elec. Corp. v Public Serv. Comm'n*, 447 U.S. 557 (1980), to FDCA regulations governing the promotion of compounded prescription drugs); *Rubin v. Coors Brewing Co.*, 514 U.S. 476, 481 (1995) ("information on beer labels constitutes commercial speech" subject to the *Central Hudson* factors analysis); *accord, Zauderer*, 471 U.S. at 651 ("[I]n virtually all our commercial speech decisions . . . , we have emphasized that because disclosure requirements trench much more narrowly on [constitutional] interests than do flat prohibitions on speech, *[warnings] or [disclaimers] might be appropriately required . . . in order to dissipate the possibility of consumer confusion or deception.*") (emphasis added, internal quotation marks and citation omitted).

But the most significant reason that Defendant avoids the *Central Hudson* "commercial speech" standard is this: ***"The States and the Federal Government are free to prevent the dissemination of commercial speech that is false, deceptive, or misleading . . . ."*** *Zauderer*, 471 U.S. at 638 (emphasis added); *see Thompson*, 535 U.S. at 367 (under *Central Hudson*, ***"we ask as a threshold matter whether the commercial speech concerns unlawful activity or is misleading. If so, then the speech is not protected by the First Amendment"***) (emphasis added). It is without question that the jury found both the 2003 Dear Doctor Letter and Risperdal label to be "deceptive" based upon sufficient record evidence. Those materials are not entitled to First Amendment protections, therefore.

Defendant has waived any argument that the November 2003 Letter and the Risperdal label constitute protected commercial speech, and the State is under no obligation to undertake such an analysis on Defendant's behalf. Nor has Defendant addressed *any* impact the State's interest in policing commercial speech may have on First Amendment analysis here. Justice Stevens, joined by Justices Ginsburg and Souter, recognized in *Nike, Inc. v. Kasky* that the "blending of commercial speech, noncommercial speech and debate on an issue of public performance" is a "novel First Amendment question[]" that is yet unaddressed by the United States Supreme Court. 539 U.S. 654, 663 (2003) (Stevens, J., concurring). Apparently Defendant hopes this Court will undertake that novel question *sua sponte*. Of course, it should not.[18]

The Court should deny Defendant's First Amendment challenge to the jury verdict.[19]

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[18] The burden of establishing an affirmative defense is on the defendant. *McClain v. Anderson Free Press*, 232 S.C. 448, 102 S.E.2d 750 (1958) (finding that, in action for libel, where answer pleads affirmative defense of qualified privilege, burden of proof is upon defendant to establish such defense by a preponderance of the evidence); *Lorick & Lowrance, Inc. v. Julius H. Walker & Co.*, 153 S.C. 309, 150 S.E. 789 (1929)(when a defendant interposes an affirmative defense, he becomes as to that matter the actor in the suit, and burden of proof rests upon him to establish his affirmative defense by preponderance of the evidence).

[19] A final point as to Defendant's First Amendment challenge to the jury's verdict on the Risperdal label: Defendant contended throughout trial—expressly representing to the jury—that the FDA is responsible for the content of Risperdal's label, "determin[ing] everything down to the size of the print." (Trial Tr. at 2699; *see id.* at 245-46, 249, 2049, 2249, 2253, 2410, 2699 (Ex. A).) And, while *Levine* makes clear that *Defendant, not the FDA*, is ultimately and forever responsible for the content of Risperdal's labeling as long as the drug is on the market (*see* § II.E, *supra*), Defendant persists in arguing in this Motion that the Risperdal label, which the jury found to be deceptive and unfair, was "required by the agency . . . ." (Def.'s Mem. at 7; *id.* ("FDA . . . requir[ed] Janssen to use 'identical' or 'verbatim' language in Risperdal labeling.").) Indeed, it is on that basis that Defendant seeks protection under SCUTPA's "safe harbor" provision (Def.'s Mem. at 6-11)—albeit protection to which it is not entitled. (*See* § II.B, *supra.*)

Characteristically in this litigation, where it has been advantageous for Defendant to hide behind the FDA in an effort to shield itself from State law liability, it has done so both at trial and in its legal arguments to this Court. From distancing itself from responsibility for Risperdal's label in front of the jury (see above), to seeking "safe harbor" from SCUTPA liability, to characterizing the State's SCUTPA claim as a disguised FDCA or fraud-on-the-FDA claim for so-called "primary jurisdiction" or federal preemption purposes, Defendant has consistently tried to cloak itself in FDA protections. (At the same time, Defendant contends—again inconsistently—that *the jury should not have considered the State's* FDA/federal regulatory evidence.)

But, with respect to Defendant's First Amendment challenge to the labeling verdict, Defendant must change horses (for the first time ever in this Court) and claim the label's language as its own. That is because speech that is compelled by the government—in the form of a product label or information about a product, for example—properly falls into the category of "government speech," which is entitled to ***no First Amendment***

## G. The State Has Proven All Elements Of Its SCUTPA Claim.

Apparently abandoning its flawed, former attempts to convince this Court of "reliance" and "causation" elements purportedly required by SCUTPA § 39-5-110(a) in light of federal court interpretations of the Federal Trade Commission ("FTC") Act, Janssen nevertheless relies exclusively on a lone FTC case from the United States Court of Appeals for the Eleventh Circuit to establish the elements of a SCUTPA penalties claim. (Def.'s Mem. at 31 (citing *FTC v. Tashman*, 318 F.3d 1273, 1277 (11th Cir. 2003).) Janssen then virtually ignores all other applicable South Carolina precedent, preferring to cite federal FTC cases to support its arguments that the State has not satisfied its evidentiary burden for proving deceptive and unfair trade practices under SCUTPA. Defendant's arguments fail, as discussed below.

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### *1. The State Offered Ample Evidence in Support of its Unfair Trade Practices Claim.*

As an initial matter, Defendant presents two untenable arguments relative to the Court's rulings on the permissible scope of the State's SCUTPA claim. First, Defendant argues that the "use of an FDA-approved package insert cannot be the basis of an 'unfair' trade practice[s]"

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*protections. See, e.g., Johanns v. Livestock Mktg. Assoc.*, 544 U.S. 550 (2004); *United States v. Frame*, 885 F.2d 1119 (3d Cir. 1988). Thus, assuming *arguendo* the Risperdal label is the "FDA's label," as Defendant has unwaveringly asserted, then Defendant simply has no First Amendment challenge to the jury's labeling verdict.

Obviously, Defendant cannot have it both ways. Due to the overriding "government speech" exception, only if Defendant were willing to abandon its "safe harbor," federal preemption, "primary jurisdiction," and any other arguments that depend upon Risperdal's labeling being dictated at all times by the FDA—which Defendant is quite unwilling to do—might Defendant possibly succeed on its First Amendment defense to the jury's labeling verdict.

In reality, Defendant cannot successfully argue that it was powerless to change the label. The State's unequivocal position has been that, under *Levine* and the applicable CBE regulations, Defendant had ultimate responsibility at all relevant times for strengthening (or adding) warnings to Risperdal's label. It was unlawful for Defendant not to have strengthened or added to Risperdal's warnings at any point that it had knowledge of reasonable evidence of an association between Risperdal and a serious hazard. 21 C.F.R. § 201.57(e) (2006). The State introduced overwhelming evidence supporting the jury verdict relative to Defendant's knowledge of Risperdal's serious risks that should have triggered a timely CBE amendment, but instead Defendant hid that knowledge from outsiders, including South Carolina prescribers and patients, as described herein. To the extent that Defendant refuses to adopt the State's foregoing view of Defendant's labeling obligations—which it will so refuse—then Defendant's First Amendment defense fails as to the Risperdal label under the "government speech" exception.

claim but ignores that this Court and the United States Supreme Court in *Levine* both firmly rejected this proposition. *Levine*, 129 S. Ct. at 1199 (rejecting argument that because its prescription drug labeling was FDA-approved and regulated, the company could not comply with conflicting state law); *Lilly*, slip op. at 23 (determining "as a matter of law that the fact that an FDA approved label is in effect does not bar an action under SCUTPA"). (Def.'s Mem. at 27.) .(*See* discussion, *supra* at §§ II.B.1. and II.C.) Also contrary to Defendant's contentions, this Court relied on *Levine*, *inter alia*, in so ruling in this case as well as in the *Lilly* case and, further, correctly relied on the South Carolina Supreme Court's interpretation of "unfair" under *South Carolina* consumer protection law in *Gentry v. Yonce*, 522 S.E.2d 137 (1999). (*Lilly*, slip. op. at 22-23 (relying on *Levine*, 129 S.Ct. at 1197, in permitting State's SCUTPA claim to proceed notwithstanding FDA approval of Zyprexa label); *see* Trial Tr. at 2767, 2815 correctly charging the jury, consistent with the *Gentry* Court's articulation of SCUTPA and all other relevant South Carolina case law, that "a trade, practice or act is an unfair trade, practice or act if it offends established public policy, or it is immoral, unethical, or oppressive") (Ex. A).) Defendant's attempt to apply irrelevant, non-authoritative extra-jurisdictional case law notwithstanding relevant and controlling United States and South Carolina Supreme Court precedent has correctly been and should further be rejected.

