CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021346Orig1s058

Trade Name:	RISPERDAL CONSTA
Generic or Proper Name:	(risperidone)
Sponsor:	Janssen Pharmaceuticals Inc.
Approval Date:	July 27, 2018
Indication:	RISPERDAL® CONSTA® is an atypical antipsychotic indicated: • for the treatment of schizophrenia. • as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 020272/S-080
NDA 020588/S-068
NDA 021444/S-054
NDA 021346/S-058

SUPPLEMENT APPROVAL

Janssen Research & Development, L.L.C.
Attention: James Tan, PhD
Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Dr. Tan:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received November 17, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Risperdal (risperidone) 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets (NDA 020272), Risperdal (risperidone) 1 mg/mL oral solution (NDA 020588), Risperdal M-Tab (risperidone) orally disintegrating 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg tablets (NDA 021444), and Risperdal Consta (risperidone) 12.5 mg, 25 mg, 37.5 mg and 50 mg long-acting injection (NDA 021346).

These Prior Approval supplemental new drug applications provide for revisions to the US Prescribing Information (USPI) as required according to *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR, or final rule).

APPROVAL & LABELING

We have completed our review of these supplemental applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at

http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please email Ann Sohn, Regulatory Project Manager, at ann.sohn@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, MD
Division Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Contents of Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MITCHELL V Mathis
07/27/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERDAL CONSTA® safely and effectively. See full prescribing information for RISPERDAL CONSTA®.

RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION

Initial U.S. Approval: 2003

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. RISPERDAL CONSTA® is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.4)		07/2018
Warnings and Precautions, Suicide (5.18)	Removed	07/2018
Warnings and Precautions, Monitoring: Laboratory Tests (5.21)	Removed	07/2018

----------INDICATIONS AND USAGE----------

RISPERDAL CONSTA® is an atypical antipsychotic indicated:

- for the treatment of schizophrenia. (1.1)
- as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

- For patients who have never taken oral RISPERDAL®, tolerability should be established with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. (2)
- Administer by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle (1-inch for deltoid administration alternating injections between the two arms and 2-inch for gluteal administration alternating injections between the two buttocks). Do not administer intravenously. (2)
- 25 mg intramuscular (IM) every 2 weeks. Patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks. (2)
- Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA®, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations from RISPERDAL CONSTA®. (2)
- Upward dose adjustment of RISPERDAL CONSTA® should not be made more frequently than every 4 weeks. Clinical effects of each upward dose adjustment should not be anticipated earlier than 3 weeks after injection. (2)
- Avoid inadvertent administration into a blood vessel. (5.16)
- See Full Prescribing Information Section 2.8 for instructions for use.

---------- DOSAGE FORMS AND STRENGTHS ----------

Vial kits: 12.5 mg, 25 mg, 37.5 mg, and 50 mg (3)

---------- CONTRAINDICATIONS ----------

- Known hypersensitivity to risperidone, paliperidone, or to any excipients in RISPERDAL CONSTA®. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. RISPERDAL CONSTA® is not approved for use in patients with dementia-related psychosis (5.2)
- Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.3)
- Tardive Dyskinesia: Discontinue treatment 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. (5.5)
  - *Dyslipidemia:* Undesirable alterations have been observed in patients treated with atypical antipsychotics. (5.5)
  - *Weight Gain:* Significant weight gain has been reported. Monitor weight gain. (5.5)
- Hyperprolactinemia: Risperidone treatment may elevate prolactin levels. Long-standing hyperprolactinemia, when associated with hypogonadism, can lead to decreased bone density in men and women. (5.6)
- Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia, and syncope can occur, especially during initial dose titration with oral risperidone. Use caution in patients with cardiovascular disease, cerebrovascular disease, and conditions that could affect hemodynamic responses. (5.7)
- Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotics, including RISPERDAL CONSTA®. Patients with history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood cell count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL CONSTA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.10)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.12)
- Priapism: has been reported. Severe priapism may require surgical intervention. (5.13)
- Thrombotic Thrombocytopenic Purpura (TTP): has been reported. (5.14)
- Avoid inadvertent administration into a blood vessel. (5.16)
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies: has been reported. Manifestations include mental status changes, motor impairment, extrapyramidal symptoms, and features consistent with Neuroleptic Malignant Syndrome. (5.18)
- Diseases or conditions that could affect metabolism or hemodynamic responses: Use with caution in patients with such medical conditions (e.g., recent myocardial infarction or unstable cardiac disease). (5.18)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions in clinical trials in patients with schizophrenia (≥ 5%) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and parkinsonism (≥ 10% in adjunctive therapy trial). (6)