In addition, Defendant argues that the Court erred by not limiting the State's SCUTPA claim at trial despite that the State presented the same case at trial as that set forth in its Second Amended Complaint (as well as in its Original Complaint filed nearly four years prior to the start of trial) and identified in its discovery responses and this Court's February 25, 2011 Order. Specifically and as addressed more fully herein at II.K.1, *infra*, Defendant has been on notice of the State's SCUTPA claims for both Defendant's "deceptive" and "unfair" Risperdal labeling at

the very latest, since the State filed its Second Amended Complaint in January 2010. (*See, e.g.*, Pl.'s Second Am. Compl. ¶¶ 8, 11, 13, 24, 26, 45-49, 54.) The State also argued that Defendant's labeling was unfair under SCUTPA in its discovery responses served nearly a year in advance of trial. (*See, e.g.*, Pl.'s Supplemental Answers to Defs.' Fifth Set of Interrogs., No. 9; Pl.'s Answers to Defs.' Fifth Set of Interrogs., No. 9.) Further, in denying Defendant's motions for summary judgment, the Court plainly articulated "[t]he question to be decided in this case under S.C. Code Ann. § 39-5-110(a)": "whether or not unfair methods of competition and unfair or deceptive acts have occurred in the conduct of the Defendant's trade or commerce as is defined in S.C. Code Ann. § 39-5-20," and "whether or not those illegal acts or practices have been employed 'willfully.'" (Order on Defendant's Motions for Summary Judgment and Partial Summary Judgment, Feb. 25, 2011, at 4; *see also id.* at 1 (stating that "the State initiated this action against Defendants . . . to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for their willful, deceptive *and* unfair course of conduct in Risperdal's product *labeling*") (emphases added).

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Turning to the elements of the State's unfair trade practices claim, Defendant again chooses to rely on extra-jurisdictional case law as it has throughout this litigation. Defendant suggests that the Court follow Tennessee law to interpret SCUTPA and its evidentiary burden, and ignores the State's previously cited, applicable South Carolina precedents. As noted above, the overriding concern of SCUTPA is not which person in particular (consumer or otherwise) received or was affected by a deceptive representation about a product, but is instead unfairness or deception "in the conduct of any trade or commerce . . ." ***that affects the public interest generally***. S.C. Code Ann. § 39-5-20(a) (2009). (*See* § II.D, *supra* (citing cases and quoting *Lilly,* slip op. at 27-28 (Ex. B)).) In line with Defendant's acknowledgement that "[p]ractices

that unreasonably interfere with consumer decision-making include (1) withholding information from consumers," and (2) "exercising undue influence over a highly susceptible class of consumers" (Def.'s Mem. at 16 (citation omitted)), this Court should find that the State has met its evidentiary burden for proving unfair conduct in violation of SCUTPA under relevant South Carolina case law.

*2. The State Offered Ample Evidence in Support of its Deceptive Trade Practices Claim.*

Janssen additionally asserts (1) that the State lacks an actionable representation under the cited FTC elements; (2) that the State has not shown the representation was likely to mislead (as opposed to having a "capacity" or "tendency to deceive" under South Carolina precedent, *McLeod*, 313 S.E.2d at 338); and (3) that the representation was material. (Def.'s Mem. at 31-36.) Not only does Janssen improperly rely on federal as opposed to ample State precedent interpreting SCUTPA, each of the aforementioned elements is satisfactorily met.

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**a. The Representations Offered by the State Are Actionable.**

Although the State is only required to prove that a representation "had the capacity or effect or tendency to deceive," *McLeod*, 313 S.E.2d at 338, the State also fulfilled the additional (overlapping) element Defendant imposes in terms of identifying an "actionable representation." The State has already demonstrated why the November 10, 2003 Dear Doctor letter is actionable under SCUTPA—i.e., that misrepresentations regarding Risperdal's absence of diabetes risk in the Dear Doctor letter tended to deceive South Carolina physicians and patients. While Defendant disclosed some sources allegedly supporting their position that Risperdal was "devoid of diabetic risk potential" (Trial Tr. at 458), ***Defendant nevertheless plainly omitted other information it had hidden from doctors, patients, the FDA, and the public at large that demonstrated a very real diabetes risk potential.*** As this Court found in denying Defendants'

summary judgment motions, "[i]t appears from the November 2003 'Dear Doctor' letter that Janssen may have actually taken affirmative action to confuse the issue, so as to hide the disparity between what was being told to the prescribing public and what its own professionals and experts knew." (Order of Feb. 25, 2011 at 6.) The failure to disclose relevant information is actionable under SCUTPA. *See York v. Conway Ford, Inc.*, 480 S.E.2d 726, 727-28 (S.C. 1997) (holding that the representation that a truck sold to plaintiff was a "like new" demonstrator that had never before been titled to an individual, while failing to disclose that the truck had a bent frame from a previous accident, was actionable under SCUTPA); *Inman v. Ken Hyatt Chrysler Plymouth, Inc.*, 363 S.E.2d 691, 692 (S.C. 1988) (selling repossessed vehicle as new without disclosure is a deceptive trade practice); *Estate of Carr v. Circle S Enters.*, 664 S.E.2d 83, 89 (S.C. Ct. App. 2008) (including in SCUTPA's ambit the "failure to disclose a material fact"); *Wright*, 640 S.E.2d at 499-500 (holding duty to disclose is applicable to a SCUTPA claim). Unlike the *Bruette v. Stokes, Kia, Isuzu, Subaru, Inc.* case Defendants cite, here there was no "equal and ample opportunity" for South Carolina doctors and their patients "to ascertain the truth" about the knowing, willful misrepresentations in the Dear Doctor letter because only Defendant possessed the relevant results of Trial 113 and the ERI study, which Defendant chose not to disclose.

The same holds true for Defendant's argument that the warnings in the package insert were not deceptive. For example, whether or not the label is based on judgments by Janssen and/or the FDA as to the significance of the scientific evidence, only Defendant had possession of the revealing Trial 113 and ERI results and opted to keep those results from public and regulatory view. The failure to disclose those results demonstrating a reasonable association with the serious hazards of diabetes/hyperglycemia and weight gain permitted Janssen to steer

clear of strengthening Risperdal's warnings—a requirement that Janssen desperately sought to avoid. (*See, e.g.*, Pl. Ex. 254, 1105, 1264, 1552, 2651; Trial Tr. at 670-71, 778-81, 788-90, 791-95, 871-73 (Ex. A).)

In sum, notwithstanding Janssen's characterizations that its November 10, 2003 Dear Doctor letter and labels were "reasonable expressions of scientific opinion," that argument wholly ignores the inherent deception in Janssen's failure to disclose fully what it knew to be the true attendant health risks of consuming Risperdal. This is not a matter of "scientific debate," as Janssen seeks to convince the jury and Court. This is a matter of a drug company withholding vital safety information in order to maintain its market status. As such, the conduct is actionable under SCUTPA for the reasons shown above.

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**b. The State Proved Tendency to Deceive.**

Defendant again seeks to convince this Court that in order to prove a tendency to deceive, the State must show, for example, that the November 10, 2003 Dear Doctor letter and the Risperdal labels "actually deceived or were 'likely to deceive'" South Carolina physicians or had *actual* impact on the South Carolina marketplace. (Def.'s Mem. at 33-35 (citing *deBondt* v. Carlton Motorcars, Inc., 536 S.E.2d 399, 407 (S.C. Ct. App. 2000) and attempting to convert the applicable objective standard there into a subjective one to require proof of actual deception).)

That, however, is not the law in South Carolina, as the Court knows. "[T]here is no need to show that a claim or representation was intended to deceive, but only that it had the capacity or effect or tendency to deceive." *McLeod*, 313 S.E.2d at 338 (citing *Federal Trade Comm'n v. Algoma Lumber Co.*, 291 U.S. 67 (1934); *D.D.D. Corp. v. Federal Trade Comm'n*, 125 F.2d 679 (7th Cir. 1942)); *see also Dowd*, 381 S.E.2d at 213-214 ("To recover for fraud, the familar [sic] nine elements must be proved 'by clear, cogent, and convincing evidence.' No such proof is required to recover under [SCUTPA].") Similarly, South Carolina law does not require the State

to prove "actual" impact, but, rather, that the alleged unfair or deceptive act or practice had the mere *potential* for repetition, at most—which the State has decidedly demonstrated. *See Wright*, 640 S.E.2d at 501; *accord Dowd*, 381 S.E.2d at 214.

Further, contrary to Defendant's assertions, the State's psychiatrist expert, Dr. Wirshing, did not take "the position that the November 2003 mailing was somehow inherently 'deceptive' and that the Risperdal package insert was 'inadequate' as to certain risks." (Def.'s Mem. at 34.) Instead, Dr. Wirshing explained in great detail the bases for each of his opinions that the November 10, 2003 Dear Doctor letter and the package insert were deceptive and untrue. (*See, e.g.*, Trial Tr. at 358 (Dr. Haas's statement that Janssen first warned of weight gain risk in 1994 label was untrue, no warning contained in that label); *id.* at 458 (Janssen statement that Risperdal has no increased risk of diabetes as compared to untreated patients was untrue because of potential for clinically significant weight gain, which axiomatically increases diabetes risk); *id.* at 459 (Janssen's assertion that Risperdal was devoid of diabetes risk was untrue based on Trial 113 and other evidence); *id.* (assertion that Risperdal had lower diabetes risk was untrue based on Trial 113); *id.* at 484 (Nov. 10, 2003 Dear Doctor letter omitting material information and reference list was "far from exhaustive"); *id.* at 521 (sales materials characterizing Zyprexa as having diabetes risk and Risperdal as not having that risk were untrue in light of Trial 113 results); *id.* at 525-26 (assertion that Risperdal has zero percent association with diabetes in double-blind trials was untrue given previously revealed 2.8% diabetes risk and Trial 113 results) (Ex. A).) Such testimony is far from "speculation of experts," as Janssen attempts to characterize it.

Additionally, the State introduced overwhelming evidence of the public impact of Defendant's unfair and deceptive trade practices under SCUTPA. (*See* discussion, *infra* at II.H.)

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Despite Defendant's insistence, the testimony of Drs. Bank and Ratliff regarding the purported lack of actual impact on their own prescribing practices or those of any South Carolina prescriber, is immaterial to the Court's determination, consistent with all relevant evidence, at II.H., *infra*, that the dissemination of the November 2003 Dear Doctor letter to thousands of South Carolina prescribing physicians[20] and related deceptive labeling was offensive to and affected the public interest in that it had the "potential for repetition." *Wright*, 640 S.E.2d at 501 (impact on the public interest may be shown if the acts or practices have the "potential for repetition"); *accord Dowd*, 381 S.E.2d at 214. (*See also* discussion, *infra* at II.J.1.d.) For those and other reasons discussed herein, *see infra*, II.K.4.c. and II.K.4.e., the calculations of Dr. Wecker purportedly "showing that there was no change in Risperdal's share of prescriptions for antipsychotics filled for South Carolina Medicaid and State Health Plan participants" after Janssen sent the November 2003 Dear Doctor letter and related Corrective Letter, are wholly irrelevant to the question of whether Defendant's dissemination of Risperdal's labeling, including the 2003 Dear Doctor Letter, had the "potential for repetition." (Def.'s Mem. at 35.)[21]

There is sufficient evidence for the jury to determine finally whether Defendant's representations regarding Risperdal had a tendency to deceive.

**c. Materiality Is Not a Required Element of the State's Claim.**

Devoid of support in the South Carolina case law, Defendant's cursory argument that the State failed to prove that the November 2003 mailing or the Risperdal package insert were "material" to any prescribing decision by any South Carolina doctor must fail. "Materiality" sounds like code language for "reliance" or "causation," neither of which the State is required to

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[20] *See* Trial Tr. at 1317 (Ex. A).

[21] In addition, Defendant incorrectly contends that relative to Dr. Wecker's calculations, the State purportedly stipulated "that there was no change in Risperdal's share of prescriptions for antipsychotics filled for South Carolina Medicaid and State Health Plan participants after the November 2003 mailing or after Janssen sent a follow-up letter in July 2004." (Def.'s Mem. at 35.)

prove, as shown above. All that need be shown is a "tendency to deceive," as amply repeated above and in the Court's prior rulings.

**H. The State Has Proven Public Impact Of Defendant's Unfair And Deceptive Trade Practices Under SCUTPA.**

Despite Defendant's claim that "the State did not introduce sufficient evidence for the jury to find that the alleged unfair or deceptive trade practice adversely affected the public interest," South Carolina law and applicable federal law do not require the State to prove "actual" impact, but, rather, that the alleged unfair or deceptive act or practice had the mere *potential* for repetition, at most—which the State has decidedly demonstrated. (Def.'s Def.'s Mem. at 3; *see also* Def.'s Mem. at 37-40.) With respect to its impact on the public, this Court has already ruled that labeling, promotions, and other such communications by a pharmaceutical manufacturer to the public, including prescribing physicians, are of "considerable importance" to the State, the public and the medical community. *Lilly*, 2007-CP-42-1855, at *18-20. Beyond that, the State is not required to proffer evidence of the November 2003 Dear Doctor letter's or the Risperdal package insert's "actual" public impact for its dissemination to be actionable under SCUTPA.

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Rather, and as Janssen acknowledges (despite its contemporaneous contention that the State's claim must fail because it, allegedly, "presented no factual evidence that either the November 2003 mailing or the Risperdal package insert had an *actual* adverse affect on the public or on physicians," Def.'s Mem. at 39), "[a]n impact on the public interest may be shown if the acts or practices have the potential for repetition." *Wright*, 640 S.E.2d at 501; *accord Dowd*, 381 S.E.2d at 214 (holding that, in order to impact the public interest, unfair or deceptive acts or practices in the conduct of trade or commerce must simply have "the *potential* for repetition") (emphasis added) (citations omitted). "The potential for repetition may be demonstrated in either

of two ways: (1) by showing the same kind of actions occurred in the past, thus making it likely they will continue to occur absent deterrence; or (2) by showing the company's procedures create a potential for repetition of the unfair and deceptive acts." *Id.* at 502. Of course, "[t]hese two ways are not the only means for showing the potential for repetition or public impact, and each case must be evaluated on its own merits[.]" *Id.*; *accord Crary*, 496 S.E.2d at 23. A "plaintiff need not allege or prove anything further in relation to the public interest[.]" *Crary*, 496 S.E.2d at 23.

Indeed, the purpose of the "public impact" requirement is simply to exempt actions for *private* wrong where the public interest is unaffected. *See Noack Enters., Inc.*, 351 S.E.2d at 349-50; *see also Wright*, 640 S.E.2d at 501 ("Since 1986, South Carolina courts have required that a Plaintiff bringing a private cause of action under UTPA allege and prove the defendant's actions adversely affected the public interest." (quoting *Daisy Outdoor Adver. Co. v. Abbott*, 473 S.E.2d 47, 49 (S.C. 1996))). Therefore, the South Carolina Supreme Court has "***expressly reject[ed] any rigid, bright line test*** that delineates in minute detail exactly what a plaintiff must show to satisfy the potential for repetition/public impact." *Daisy*, 473 S.E.2d at 51 (emphasis added).

In that connection, the State has proffered "impact evidence" sufficient to show that the dissemination of the November 2003 Dear Doctor letter to thousands of South Carolina prescribing physicians[22] and related deceptive labeling was offensive to and affected the public interest in misleading the public, and in particular the South Carolina medical community, by "fail[ing] to disclose the addition of information relating to hyperglycemia and diabetes mellitus

22 *See* Trial Tr. at 1317 (Ex. A).

to the approved product labeling";[23] "minimiz[ing] the risk of hyperglycemia-related adverse events, which . . . is associated with serious adverse events including ketoacidosis, hypersmolar coma, and death";[24] "fail[ing] to recommend regular glucose control monitoring to identify diabetes mellitus as soon as possible";[25] and, "misleadingly claim[ing] that Risperdal is safer than other atypical antipsychotics,"[26] despite the FDA's unequivocal instruction that all product labeling be updated to include information about diabetes mellitus adverse events.[27]

For example, in its April 2004 Warning Letter to Janssen, the FDA recognized the significant and detrimental impact of the November 2003 Dear Doctor letter on the South Carolina public:

> The healthcare community relies on [Dear Doctor] letters for accurate and timely information regarding serious risks and associated changes in labeling and the dissemination of this letter at a time critical to educating healthcare providers ***is a serious public health issue.***[28]

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In addition to demonstrating its public impact, the State established the potential for repetition and the actual repetition of Defendant's November 2003 Dear Doctor letter—a fact to which Defendant actually stipulated. Indeed, relative to the State's inquiry as to the number of November 2003 Dear Doctor letters distributed in the State of South Carolina, Defendant stipulated "that based upon their available distribution list, there were 7,194 copies of that letter sent to addresses of physicians in the State of South Carolina." (Trial Tr. at 1317-1318 (Ex. A).) The State demonstrated not only the repetition of the letter itself, but also the repetition of the

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23 Pl. Ex. 1729.

24 *Id.*

25 *Id.*

26 *Id.*

27 Pl. Ex. 520.

28 Pl. Ex. 1729 (emphasis added).

specific unfair and deceptive content of the letter through other of Defendant's false and misleading promotional materials relative to Risperdal. Specifically, Dr. Plunkett testified regarding certain of Defendant's communications with the FDA, particularly that in response to the FDA's April 2004 Warning Letter reprimanding Janssen for its brazenly "false," "misleading," and illegal representations made to more than 7,000 South Carolina physicians in the November 2003 Dear Doctor letter, and requiring immediate corrective action. (Trial Tr. at 825-828; Pl. Ex. 232; *see* Pl. Ex. 436.) She identified that in Janssen's April 28, 2004 letter to the FDA, Janssen enumerated, pursuant to the FDA's request, additional promotional items of broad dissemination "containing same or similar claims to those addressed in [the] April 19, 2004 [Warning] [L]etter" regarding the "omission of material information and minimization of risks/misleading comparative claims" made in the November 2003 Dear Doctor letter. (Pl. Ex. 436 (identifying additional violative promotional items at Attachment B).)

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Relative to the Risperdal labeling, or package insert, the State has also introduced evidence of the extent to which the South Carolina public was impacted by Defendant's false and misleading labeling and the extent to which Defendant's actionable conduct was repetitious. Through the testimony of Dr. David Patterson, for example, the State presented evidence of the accurate number of Risperdal prescriptions filled in the State of South Carolina between 1994 and 2007, which included, *inter alia*, numerous prescriptions for particular patient populations to which Defendants most heavily promoted Risperdal through their labeling during the relevant time period, as described more fully above. (*See* Pl. Ex. 2670; Pl. Ex. 2671; Pl. Ex. 2672; Trial Tr. at 1292-1307 (Ex. A).) With each such prescription, Defendant's false and misleading labeling was disseminated. (*See* Trial Tr. at 1061-1075, 1084-1085 (Ex. A).)