The most common adverse reactions that were associated with discontinuation from clinical trials in patients with schizophrenia were agitation, depression, anxiety, and akathisia. Adverse reactions that were associated with discontinuation from bipolar disorder trials were hyperglycemia (one subject monotherapy trial) and hypokinesia and tardive dyskinesia (one subject each in adjunctive therapy trial). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- DRUG INTERACTIONS ----------

- Due to CNS effects, use caution when administering with other centrally-acting drugs. Avoid alcohol. (7.1)
- Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. (7.2)
- Effects of levodopa and dopamine agonists may be antagonized. (7.3)
- Cimetidine and ranitidine increase the bioavailability of risperidone. (7.5)
- Clozapine may decrease clearance of risperidone. (7.6)
- Fluoxetine and paroxetine increase plasma concentrations of risperidone. (7.11)
- Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone. (7.12)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Renal or Hepatic Impairment: dose appropriately with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. A lower starting dose of RISPERDAL CONSTA® of 12.5 mg may be appropriate in some patients. (2.4)
- Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
- Elderly: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly may be more predisposed to orthostatic effects than nonelderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2018

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

1 INDICATIONS AND USAGE

1.1 Schizophrenia

RISPERDAL CONSTA® (risperidone) is indicated for the treatment of schizophrenia *[see Clinical Studies (14.1)]*.

1.2 Bipolar Disorder

RISPERDAL CONSTA® is indicated as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder *[see Clinical Studies (14.2, 14.3)]*.

2 DOSAGE AND ADMINISTRATION

For patients who have never taken oral RISPERDAL®, it is recommended to establish tolerability with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®.

RISPERDAL CONSTA® should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection. Each injection should be administered by a health care professional using the appropriate enclosed safety needle *[see Dosage and Administration (2.8)]*. For deltoid administration, use the 1-inch needle alternating injections between the two arms. For gluteal administration, use the 2-inch needle alternating injections between the two buttocks. Do not administer intravenously.

2.1 Schizophrenia

The recommended dose for the treatment of schizophrenia is 25 mg IM every 2 weeks. Although dose response for effectiveness has not been established for RISPERDAL CONSTA®, some patients not responding to 25 mg may benefit from a higher dose of 37.5 mg or 50 mg. The maximum dose should not exceed 50 mg RISPERDAL CONSTA® every 2 weeks. No additional benefit was observed with dosages greater than 50 mg RISPERDAL CONSTA®; however, a higher incidence of adverse effects was observed.

The efficacy of RISPERDAL CONSTA® in the treatment of schizophrenia has not been evaluated in controlled clinical trials for longer than 12 weeks. Although controlled studies have not been conducted to answer the question of how long patients with schizophrenia should be treated with RISPERDAL CONSTA®, oral risperidone has been shown to be effective in delaying time to relapse in longer-term use. It is recommended that responding patients be

continued on treatment with RISPERDAL CONSTA® at the lowest dose needed. The physician who elects to use RISPERDAL CONSTA® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.2 Bipolar Disorder

The recommended dose for monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder is 25 mg IM every 2 weeks. Some patients may benefit from a higher dose of 37.5 mg or 50 mg. Dosages above 50 mg have not been studied in this population. The physician who elects to use RISPERDAL CONSTA® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2.3 General Dosing Information

A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic or renal impairment, for certain drug interactions that increase risperidone plasma concentrations *[see Drug Interactions (7.11)]* or in patients who have a history of poor tolerability to psychotropic medications. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Oral RISPERDAL® (or another antipsychotic medication) should be given with the first injection of RISPERDAL CONSTA® and continued for 3 weeks (and then discontinued) to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site *[see Clinical Pharmacology (12.3)]*.

Upward dose adjustment should not be made more frequently than every 4 weeks. The clinical effects of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose.

In patients with clinical factors such as hepatic or renal impairment or certain drug interactions that increase risperidone plasma concentrations *[see Drug Interactions (7.11)]*, dose reduction as low as 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Do not combine two different dose strengths of RISPERDAL CONSTA® in a single administration.

2.4 Dosage in Special Populations

Elderly

For elderly patients treated with RISPERDAL CONSTA®, the recommended dosage is 25 mg IM every 2 weeks. Oral RISPERDAL® (or another antipsychotic medication) should be given

with the first injection of RISPERDAL CONSTA® and should be continued for 3 weeks to ensure that adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site *[see Clinical Pharmacology (12.3)]*.