Further, the State presented evidence of Janssen's uniform dissemination of the Risperdal package insert on each Risperdal sales call. In particular, Janssen's Senior Product Director for Risperdal, Riley Smith, confirmed that its sales representatives "certainly leave the package insert on all sales calls with physicians, so that information is there for them to read." (Riley Smith Dep. Tr. at 403, a true and correct copy of which is attached hereto as Exhibit C; *see* Trial Tr. at 1201 (publishing excerpts of the videotaped deposition of Riley Smith to the jury) (Ex. A).) He additionally testified regarding Defendant's sales representatives' dissemination of accompanying false and misleading labeling with the package insert, including "sales aids," such as those described in Janssen's 2004 Risperdal Business Plan, *see* Pl. Ex. 77, and Dear Doctor letters. (*Id.* at 247-248, 253-254, 402-404; *see* Trial Tr. at 1201.) Relatedly, Janssen's marketing director, Ronald Kalmeijer, testified that the objective of a Risperdal sales representative is ultimately "to get the doctors to write more prescriptions." (Ronald Kalmeijer Dep. Tr. at 61, a true and correct copy of which is attached hereto as Exhibit D; *see* Trial Tr. at 1274 (publishing excerpts of the videotaped deposition of Ronald Kalmeijer to the jury).)

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The State elicited testimony from Janssen's sales representative, Angelina Alderman, who both confirmed this uniform practice of disseminating Risperdal labeling at each sales call and also identified instances of repetition of Janssen's false and misleading labeling, or package insert, as well as the November 2003 Dear Doctor letter through sales calls and sampling. (*See* Trial Tr. at 1151-1156, 1158-1161 (Ex. A).) More specifically, she verified that she "present[ed] the information that [the] company told [her] to" present, which included the November 2003 Dear Doctor letter that Janssen instructed its sales representatives to present to physicians on sales calls. (Trial Tr. at 1154-1156, 1158-1161 (Ex. A).) Additionally, she established that

every Risperdal sample provided includes a package insert. (Trial Tr. at 1177 (Ex. A); *see also id.* (confirming that when she calls on healthcare providers, she distributes samples.)

The South Carolina Supreme Court has determined that evidence such as the foregoing is particularly responsive to the public impact requirement of SCUTPA. *See, e.g., Daisy,* 473 S.E.2d at 50. It has found that evidence of other instances of the alleged deceptive or unfair conduct at issue is "directly relevant to UTPA's public interest requirement" and "[establishes] a potential for repetition of the defendant's unfair and deceptive acts." *Id.* More specifically, the Supreme Court has held that the potential for repetition requirement is satisfied where the unfair or deceptive communication at issue has been repeated through publication to other consumers, as has Defendant's Risperdal labeling. *See Haley Nursery Co. v. Forrest,* 381 S.E.2d 905, 908 (S.C. 1989).

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Thus, contrary to Defendant's arguments, SCUTPA does not condition the prosecution of a government enforcement action under section 39-5-110 upon demonstration of actual public impact, and the State has presented evidence sufficient to demonstrate that Defendant's Risperdal labeling, including the dissemination of the November 2003 Dear Doctor letter, had the potential for repetition, was repeated to numerous consumers and did impact the South Carolina public. *See Wright,* 640 S.E.2d at, 501-02; *Dowd,* 381 S.E.2d at 214.

## I. The State's Evidence of Willfulness Was More than Sufficient Under South Carolina Law.

Defendant is simply wrong that South Carolina law requires a willfulness finding under SCUTPA to incorporate the violation of "a specific South Carolina statute that expressly prohibits the precise practice that the Attorney General alleges is a violation of SCUTPA." (Def.'s Mem. at 40.) Neither SCUTPA itself—which requires only that the Defendant knew or should have known its conduct was in violation of section 39-5-20—nor *State ex rel. Medlock v.*

*Nest Egg Soc'y Today, Inc.*, on which Defendant relies, establish such a restrictive rule. 348 S.E.2d 381, 384 (S.C. Ct. App. 1986) ("We hold that . . . conduct is 'willful' if the defendant 'should have known' it ***violates Section 39-5-20.*** . . . . If, in the exercise of due diligence, a person of ordinary prudence engaged in trade or commerce could have ascertained that ***his conduct violates the Act,*** then such conduct is 'willful' within the meaning of the statute.") (emphasis added). *Gentry v. Yonce*, on which Defendant also relies for this proposition, did not even address SCUTPA's willfulness standard. 522 S.E.2d 137, 143 (S.C. 1999).

Defendant next argues that the State must additionally show that the conduct was "prohibited." Yet, the flipside of that argument is that Defendant fails to explain how Risperdal's labeling would qualify as "permitted" for purposes of statutory exemption in light of its willful refusal to strengthen Risperdal's warnings section in the labeling, as they were required to do by the FDA, once they became aware of reasonable evidence of an association between Risperdal use and a serious hazard. 21 C.F.R. § 201.57(e) (2006). (*See* discussion, *supra* at §§ II.B, II.C, II.E.) More specifically, Risperdal labeling contained false and misleading information, and omitted true information, since the drug's launch in the United States. (*See, e.g.*, Pl. Ex. 1712, Trial Tr. at 357-58, 624-25, 708-710, 843-45 (Ex. A).) Defendant's conduct with respect to the representations in the labeling was "willful" under the statute because it is merely necessary to show that Defendant knew or should have known that the labeling was unfair or deceptive. S.C. Code Ann. §§ 39-5-20, 39-5-110(c). And, most importantly for purposes of this discussion, Defendant had the opportunity to strengthen the warnings in the labeling at any time that it determined there was a reasonable association between Risperdal consumption and a serious hazard. *See* 21 C.F.R. § 201.57(e) (2006). But, Defendant continuously failed to take advantage of that regulatory self-help provision.

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Accordingly, as mentioned, this Court rejected defendant's virtually identical arguments in *Lilly* "[b]ased on [defendant's] ability to make unilateral amendments to its labeling and the further facts concerning [its] marketing and labeling methods which have been demonstrated to this Court as being in controversy." (Slip op. at 22-23 (Ex. B).) The fact that the FDA had intermediately "approved" Zyprexa's labeling, therefore, did not absolve Lilly from its duty to update the labeling to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product." *See* 21 C.F.R. § 314.70(c)(6)(iii)(A), (C); *accord Levine*, 129 S. Ct. at 1197. Janssen's failure to do so here, in view of overwhelming evidence in support of such a labeling change, was willful in that Janssen knew or should have known its conduct would violate SCUTPA.

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And, as to the willfulness of Defendant's actions with respect to the November 2003 Letter, the State proved, through the testimony of Drs. Wirshing and Plunkett, Defendant's own witnesses, and the documentary evidence, that Defendant knew or should have known that the letter would violate SCUTPA as being deceptive or unfair, as discussed elsewhere herein.

Plainly, the State adduced sufficient evidence of willfulness to demonstrate that Defendant knew or should have known its conduct was deceptive or unfair in violation of SCUTPA.

**J. The State's SCUTPA Claim Is Not Time-Barred.**

***1. Janssen Was Not Entitled to a Directed Verdict Because the State Advanced Evidence Sufficient to Show that Its Claims Were Not Time-Barred by General or Anecdotal Knowledge of Risperdal's Side-Effects.***

As in its Motion for a Directed Verdict, Janssen misapprehends the State's claims and the appurtenant trigger that commences the running of the statute of limitations period. In attempts to divert this Court's attention from the State's actual or constructive knowledge of Janssen's

wrongful conduct in South Carolina, which would start the limitations period, Janssen contends that the very publications for which the State seeks civil penalties under SCUTPA for being "false" and "misleading"—the November 2003 Dear Doctor letter and Risperdal labeling, more generally—commenced the running of the limitations period under SCUTPA, thus barring the State's claims. Janssen bases its unsuccessful argument on two flawed premises: that, allegedly, "any of the physicians and other prescribers to whom the letter was addressed—and the State—had the ability to review the publically-available published studies to which Janssen pointed them and to 'discover' any alleged deception in the opinion Janssen offered about them"; and, relative to Risperdal labeling, more generally, that the State's experts—pharmacologist, toxicologist, and regulatory expert, Dr. Laura Plunkett, and psychiatrist, Dr. William Wirshing—could have known of the risks associated with Risperdal based on "the chemical compound of Risperdal itself," and "instances of weight gain, hyperglycemia, and hyperprolactinemia that were seen in the pre-marketing clinical studies of Risperdal." (Def.'s Mem. at 43-44.) Janssen's arguments are unsound and belied by the fact that the publically-available published studies to which Janssen cited were admittedly flawed, company-sponsored, or otherwise unreliable, as well as the fact that even if industry experts or medical professionals could have had requisite knowledge, their knowledge is immaterial to what the *State* knew relative to Risperdal's safety profile prior to commencing this action.

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Denying Janssen's motions for summary judgment and concluding that the State is not barred from proceeding under the applicable statute of limitations, the Court carefully distinguished the requisite knowledge of the Attorney General's Office of "[u]nfair methods of competition and unfair or deceptive acts or practices in the conduct of any trade or commerce . . . in the Defendants' marketing and labeling relative to the sale of Risperdal," from "medical

professionals' . . . concern[s] about the side effects of the drugs in question." (Order, Feb. 25, 2011, at 6.) Consistent with all relevant South Carolina law, the Court further emphasized that "the essential question . . . is when the State Attorney General's Office would have become aware of 'unfair or deceptive acts or practices' in the Defendants' marketing and labeling [of Risperdal]"—not when "the medical community nationally and in this State [would have become] aware." (*Id.*) Additionally, the Court considered that "Janssen may have actually taken affirmative action to confuse the issue, so as to hide the disparity between what was being told to the prescribing public and what its own professionals and experts knew" relative to Risperdal's true safety profile, and that "[t]his could in some situations even justify an equitable tolling of the Statute of Limitations."[29] (*Id.*)

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[29] As this Court acknowledged, even it could find that the State tardily filed its Complaint in this lawsuit—which for clear reasons amply described herein it did not—the doctrines of equitable estoppel and/or equitable tolling nevertheless permit the State to bring its claims. Because Janssen's intentionally deceptive conduct was designed to avoid detection, Janssen is equitably stopped from asserting a limitations defense and/or the applicable limitations period is equitably tolled. *See Hooper v. Ebenezer Senior Servs. & Rehab. Ctr.*, 659 S.E.2d 213, 225 (S.C. Ct. App. 2008) ("A defendant will be estopped to assert the statute of limitations in bar of a plaintiff's claim when the delay that otherwise would give operation to the statute has been induced by the defendant's conduct."). Moreover, "[s]ilence, when it is intended, or when it has the effect of misleading a party, may operate as equitable estoppel." *Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 339 (S.C. Ct. App. 2001).

With respect to equitable tolling, the Court of Appeals of South Carolina observed that "[i]t has been held that equitable tolling applies principally if the plaintiff is actively misled by the defendant about the cause of action or is prevented in some extraordinary way from asserting his or her rights." *Hooper*, 659 S.E.2d at 221. "[T]he equitable tolling doctrine does not require wrongful conduct on the part of the defendant, such as fraud or misrepresentation." *Id.*

As this Court further recognized, Janssen's false representations, concealment of material facts, and knowledge of the true facts, intending to mislead the State about any cause of action it may have had against Janssen, demands the application of the equitable estoppel or equitable tolling doctrines here. (Trial Tr. at 2584-2585 ("I am somewhat concerned about the label because of the fact that there is evidence that studies had been performed by Janssen that for one reason or another were not published. The allegations are – and the inferences drawn from those allegations – were that Janssen somehow prevented those from being published, did not allow them to be published, and, to a certain degree, shielded them from public knowledge. And, of course, that brings into question the equitable tolling of the statute of limitations under South Carolina law. And that is, where a Defendant takes actions to conceal possible culpability, the statute of limitations would be tolled during that period of time at which that information was suppressed or shielded from public knowledge. Also, again, the evidence given by the witnesses from the State did not indicate that they felt like the labeling was ever misleading, in specific, and there is, again no evidence that that information was transmitted of a possible deception in the label to the Attorney General.").)

Similarly, in the *Lilly* case, the Court opined that "[k]nowledge by the State that" a prescription drug "may have contributed to weight gain, diabetes, or related diseases . . . does not place the State on notice that [the defendant] is involved in any of the enumerated wrongful acts." *Lilly*, slip op. at 10. More specifically, the Court detailed the applicable statute of limitations, attendant to the "discovery rule," which runs from the date the injured party either knows or should have known by the exercise of reasonable diligence that *a cause of action arises from the wrongful conduct* of the defendant. *See id.* at *9 (citing S.C. Code Ann. § 15-3-535 (Supp. 2007); *Burgess v. Am. Cancer Soc'y, South Carolina Div., Inc.*, 386 S.E.2d 798, 800 (S.C. Ct. App. 1989); *Epstein v. Brown*, 610 S.E.2d 816, 818 (S.C. 2005)) (emphasis added). The Court emphasized that the State's acquisition of bits and pieces of anecdotal information about Zyprexa prior to the filing of its Original Complaint is insufficient to trigger the running of the statute. *Lilly*, slip op. at 11. Without "facts concerning the . . . specified incidences of wrongdoing, of which the State was aware or should have been aware prior to February 27, 2004 or 2005," defendant's argument that the statute had been triggered in 2004, and had run, would fail. *Id.* Indeed, "[t]he burden of establishing the bar of the statute of limitations rests upon the one interposing it . . . ." *Turner v. Milliman*, 671 S.E.2d 636, 641 (S.C. Ct. App. 2009). "The limitations period is intended to run against those who are neglectful of their rights and who fail to exercise reasonable diligence in enforcing their rights. However, it is not the policy of the law to unjustly deprive an injured person of a remedy." *Moriarty v. Garden Sanctuary Church*, 534 S.E.2d 672, 679 (S.C. 2000).

Further guided by these principles, the Court correctly denied Defendants' Motion for a Directed Verdict on their statutes of limitations defense and, correspondingly, granted the State's Motion for Directed Verdict as to Defendants' Eighth Affirmative Defense on Statute of

Limitations. (Trial Tr. at 1805 (denying Defendants' motion); Trial Tr. at 2580-2585 (granting the State's motion).)

But, Janssen boldly ignores the Court's consistent rulings and reasoning relative to its limitations defense and, in particular, its prior order denying defendant's Motion for Summary Judgment on Statute of Limitations Grounds in *Lilly*:

> The information cited by Lilly stating that the Plaintiff should have been on notice that it had a claim or potentially had a claim is *separate and distinct from the wrongs alleged by the State. Knowledge by the State that Zyprexa may have contributed to weight gain, diabetes or related diseases . . . does not place the State on notice* that Lilly is involved in any of the enumerated wrongful acts above[,]

which include

> deceptive promotions, misrepresentations and concealment of information about the safety and efficacy **of Zyprexa.**
>
> **Further,** the anecdotal information . . . does not rise to the level of putting the State on notice **that Lilly was involved in any of the above specified wrongs.**
>
> * * *
>
> In this case at the very least there is a substantial conflict of evidence as to the date upon which the statute of limitations would have begun to run. In such cases, "*where there is conflicting testimony regarding the time of discovery, it becomes an issue for the jury to decide.*" *Arrant v. Kressler*, 489 S.E.2d 206 (S.C. 1997).

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*Lilly*, slip op. at 10-11 (emphases added).

Accordingly, Janssen's conclusory assertion that by virtue of the November 2003 Dear Doctor letter and well as industry and medical experts' purported notice, the State was on notice, or should have been on notice, at that time, of Janssen's wrongdoing with respect to its labeling of Risperdal, is entirely incommensurate with the Court's prior rulings in this regard and should be rejected. Like defendant's failed argument in *Lilly*, Janssen "reveals *no facts* concerning the

. . . *specified incidences of wrongdoing*, of which *the State* was aware or should have been aware," prior to February 2004. *Lilly*, slip op. at 11 (emphases added).

Rather, Janssen claims, without more, that because Drs. Plunkett and Wirshing (allegedly) could have had knowledge of the misrepresentations in Janssen's labeling, the State should also have had such knowledge at the time they were first made. (*See* Def.'s Mem. at 43-44.) In addition, Janssen speculates that "any reader" of the November 2003 Dear Doctor letter, including the State, knew or should have known that a cause of action arose from Janssen's willful, deceptive and unfair course of conduct in violation of SCUTPA upon its dissemination, purely because they, allegedly, "had the ability to review the publicly-available published studies to which Janssen pointed them." (Def.'s Mem. at 43.)

Fundamentally, Janssen fails to show, if and when the State had notice of the November 2003 Dear Doctor letter *at all*—e.g., there is no testimony that the letter was ever received or read by any State official that would even approach "notice" for purposes of triggering the limitations period. Moreover, the mere fact that the November 2003 Dear Doctor letter references "publicly-available published studies" is wholly insufficient to show what the State and its healthcare providers knew, or should have known, relative to Janssen's misrepresentations *and when they knew it*, so as to trigger the running of the statute. Janssen's reference to these publications—the majority of which are *Janssen-sponsored* and some of which do not stand for the proposition for which Janssen claims in its letter—has no bearing on the State's discovery at that time or at any other time thereafter, and, if anything, only advanced the misrepresentations in the November 2003 Dear Doctor letter. Drs. Plunkett and Wirshing have testified regarding the same. (*See* Trial Tr. at 746-748 (Plunkett); Trial Tr. at 455-465 (Wirshing).)

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In order to charge the State with notice of Janssen's wrongdoings by way of publication, the referenced publications must be of sufficient "widespread publicity and awareness" to place the State on notice of the *particularized harm* that it seeks to redress. *See Hedgepath v. Am. Tel. & Tel. Co.*, 559 S.E.2d 327, 333-34, 337-38 (S.C. Ct. App. 2001) (holding that plaintiffs' claims would be barred by the applicable statute of limitations only where "the record is ***replete*** with ***uncontested evidence of widespread publicity and awareness of the alleged [wrongdoing]***," combined with (1) plaintiffs' "***affidavits affirm[ing] that [p]laintiffs knew***," prior to the running of the statute of limitations "of the alleged problems concerning" defendants' plant emitting environmental pollution, the basis of plaintiffs' nuisance causes of action, and ***affirming that plaintiffs 'felt that they had claims arising out of [defendant's] operation of the facility for injuries to their person and property***'"; and, with (2) the "permanency of the claimed property damages") (emphases added); *see id.* at 333-34 ("widespread publicity" included "widespread . . . community concerns and allegations that the plant was the alleged source of personal injury and property damage in the surrounding areas," "community forums, town meetings, government involvement, local political debates, door-to-door communications, media coverage, grassroots organization initiated by local citizens groups, and lawsuits brought by hundreds of residents . . . who . . . were friends, neighbors, and, in many instances, relatives of [p]laintiffs," in the action at bar, *inter alia*). Janssen's labeling-based publications, like its Motion, are clearly devoid of evidence of "widespread publicity and awareness" of its illegal conduct in South Carolina.