Renal or Hepatic Impairment

Patients with renal or hepatic impairment should be treated with titrated doses of oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. The recommended starting dose is 0.5 mg oral RISPERDAL® twice daily during the first week, which can be increased to 1 mg twice daily or 2 mg once daily during the second week. If a total daily dose of at least 2 mg oral RISPERDAL® is well tolerated, an injection of 25 mg RISPERDAL CONSTA® can be administered every 2 weeks. Oral supplementation should be continued for 3 weeks after the first injection until the main release of risperidone from the injection site has begun. In some patients, slower titration may be medically appropriate. Alternatively, a starting dose of RISPERDAL CONSTA® of 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Patients with renal impairment may have less ability to eliminate risperidone than normal adults. Patients with impaired hepatic function may have an increase in the free fraction of the risperidone, possibly resulting in an enhanced effect *[see Clinical Pharmacology (12.3)]*. Elderly patients and patients with a predisposition to hypotensive reactions or for whom such reactions would pose a particular risk should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). These patients should avoid sodium depletion or dehydration, and circumstances that accentuate hypotension (alcohol intake, high ambient temperature, etc.). Monitoring of orthostatic vital signs should be considered *[see Warnings and Precautions (5.7)]*.

2.5 Reinitiation of Treatment in Patients Previously Discontinued

There are no data to specifically address reinitiation of treatment. When restarting patients who have had an interval off treatment with RISPERDAL CONSTA®, supplementation with oral RISPERDAL® (or another antipsychotic medication) should be administered.

2.6 Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients from other antipsychotics to RISPERDAL CONSTA®, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of RISPERDAL CONSTA® to ensure that therapeutic concentrations are maintained until the main release phase of risperidone from the injection site has begun *[see Clinical Pharmacology (12.3)]*. For patients who have never taken oral RISPERDAL®, it is recommended to establish

tolerability with oral RISPERDAL® prior to initiating treatment with RISPERDAL CONSTA®. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

2.7 Co-Administration of RISPERDAL CONSTA® with Certain Other Medications

Co-administration of carbamazepine and other CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, phenobarbital) with risperidone would be expected to cause decreases in the plasma concentrations of the sum of risperidone and 9-hydroxyrisperidone combined, which could lead to decreased efficacy of RISPERDAL CONSTA® treatment. The dose of risperidone needs to be titrated accordingly for patients receiving these enzyme inducers, especially during initiation or discontinuation of therapy with these inducers *[see Drug Interactions (7.11)]*. At the initiation of therapy with carbamazepine or other known CYP 3A4 hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL CONSTA® and discontinuing from carbamazepine or other CYP3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. The dose of risperidone needs to be titrated accordingly when fluoxetine or paroxetine is co-administered. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of RISPERDAL CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL CONSTA®, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to

12.5 mg or necessitates interruption of RISPERDAL CONSTA® treatment. When RISPERDAL CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied. *[see Drug Interactions (7.11)]*

2.8 Instructions for Use

For deltoid or gluteal intramuscular injection only

IMPORTANT RESOURCES

For additional information, visit www.risperdalconsta.com or call Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736).

Important Information

RISPERDAL CONSTA® requires close attention to these step-by-step Instructions for Use to help ensure successful administration.

Use components provided

The components in this dose pack are specifically designed for use with RISPERDAL CONSTA®. RISPERDAL CONSTA® must be reconstituted only in the diluent supplied in the dose pack.

Do not substitute ANY components of the dose pack.

Do not store suspension after reconstitution

Administer dose as soon as possible after reconstitution to avoid settling.

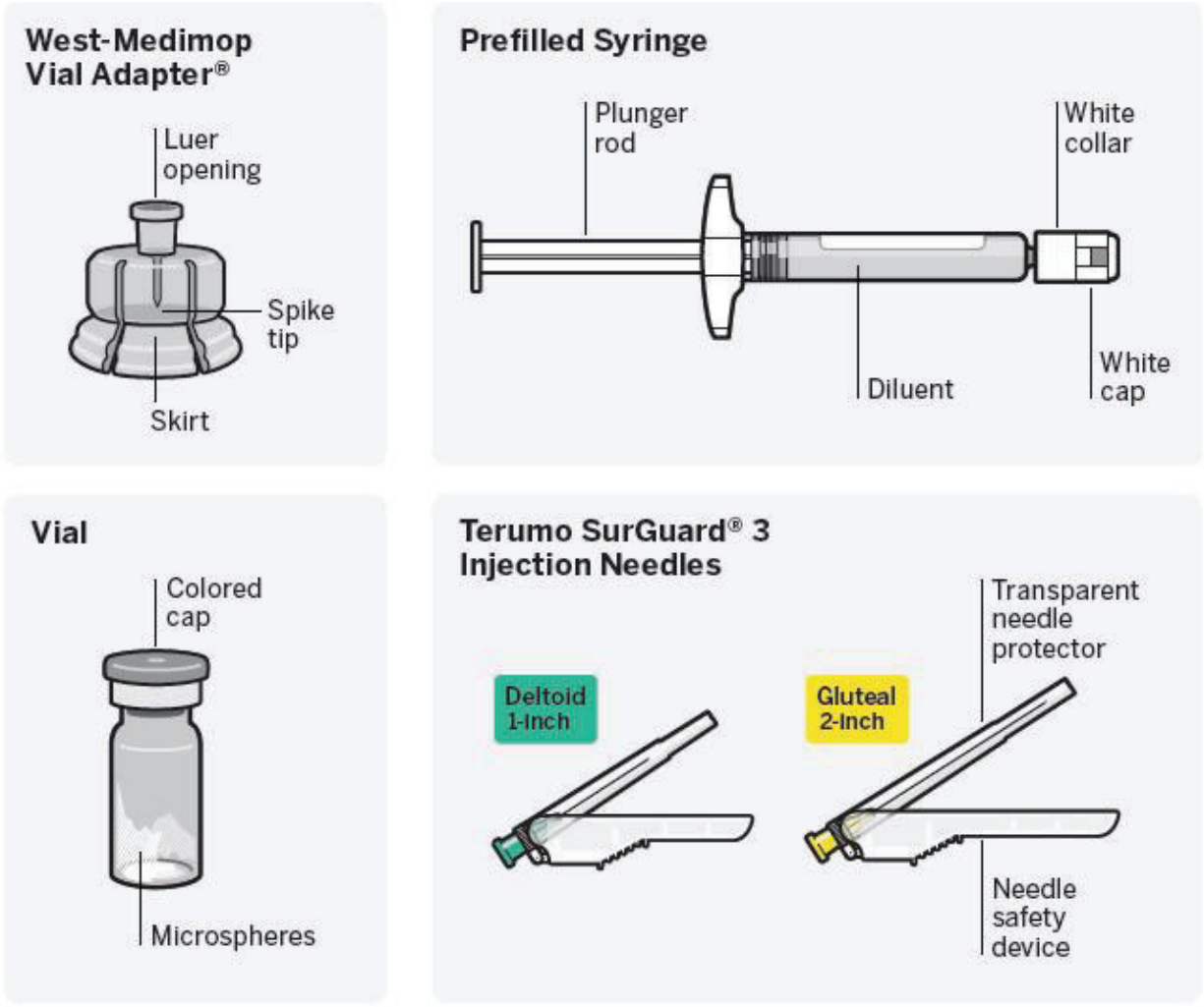
Proper dosing

The entire contents of the vial must be administered to ensure intended dose of RISPERDAL CONSTA® is delivered.

SINGLE-USE DEVICE

Do not reuse. Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.

Dose pack contents



Step 1 Assemble components

Take out dose pack *Connect vial adapter to vial*

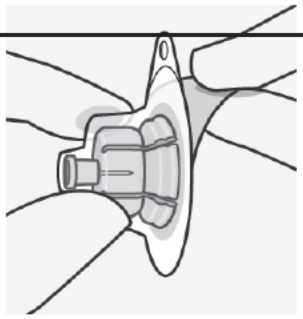
Wait 30 minutes
Remove dose pack from the refrigerator and allow to sit at room temperature for at least **30 minutes** before reconstituting.

Do not warm any other way.

Remove cap from vial
Flip off colored cap from vial.

Wipe top of the grey stopper with an alcohol swab. Allow to air dry.

Do not remove grey rubber stopper.



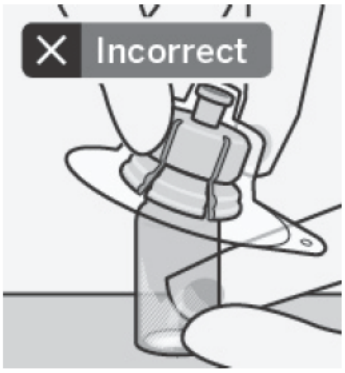
Prepare vial adapter
Hold sterile blister as shown. Peel back and remove paper backing.

Do not remove vial adapter from blister.

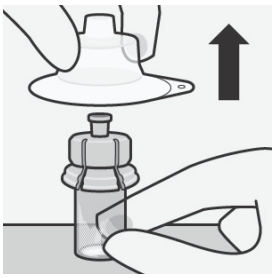
Do not touch spike tip at any time. This will result in contamination.

Connect vial adapter to vial
Place vial on a hard surface and hold by the base. Center vial adapter over the grey rubber stopper. Push vial adapter straight down onto vial top until it snaps securely into place.

Do not place vial adapter on at an angle or diluent may leak upon transfer to the vial.



Connect prefilled syringe to vial adapter

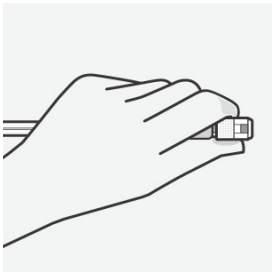


Remove sterile blister

Keep vial vertical to prevent leakage.
Hold base of vial and pull up on the sterile blister to remove.