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Further, Janssen's Motion fails to squarely address *misrepresentations and concealed information in the November 2003 Dear Doctor letter and product labeling*—the very "specified incidences of wrongdoing" of which the State was allegedly aware. *See id.*

In sum, Janssen wholly fails to tie to the State any alleged notice of such ***actionable offenses in South Carolina causing the State injury***, or legitimately explain how with reasonable diligence the State should have known of such allegations through the November 2003 Dear Doctor letter, the product labeling, or otherwise, as it must.

For purposes of the limitations period, the State was arguably not aware of the alleged deception by Janssen, through its labeling, until April 2007 upon the filing of its Original Complaint. Janssen has again entirely failed to meet its burden to show otherwise, and its Motion must be denied.

**a. A directed verdict as to Janssen's Eighth Affirmative Defense on statute of limitations was proper, as Janssen failed to offer *any* evidence to justify sending the issue to the jury.**

The Court correctly granted the State's Motion for Directed Verdict as to Janssen's Eighth Affirmative Defense on Statute of Limitations, because Defendant was unable to demonstrate requisite actual or constructive knowledge by the Attorney General's Office of Defendant's unlawful conduct in South Carolina before January 24, 2004. In fact, Defendants failed to offer *any* evidence to justify sending that issue to the jury. Unable to demonstrate the Attorney General's actual or constructive knowledge of Janssen's unlawful conduct in South Carolina, Defendants instead presented evidence that the State, certain employees, and (by inference) other South Carolina prescribers already had knowledge of the general risks of antipsychotic use, without more. Defendants apparently overlooked this Court's repeated and consistent rulings on the requisite notice due the State relative to Janssen's limitations defense and the relevant inquiry of "*when the State Attorney General's Office would have become aware* of 'unfair or deceptive acts or practices' in the Defendants' marketing and labeling [of

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Risperdal]"—not when "the medical community nationally and in this State [would have become] aware" of Risperdal's side effects.[30]

**b. Unlawful Conduct Must Be Discovered in Order to Trigger the Statute of Limitations.**

The applicable statute of limitations for the State's SCUTPA action is found in S.C. Code Ann. § 39-5-150. Under that section, "[n]o action may be brought under [SCUTPA] more than three years after discovery of the unlawful conduct which is the subject of the suit." *Id.*

South Carolina's "discovery rule" applies to SCUTPA claims, which tolls the statute of limitations until a cause of action reasonably ought to have been discovered. *See id.*; *Hedgepath v. AT&T, Co.*, 559 S.E.2d 327, 336 (citing *Dean v. Ruscon Corp.*, 468 S.E.2d 645, 647 (1996)). More specifically, South Carolina law instructs that limitations begin to run "from the date that the injured party either knows or should have known by the exercise of reasonable diligence that a cause of action arises from the wrongful conduct." *Hedgepath*, 559 S.E.2d at 355-56; *see Anonymous Taxpayer v. S.C. Dep't of Revenue*, 661 S.E.2d 73, 80 (S.C. 2008) (quoting *Epstein v. Brown*, 610 S.E.2d 816, 818 (S.C. 2005) ("Under the discovery rule, the statute of limitations begins to run from the date the injured party either knows or should know, by the exercise of reasonable diligence, that a cause of action exists for the wrongful conduct."); *Guillo v. Speedrite Prods., Inc.*, 532 S.E.2d 1, 3 (S.C. Ct. App. 2000) ("[T]he statute of limitations is triggered not merely by knowledge of an injury, but by knowledge of facts, diligently acquired, sufficient to put a person on notice of the existence of a cause of action against another."); *Lilly*, slip op. at *9 (detailing the applicable statute of limitations, attendant to the "discovery rule," which runs from the date the injured party either knows or should have known by the exercise of reasonable diligence that *a cause of action arises from the wrongful conduct* of the defendant

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[30] Order, Feb. 25, 2011, at 6 (emphasis added).

(citing S.C. Code Ann. § 15-3-535 (Supp. 2007); *Burgess v. Am. Cancer Soc'y, South Carolina Div., Inc.*, 386 S.E.2d 798, 800 (S.C. Ct. App. 1989); *Epstein*, 610 S.E.2d at 818)) (emphasis added). (*See also* Order, Feb. 25, 2011, at 5.) "The date on which discovery should have been made is an objective, not subjective, question[,]" and there exists no duty to discover such information or to otherwise undertake a fishing expedition in an effort to find evidence of the wrongful conduct at issue. *Arant v. Kressler*, 489 S.E.2d 206, 208 (S.C. 1997); *see State v. Von Dohlen*, 471 S.E.2d 689, 693 (S.C. 1996) (government "has no duty to undertake a fishing expedition . . . to find . . . evidence" of unlawful activity). While "[t]he limitations period is intended to run against those who are neglectful of their rights and who fail to exercise reasonable diligence in enforcing their rights[,] . . . it is not the policy of the law to unjustly deprive an injured person of a remedy." *Moriarty v. Garden Sanctuary Church*, 534 S.E.2d 672, 679 (S.C. 2000). Accordingly, the three-year limitations period is triggered from the *discovery* of facts underlying the State's SCUTPA claim arising from Defendant's unlawful conduct.

**c. The Attorney General's Office Must Have Had Actual or Constructive Knowledge.**

Under the applicable statute of limitations, the State's lawsuit must have been filed within three years after the Attorney General's Office discovered the unlawful conduct that is subject of the State's Complaint. S.C. Code Ann. § 39-5-150. As described herein, the "discovery rule" as applied to the statute of limitations relates to the point in time when the Attorney General knew or should have known that some legal right had been invaded. *See Hedgepath*, 559 S.E.2d at 336; *Epstein*, 610 S.E.2d at 818; *see also Arant*, 489 S.E.2d at 208.

The Attorney General is the only South Carolina government official who may bring a claim for civil penalties pursuant to S.C. Code Ann. § 39-5-110(a), and, therefore, the requisite actual or constructive knowledge relative to the "discovery rule" must be that of the Attorney

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General's Office. The knowledge of another state agency or employee cannot be imputed to the Attorney General's office for purposes of triggering the limitations period. *See Von Dohlen*, 471 S.E.2d at 693 ("Although information known to . . . agencies may, under certain circumstances, be imputable to the State, the government has no 'affirmative duty to take action to discover information which it does not possess . . . .'"); *see also Midtrust Bank, SSB v. C.W. Haynes & Co.*, 893 F. Supp. 1304, 1316 (D.S.C. 1994) (holding that although two governmental agencies were divisions of the same department, "the entities operate[d] independently of each other" and it was "unrealistic to charge" one agency with the other agency's "employee's knowledge" (citing *Wyler v. Korean Air Lines Co.*, 928 F.2d 1167, 1171 (D.C. Cir. 1991) ("One . . . agency 'should not be charged with knowledge of what another is doing simply because both are components of the same . . . government.") (citation omitted))). "Therefore, the essential question before this Court is when the State Attorney General's Office would have become aware of 'unfair or deceptive acts or practices' in the Defendant's marketing and labeling actions relative to the sale of Risperdal"—clearly "a separate and distinct issue from the question of when [State] medical professionals became concerned about the side effects of the drugs in question." (Order, Feb. 25, 2011, at 6.)

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Defendant, however, contends that "this Court's determination that a plaintiff, including the attorney general, must have actual knowledge of wrongdoing, is inconsistent with well-settled South Carolina law." (Def.'s Mem. at 45 (internal citations omitted).) In reliance, Defendant cites to several inapposite decisions, including a federal bankruptcy court decision, *Willcox v. Stroup*, 358 B.R. 824 (D.S.C. 2006), which this Court has carefully distinguished. (*See* Trial Tr. at 2580-2581.) (Def.'s Mem. at 44-45 (citing *State of Delaware ex rel. Brady v.*

*Pettinaro Enters.*, 870 A.2d 513, 532 (Del. Ch. 2005); *Prestwick Golf Club, Inc.*, 503 S.E.2d at 188; *Gibson*, 680 S.E.2d at 782-83).)[31]

In *Willcox*, the State asserted superior title to Civil War era documents held by Willcox. 358 B.R. 824, 831 (D.S.C. 2006). The court determined that the documents were not state records when the Willcox family came into possession of them in the late 1860s, and title to the documents was properly held by Willcox. *Id.* at 831. The court then considered when the six-year statute of limitations began to run against the State's superior title claim. *Id.* at 831-32. Although the State made no claim of ownership prior to the pending action, the court held "the State, with minimal inquiry, ought to have discovered this alleged injury many years prior to the instant case." *Id.* at 833-34.