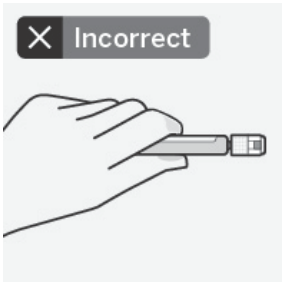
Do not shake.

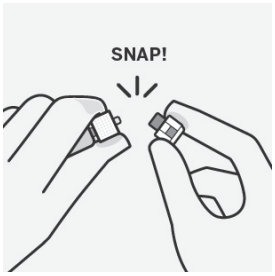
Do not touch exposed luer opening on vial adapter.
This will result in contamination.



Use proper grip
Hold by white collar at the tip of the syringe.

Do not hold syringe by the glass barrel during assembly.

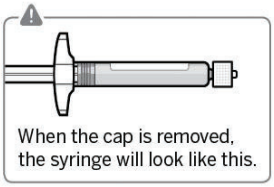




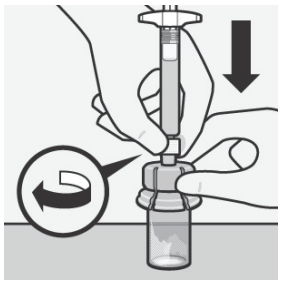
Remove cap
Holding the white collar, snap off the white cap.

Do not twist or cut off the white cap.

Do not touch syringe tip. This will result in contamination.



The broken-off cap can be discarded.



Connect syringe to vial adapter
Hold vial adapter by skirt to keep stationary.

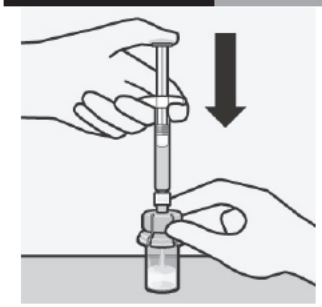
Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

Do not hold the glass syringe barrel. This may cause the white collar to loosen or detach.

Attach the syringe to the vial adapter with a firm **clockwise twisting motion** until it feels snug.

Do not over-tighten. Over-tightening may cause the syringe tip to break.

Step 2 Reconstitute microspheres



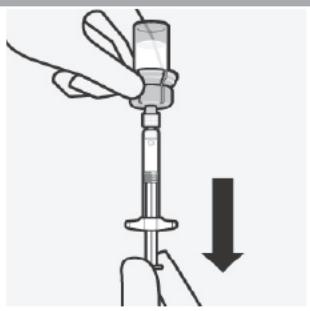
Inject diluent
Inject entire amount of diluent from s ringe into the vial.

Vial contents will now be under pressure.
Keep holding the plunger rod down with thumb.

Suspend microspheres in diluent
Continuing to hold down the plunger rod, **shake vigorously for at least 10 seconds**, as shown.

Check the suspension. When properly mixed, the suspension appears uniform, thick and milky in color. Microspheres will be visible in the liquid.

Immediately proceed to the next step so suspension does not settle.



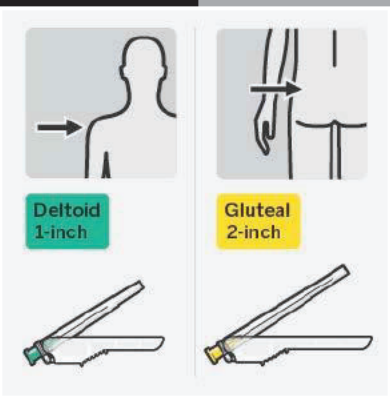
Transfer suspension to syringe
Invert vial completely. Slowly pull plunger rod down to withdraw entire contents from the vial into the syringe.

Remove vial adapter
Hold white collar on the syringe and unscrew from vial adapter.

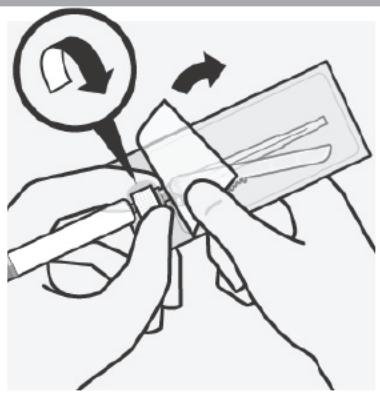
Tear section of the vial label at the perforation. Apply detached label to the syringe for identification purposes.

Discard both vial and vial adapter appropriately.