In that connection, a member of the Willcox family had communicated with an employee of the South Carolina Library, a branch of the University of South Carolina, regarding the family's possession of the documents as early as 1947, and he acted under the assumption that the family was the rightful owner of the documents. *Id.* at 833. In addition, microfilm versions

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[31] *Pettinaro*, a Delaware Chancery Court case, is distinguishable in that it involved the closure of a condominium's on-site health club that was both *obvious* and *unconcealed* such that the residents and Attorney General's office were on inquiry notice of the closure prior to alleging DTPA causes of action relative thereto. 870 A.2d at 533.

Furthermore, both *Prestwick* and *Gibson* are inapposite to Defendant's contention that *knowledge of specified instance of wrongdoing* is not the applicable standard under SCUTPA. The Prestwick court reversed the trial court's grant of summary judgment where questions of fact existed as to whether there was a SCUTPA violation and where "the statute of limitations [did] not bar the UTPA claim" because club member plaintiffs filed their UTPA claims within three years of the club's formal announcement of the eventual revocation of the tee-time schedule at issue. 503 S.E.2d at 188. In so ruling, the court considered that the club members had been involved in an escalating dispute over the tee-time schedule and the interference of non-member play with the schedule for years prior to the revocation of the schedule in 1996 but had also been subject to the club's unfair marketing and sales practices "to lure prospective [membership] purchasers" at their expense and without their knowledge. *Id.* at 186, 188. Thus, for purposes of the limitations period, the club members were arguably not on notice of their claims until the formal announcement and revocation of the schedule at issue, despite their knowledge of open interference with the schedule. The *Gibson* court did not interpret the statute of limitations under SCUTPA but interpreted "South Carolina's version of the U.C.C." which provides that a person has notice of a cause of action for purposes of triggering applicable limitations period when "he has *actual* knowledge of it." 680 S.E.2d at 783.

of the documents had been accessible to the public since the 1940s at the University of North Carolina, and originals were at the Library of Congress. *Id.* The court considered this open and unabashed possession and exercise of ownership over the documents sufficient to put the State on notice of its ownership claim. *Id.* at 833-34.

At issue in the State's case against Janssen is whether unfair methods of competition and unfair or deceptive acts or trade practices in Janssen's labeling of Risperdal, including Janssen's November 2003 Dear Doctor letter to physician members of the South Carolina DUR Board, and possibly other state employees, are sufficient to put the State on notice of its claim under SCUTPA. Alternatively, *Willcox* involved the State's failure to timely assert superior title to documents openly possessed by the Willcox family for over one hundred years. Further, the relevant claims in *Willcox* were based on ownership of the documents, not on claims relative to information contained therein or information allegedly concealed from the Willcox family by way of the documents, as in this case.

Accordingly, the *Willcox* decision does not support or lend value to the proposition Defendant advances by its Motion that the knowledge of the Attorney General's Office is immaterial to the question of requisite notice. (*See* Def.'s Mem. at 44-45.) As the Court more specifically articulated, *Willcox* does not present "an analogous situation to the one that we have in this case, because this is a situation where we are alleging that knowledge on the part of one state agency would be imputed to another state agency concerning matters that are not tangible, that don't involve possession of property." (Trial Tr. at 2581.)

**d. The only evidence Defendant presented is general knowledge about the side effect of their drug by certain State employees.**

Defendant entirely failed to meet its burden of proving by the greater weight of the evidence that the statute of limitations bars the State's SCUTPA claim. Rather, Defendant

elicited testimony and other evidence implicating certain State employees' general knowledge of the side effects and relative safety profile of Risperdal and other atypical antipsychotics, including the following:

- one Department of Mental Health prescriber's professed knowledge of atypical antipsychotics' metabolic risk profiles as well as his receipt of an "Alert Letter" in 2002 similar to one sent to another physician concerning a patient to whom that physician had prescribed Seroquel,[32, 33] despite that he purportedly knew, prior to 2002, of the relationship between atypicals and the risk of developing diabetes based on his own anecdotal information relative to Risperdal's safety profile acquired through his prescribing experiences, conversations with other physicians in the community, and review of related publications;[34] and,

- another Department of Mental Health prescriber's professed knowledge of atypical antipsychotics' various side effects as well as her review of the Consensus Statement[35] when it was published in February 2004, despite that she purportedly knew prior to February 2004 of certain aspects of Risperdal's safety profile based on her own prescribing experiences.[36]

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32 *See* Trial Tr. at 2113-2118.

33 Def.'s Ex. 7336.

34 *See, e.g.*, Trial Tr. at 2111-2112 ("Q. My question, Doctor was: Are you aware of an association between atypical antipsychotics and metabolic conditions? A. Yes. Q. Would you explain to the member of the jury what is meant by metabolic conditions? A. When we treat patients, um, particularly psychiatric patients, . . . we noticed that some patients did gain weight and that some patients would be more disposed to having problems with their glucose levels. Q. Now, when you mentioned in the course of your response that you noticed that with these atypicals some patients did gain weight, when did you first notice that or become aware of that phenomena? A. Well, the first medication that became available was a medication called Clozaril, and we noticed that with that medication, there was some weight gain. As more of the medications came on the market, we observed, usually within the first year or two of prescribing the medicine, the weight gain could be a problem.") (Ex. C.); *id.* at 2118 ("Q. And how is it, Dr. Bank, that you came to know and understand before you received this letter of that relationship between atypicals and the risk of developing Type II diabetes? A. Well, there are several issues. One is that some of my patients gained weight and had elevated glucose levels. Additionally, conversations between physicians in the community.") (Ex. C.); *id.* at 2119 ("Q. Okay. Had you read any articles that discussed the association between atypical antipsychotics and Type II diabetes before you received your Alert Letter? A. There had been articles in the psychiatric literature previous to this on that subject, yes.").

35 *See id.* at 2161-2163.

36 *See, e.g., id.* at 2160 ("Q. Did you have an appreciation for the risks and side effects associated with atypical antipsychotics? A. Yes, I did. Q. And, what did you recognize and understand them to be? A. Um - - um, the newer drugs . . . we looked at blood sugar, weight gain, those were the main things.") (Ex. C); *id.* at 2161-2163 ("Q. Dr. Ratliff, when you saw this table, sort of ranking atypical antipsychotics with respect to certain side effects, was that something that was news to you or had you known that already? A. I couldn't have put it in a table like this, but I was aware of the various side effects.") (Ex. C.); *id.* at 2166 ("Q. My question to you is, with respect to that last statement, considerable variability in weight gain among the SGAs, was that something you had observed with your patients? A. Yes, I couldn't predict who would have what side effect.").

However, these "numerous indications that the medical community . . . in this State was becoming aware of an association between the use of atypical antipsychotics and weight gain . . . continuing through its 'Dear Doctor' letters in 2003 and 2004," demonstrate, at most, "an increasing concern with the side effects of these drugs." (Order, Feb. 25, 2011, at 6.) In addition, the "anecdotal information" proffered by Defendants as evidence of actual or constructive knowledge "does not rise to the level of putting the State on notice that [Defendants] [were] involved in any of the above specified wrongs." *Lilly*, slip op. at 10-11 (emphasis added). Thus, Defendants completely failed to connect any of the above-outlined evidence to the Attorney General's actual or constructive knowledge prior to January 24, 2007 that Janssen was committing actionable SCUTPA offenses in South Carolina, as they must.

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Likewise, Defendants failed to present any evidence to satisfy their burden of proving that the State knew or should have known of its claim against Janssen based specifically on Defendant's November 2003 Dear Doctor letter[37]—which it did not correct until July 21, 2004.[38] Again, Defendants failed to connect to the Attorney General's Office any actual or constructive knowledge of the November 2003 Dear Doctor letter, the related April 2004 Warning Letter from the FDA, or the July 2004 Correction Letter. Indeed, assuming the Attorney General's Office had been aware of the 2003 Dear Doctor letter (which it was not), it could not reasonably have had reason to investigate the violative nature of that letter under South Carolina law until the FDA issued its April 2004 Warning Letter, regarding which (1) there is no evidence the Attorney General's Office received or was otherwise aware of the FDA's Warning Letter or should have been aware of it (as it was addressed to Defendants only), and (2) by its issue in

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37 Pl. Ex. 1736.

38 *See* Pl. Ex. 438.

April 2004, the FDA Warning Letter was *after* January 24, 2004 and, therefore, *not* notice to the State that fell outside the limitations period.

**K. The Court Did Not Abuse Its Discretion In Its Evidentiary Rulings.**

Defendant makes an array of meritless challenges to the Court's evidentiary rulings, none of which "taint" the jury's verdict, as Defendant asserts. Defendant fails to show that the Court committed an abuse of discretion amounting to an error of law in making any of those rulings. *See Vaught v. A.O. Hardee & Sons, Inc.*, 623 S.E.2d 373, 375 (S.C. 2005) ("The admission of evidence is within the sound discretion of the trial judge, and absent a clear abuse of discretion amounting to an error of law, the trial court's ruling will not be disturbed on appeal."); *Conner v. City of Forest Acres*, 611 S.E.2d 905, 908 (S.C. 2005) ("An abuse of discretion occurs when the ruling is based on an error of law or a factual conclusion without evidentiary support."). Defendant also fails to show that it was prejudiced by any of those rulings. *See Conner*, 611 S.E.2d at 909 ("To warrant reversal based on the admission or exclusion of evidence, the appellant must prove both the error of the ruling and the resulting prejudice, *i.e.*, there is a reasonable probability the jury's verdict was influenced by the wrongly admitted or excluded evidence.").