Step 3 Attach needle



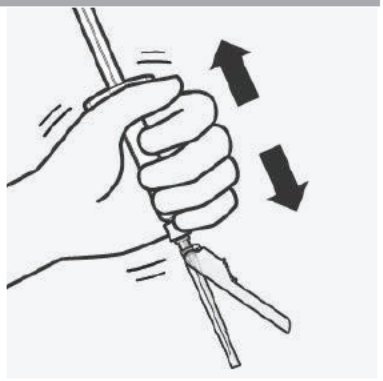
Select appropriate needle
Choose needle based on injection location (gluteal or deltoid).



Attach needle
Peel blister pouch open part way and use to grasp the base of the needle, as shown.

Holding the white collar on the syringe, attach syringe to needle luer connection with a firm **clockwise twisting motion** until snug.

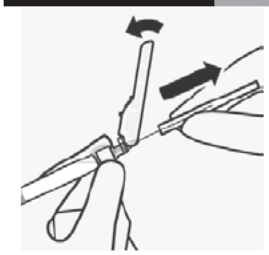
Do not touch needle luer opening. This will result in contamination.



Resuspend microspheres
Fully remove the blister pouch.

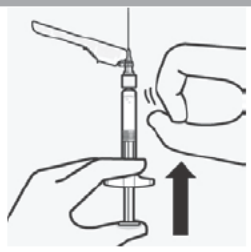
Just before injection, shake syringe vigorously again, as some settling will have occurred.

Step 4 Inject dose

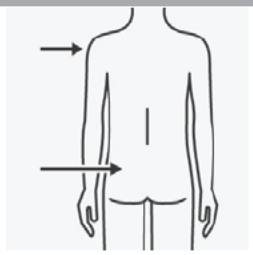


Remove transparent needle protector
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

Do not twist transparent needle protector, as the luer connection may loosen.



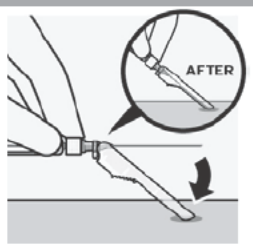
Remove air bubbles
Hold needle upright and tap gently to make any air bubbles rise to the top. Slowly and carefully press plunger rod upward to remove air.



Inject
Immediately inject entire contents of syringe intramuscularly (IM) into the gluteal or deltoid muscle of the patient.

Gluteal injection should be made into the upper-outer quadrant of the gluteal area.

Do not administer intravenously.



Secure needle in safety device
Using one hand, place needle safety device at a 45-degree angle on a hard, flat surface. Press down with a firm, quick motion until needle is fully engaged in safety device.

Avoid needle stick injury:

Do not use two hands.

Do not intentionally disengage or mishandle the needle safety device.

Do not attempt to straighten the needle or engage the safety device if the needle is bent or damaged.

Properly dispose of needles
Check to confirm needle safety device is fully engaged. Discard in an approved sharps container.

Also discard the unused needle provided in the dose pack.

3 DOSAGE FORMS AND STRENGTHS

RISPERDAL CONSTA® is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, and 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL CONSTA®, a West-Medimop Vial Adapter®, and two Terumo SurGuard® 3 Needles for intramuscular injection (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

4 CONTRAINDICATIONS

RISPERDAL CONSTA® is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the RISPERDAL CONSTA® formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone. Paliperidone is a metabolite of risperidone.

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. 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.

RISPERDAL CONSTA® (risperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2 Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of oral risperidone 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 oral risperidone compared to patients treated with placebo. RISPERDAL CONSTA® 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 antipsychotic drugs. 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 creatine 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 identify cases in which 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 uncomplicated 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.

5.4 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.

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, RISPERDAL CONSTA® 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 treated with RISPERDAL CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL CONSTA® despite the presence of the syndrome.

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 and diabetes mellitus, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, have 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. 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, including RISPERDAL®, 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, including RISPERDAL®, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including RISPERDAL®, should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics, including RISPERDAL®, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including RISPERDAL®, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of RISPERDAL®.

Pooled data from 3 double-blind, placebo-controlled studies in subjects with schizophrenia and 4 double-blind, placebo-controlled monotherapy studies in subjects with bipolar mania with oral risperidone are presented in Table 1.

Table 1. Change in Random Glucose From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects With Schizophrenia or Bipolar Mania With Oral Risperidone

		RISPERDAL®	
	Placebo	1-8 mg/day	>8-16 mg/day
	Mean change from baseline (mg/dL)		
	N=555	**N=748**	**N=164**
Serum Glucose	-1.4	0.8	0.6
	Proportion of patients with shifts		
Serum Glucose (<140 mg/dL to ≥200 mg/dL)	0.6% (3/525)	0.4% (3/702)	0% (0/158)

In longer-term, controlled and uncontrolled studies in adult subjects, RISPERDAL® was associated with a mean change in glucose of +2.8 mg/dL at Week 24 (N=151) and +4.1 mg/dL at Week 48 (N=50).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Pooled data from 7 placebo-controlled, 3- to 8- week, fixed- or flexible-dose studies in adult subjects with schizophrenia or bipolar mania are presented in Table 2.

Table 2. Change in Random Lipids From Seven Placebo-Controlled, 3- to 8-Week, Fixed- or Flexible-Dose Studies in Adult Subjects With Schizophrenia or Bipolar Mania With Oral Risperidone

		RISPERDAL®	
	Placebo	1-8 mg/day	>8-16 mg/day
	Mean change from baseline (mg/dL)		
Cholesterol	**N=559**	**N=742**	**N=156**
Change from baseline	0.6	6.9	1.8
Triglycerides	**N=183**	**N=307**	**N=123**
Change from baseline	-17.4	-4.9	-8.3
	Proportion of patients With Shifts		
Cholesterol (<200 mg/dL to ≥240 mg/dL)	2.7% (10/368)	4.3% (22/516)	6.3% (6/96)
Triglycerides (<500 mg/dL to ≥500 mg/dL)	1.1% (2/180)	2.7% (8/301)	2.5% (3/121)

In longer-term, controlled and uncontrolled studies, RISPERDAL® was associated with a mean change in (a) non-fasting cholesterol of +4.4 mg/dL at Week 24 (N=231) and +5.5 mg/dL at Week 48 (N=86); and (b) non-fasting triglycerides of +19.9 mg/dL at Week 24 (N=52).

Weight Gain

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

Data from a placebo-controlled, 12-week, fixed-dose study in adult subjects with schizophrenia are presented in Table 3.

Table 3. Mean Change in Body Weight (kg) and the Proportion of Subjects With ≥7% Gain in Body Weight From a Placebo-Controlled, 12-Week, Fixed-Dose Study in Adult Subjects With Schizophrenia

		RISPERDAL CONSTA®	
	Placebo (N=83)	25 mg (N=90)	50 mg (N=87)
Weight (kg)			
Change from baseline	-1.4	0.5	1.2
Weight Gain			
≥7% increase from baseline	6%	10%	8%

In an uncontrolled, longer-term, open-label study, RISPERDAL CONSTA® was associated with a mean change in weight of +2.1 kg at Week 24 (N=268) and +2.8 kg at Week 50 (N=199).

5.6 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents.

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. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone 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.

5.7 Orthostatic Hypotension

RISPERDAL CONSTA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period with oral risperidone, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position).

RISPERDAL CONSTA® should be used with particular caution in (1) 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, e.g., dehydration and hypovolemia, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication.

5.8 Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and,

consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

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 RISPERDAL CONSTA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and a history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of RISPERDAL CONSTA® 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 RISPERDAL CONSTA® and have their WBC followed until recovery.

5.10 Potential for Cognitive and Motor Impairment

Somnolence was reported by 5% of patients treated with RISPERDAL CONSTA® in multiple-dose trials. Since risperidone 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 treatment with RISPERDAL CONSTA® does not affect them adversely.

5.11 Seizures

During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL CONSTA®. Therefore, RISPERDAL CONSTA® should be used cautiously in patients with a history of seizures.

5.12 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 dementia. RISPERDAL CONSTA® and other antipsychotic drugs should be used

cautiously in patients at risk for aspiration pneumonia. *[see also Boxed Warning* and *Warnings and Precautions (5.1)]*

5.13 Priapism

Priapism has been reported during postmarketing surveillance *[see Adverse Reactions (6.8)]*. Severe priapism may require surgical intervention.

5.14 Thrombotic Thrombocytopenic Purpura (TTP)

A single case of TTP was reported in a 28 year-old female patient receiving oral RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

5.15 Body Temperature Regulation

Disruption of body temperature regulation has been attributed to antipsychotic agents. Both hyperthermia and hypothermia have been reported in association with oral RISPERDAL® or RISPERDAL CONSTA® use. Caution is advised when prescribing RISPERDAL CONSTA® for patients who will be exposed to temperature extremes.

5.16 Administration

RISPERDAL CONSTA® should be injected into the deltoid or gluteal muscle, and care must be taken to avoid inadvertent injection into a blood vessel. *[see Dosage and Administration (2)* and *Adverse Reactions (6.7)]*

5.17 Antiemetic Effect

Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

5.18 Use in Patients with Concomitant Illness

Clinical experience with RISPERDAL CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL CONSTA®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

Caution is advisable when using RISPERDAL CONSTA® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. RISPERDAL CONSTA® 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 clinical studies during the product's premarket testing.