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Defendant incorrectly argues that the Court erred by not limiting the State's SCUTPA claims at trial because the State presented the same case at trial as that set forth in its Second Amended Complaint and identified in its discovery responses as well as this Court's February 25, 2011 Order. Nor did the Court err in admitting the categories of evidence about which Defendant complains because they were admissible as proof in support of the elements of the State's SCUTPA claims. Defendant also identifies a range of evidence that the Court properly excluded, as set forth more fully below.

*1. The Court Correctly Allowed the State to Try Its Case.*

Defendant's argument that the Court did not properly limit the State's case to Defendant's "deceptive" conduct in disseminating Risperdal's package insert and the 2003 Dear Doctor Letter is premised on several critical misconceptions.

First, by identifying Defendant's dissemination of Risperdal's package insert and the 2003 Dear Doctor Letter as the conduct that violated SCUTPA in its Second Amended Complaint and its discovery responses, the State in no way precluded itself from introducing evidence of other conduct and information to establish its SCUTPA claim. As Defendant was well aware, the State was required to show not just that the conduct constituting the alleged SCUTPA violations had occurred, but also, *inter alia*, that such conduct was deceptive or unfair, and that Defendant acted willfully because it knew or should have known that such conduct was deceptive or unfair. The Court properly allowed the State to introduce the categories of evidence about which Defendant complain because they were relevant to those issues and otherwise admissible, as set forth more fully below.[39] Contrary to Defendant's assertion, the State's case at trial was limited to its claim that Defendant willfully violated SCUTPA by disseminating Risperdal's labeling and the 2003 Dear Doctor Letter.

Second, Defendant has been on notice that the State asserted Defendant's Risperdal labeling to be "deceptive" and/or "unfair" under SCUTPA since the State filed its Second Amended Complaint in January 2010. (*See, e.g.*, Pl.'s Second Am. Compl. ¶¶ 8, 11, 13, 24, 26,

[39] The State has certainly never "made clear that it viewed Janssen's 'promotional activities" as 'irrelevant' to the State's claim." (Def.'s Mem. at 47.) In responding to an interrogatory requesting identification of "all alleged false and deceptive promotional activity," the State objected to the interrogatory as seeking irrelevant information because, to the extent that Risperdal's labeling and the 2003 Dear Doctor Letter were not included in the term "promotional activity," Defendant's promotional activity was no longer alleged to constitute false and deceptive conduct for which the State sought civil penalties under SCUTPA. (Pl.'s Supplemental Answers to Defs.' Fifth Set of Interrogs., No. 15.) The State's answer by no means indicated that Defendant's promotional activity was not at all relevant to the State's claim, or that such evidence would not be introduced to show, among other things, that Defendant's conduct was deceptive and unfair, and that Defendant knew or should have know that its conduct was deceptive or unfair.

45-49, 54.) The State also argued that Defendant's conduct was unfair in under SCUTPA in its discovery responses.[40] (*See, e.g.*, Pl.'s Supplemental Answers to Defs.' Fifth Set of Interrogs., No. 9; Pl.'s Answers to Defs.' Fifth Set of Interrogs., No. 9.) Further, in denying Defendant's motions for summary judgment, the Court plainly articulated "[t]he question to be decided in this case under S.C. Code Ann. § 39-5-110(a)": "whether or not unfair methods of competition and unfair or deceptive acts have occurred in the conduct of the Defendant's trade or commerce as is defined in S.C. Code Ann. § 39-5-20," and "whether or not those illegal acts or practices have been employed 'willfully.'" (Order on Defendant's Motions for Summary Judgment and Partial Summary Judgment, Feb. 25, 2011, at 4; *see also id.* at 1 (stating that "the State initiated this action against Defendants . . . to recover, *inter alia*, civil penalties pursuant to S.C. Code Ann. § 39-5-110(a) for their willful, deceptive *and* unfair course of conduct in Risperdal's product *labeling*") (emphases added).

Lastly, for the reasons set forth above, Defendant was not confronted with any kind of "guessing game" or surprise. If any party is entitled to argue surprise, it is the State, as Defendant that waited until two weeks before trial, and a month after the State filed its opposition to Defendant's motions for summary judgment, to file its motion to limit the State's SCUTPA claims to "deceptive" acts or practice and to Risperdal's package insert and the 2003

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[40] Defendant mischaracterizes the State's discovery responses by asserting that the State has "repeatedly asserted that its SCUTPA claim was based only on a claim that Janssen's conduce was 'deceptive.'" (Def.'s Mem. at 47.) Defendant point to only two discovery responses where the State did not use the word "unfair." Neither of those responses indicates that the State was limiting its SCUTPA claims to Defendant's "deceptive" conduct. Further, the State made the first of those responses on May 10, 2010. (Pl.'s Supplemental Answers to Def.s' Fourth Set of Interrogs., No. 1.) One week later, however, the State served another set of discovery responses in which it identified "each version of the Risperdal package insert and the November 2003 Dear Doctor Letter" as the "'unfair, deceptive, false, incomplete, misleading, and untrue" statements it contended Defendant made. (Pl.'s Answers to Defs.' Fifth Set of Interrogs., No. 9.) In July 2011, the State gave the same response. (Pl.'s Supplemental Answers to Defs.' Fifth Set of Interrogs., No. 9.) The other discovery response to which Defendant points was served over five months later. (Pl.'s Answers to Defs.' Sixth Set of Interrogs., No. 1.) Like the response from May 2010, the State simply did not use the word "unfair"—nothing in the response limits the State's claims. Defendant made no attempt to seek clarification as to whether the State had actually abandoned its contention that Defendant's conduct was "unfair." Less than two months later, the State filed its opposition to a motion for summary judgment in which Defendant asserts it first learned the State's SCUTPA claims were based on its "deceptive" and/or "unfair" conduct.

Dear Doctor Letter. Even if Defendant had been confronted with the kind of surprise it describes—which it was not—judgment notwithstanding the verdict or a new trial would not be warranted because Defendant does not contend the State withheld evidence from Defendant during discovery, which distinguishes the cases Defendant cites where a new trial was granted. *Samples v. Mitchell*, 495 S.E.2d 213, 217-18 (S.C. Ct. App. 1997) (granting new trial because defendant withheld evidence in discovery responses); *id.* ("Unless the party who has failed to submit to discovery can show lack of prejudice, reversal is required."); *Downey v. Dixon*, 362 S.E.2d 317, 317-19 (S.C. 1987) (granting new trial because defendant withheld evidence by failing to attend deposition and answer interrogatories); *see also In re Anonymous Member of S.C. Bar*, 552 S.E.3d 10, 18 (S.C. 2001) ("'The primary objective of discovery is to ensure that lawsuits are decided by what the facts reveal, not by what facts are concealed.'") (citation omitted). Defendant does not cite a single case in which a South Carolina court has held that a plaintiff's proof at trial must conform not to its pleadings, but to its discovery responses.

Thus, the Court did not err in not limiting the State's case in the manner Defendant describes.

*2. The DDMAC Letters Were Admissible.*

Defendant's argument that DDMAC's 1994 Pre-Marketing Letter, 1999 Notice of Violation, and 2004 Warning Letter should have been excluded is without merit because the letters (1) were relevant to the elements of the State's SCUTPA claims, (2) not hearsay, let alone inadmissible hearsay, and (3) did not confuse or mislead the jury.

**a. The Court Properly Admitted the DDMAC Letters as Evidence in Support of the State's SCUTPA Claims.**

The State's consistent position in discovery and at trial was that it did not assert that Defendant's violations of federal statutes and FDA regulations alone provided the basis for

SCUTPA violation. In other words, the State did not contend that Defendant violated SCUTPA solely by virtue of violating or having been found to violate federal statutes or FDA regulations, and, accordingly, the State's SCUTPA claims were not contingent upon whether Defendant actually violated the FDCA or the FDA's regulations or upon whether the DDMAC letters are final agency actions. The State never indicated, however, that it would not introduce the DDMAC letters for other legitimate purposes, such as showing that the FDA had undertaken a review of certain materials, including the 2003 Dear Doctor Letter, why the FDA engaged in those reviews, and the official conclusions the FDA reached, all of which was relevant to whether Risperdal's package insert and the 2003 Dear Doctor Letter were deceptive or unfair, capable of repetition, and had an adverse public impact, and whether Defendant knew or should have known that its dissemination of Risperdal's package insert and/or the 2003 Dear Doctor Letter was deceptive or unfair. The State also never indicated that it would not introduce those letters to rebut Defendant's "safe harbor," federal preemption, and "primary jurisdiction" arguments.

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W. VA. CIRCUIT COURT
KANAWHA COUNTY

Because the State's SCUTPA claims were not contingent upon Defendant having violated or having been found to violate the FDCA or the FDA's regulations, Defendant's argument that the DDMAC letters should not have been admitted because they are purportedly only "informal and advisory" and do not constitute final agency actions is a red herring. In sharp contrast, all but one of the cases Defendant cites involved far different situations where the question of whether final agency action had occurred was decisive. *See State ex rel. McGraw v. Johnson & Johnson*, 704 S.E.2d 677, 687-90 (W. Va. 2010) (reversing trial court's summary judgment ruling that dear doctor letter and promotional material were false and misleading as a matter of law where trial court gave preclusive effect to DDMAC's determination in warning