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m^2) treated with oral RISPERDAL®; an increase in the free fraction of risperidone is also seen in patients with severe hepatic impairment. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal or hepatic impairment *[see Dosage and Administration (2.4)]*.

5.19 Osteodystrophy and Tumors in Animals

RISPERDAL CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks.

RISPERDAL CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. (Cellular proliferation was not measured at the low dose or in females in either study.)

The effect dose for osteodystrophy and the tumor findings is 8 times the IM maximum recommended human dose (MRHD) (50 mg) on a mg/m^2 basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the IM MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the IM MRHD on a mg/m^2 basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the IM MRHD.

Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone. Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study.

The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail in Section 13.1 (Carcinogenicity, Mutagenesis, Impairment of Fertility).

The relevance of these findings to human risk is unknown.

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions (5.2)]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions (5.3)]*
- Tardive dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic changes *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Orthostatic hypotension *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia/Neutropenia and Agranulocytosis *[see Warnings and Precautions (5.9)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.10)]*
- Seizures *[see Warnings and Precautions (5.11)]*
- Dysphagia *[see Warnings and Precautions (5.12)]*
- Priapism *[see Warnings and Precautions (5.13)]*
- Thrombotic Thrombocytopenic Purpura (TTP) *[see Warnings and Precautions (5.14)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.15)]*
- Avoidance of inadvertent injection into a blood vessel *[see Warnings and Precautions (5.16)]*
- Antiemetic effect *[see Warnings and Precautions (5.17)]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions (5.18)]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions (5.18)]*
- Osteodystrophy and tumors in animals *[see Warnings and Precautions (5.19)]*

The most common adverse reactions in clinical trials in patients with schizophrenia (≥ 5%) were: headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in the double-blind, placebo-controlled periods of the bipolar disorder trials were weight increased (5% in the monotherapy trial) and tremor and parkinsonism (≥ 10% in the adjunctive treatment trial).

The most common adverse reactions that were associated with discontinuation from the 12-week double-blind, placebo-controlled trial in patients with schizophrenia (causing discontinuation in ≥1% of patients) were agitation, depression, anxiety, and akathisia. Adverse reactions that were associated with discontinuation from the double-blind, placebo-controlled periods of the bipolar disorder trials were hyperglycemia (one patient in the monotherapy trial) and hypokinesia and tardive dyskinesia (one patient each in the adjunctive treatment trial).

The data described in this section are derived from a clinical trial database consisting of 2392 patients exposed to one or more doses of RISPERDAL CONSTA® for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received RISPERDAL CONSTA® while participating in a 12-week double-blind, placebo-controlled trial. Two hundred two (202) of the 332 were schizophrenia patients who received 25 mg or 50 mg RISPERDAL CONSTA®. The conditions and duration of treatment with RISPERDAL CONSTA® in the other clinical trials varied greatly and included (in overlapping categories) double-blind, fixed- and flexible-dose, placebo- or active-controlled studies and open-label phases of studies, inpatients and outpatients, and short-term (up to 12 weeks) and longer-term (up to 4 years) exposures. Safety was assessed by collecting adverse events and performing physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

In addition to the studies in patients with schizophrenia, safety data are presented from a trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder. The subjects in this multi-center, double-blind, placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who were stable on risperidone (oral or long-acting injection), were stable on other antipsychotics or mood stabilizers, or were experiencing an acute episode. After a 3-week period of treatment with open-label oral risperidone (N=440), subjects who demonstrated an initial response to oral risperidone in this period and those who were stable on risperidone (oral or long-acting injection) at study entry entered into a 26-week stabilization period of open-label RISPERDAL CONSTA® (N=501). Subjects who demonstrated a maintained response during this period were then randomized into a 24-month double-blind, placebo-controlled period in which they received RISPERDAL CONSTA® (N=154) or placebo (N=149) as monotherapy. Subjects who relapsed or who completed the double-blind period could choose to enter an 8-week open-label RISPERDAL CONSTA® extension period (N=160).

Safety data are also presented from a trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder. The subjects in this multi-center, double-blind, placebo-controlled study were adult patients who met DSM-IV criteria for Bipolar Disorder Type I or Type II and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12

months, including at least 2 episodes in the 6 months prior to the start of the study. At the start of this study, all patients (N=275) entered into a 16-week open-label treatment phase in which they received RISPERDAL CONSTA® in addition to continuing their treatment as usual, which consisted of various mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. Patients who reached remission at the end of this 16-week open-label treatment phase (N=139) were then randomized into a 52-week double-blind, placebo-controlled phase in which they received RISPERDAL CONSTA® (N=72) or placebo (n=67) as adjunctive treatment in addition to continuing their treatment as usual. Patients who did not reach remission at the end of the 16-week open-label treatment phase could choose to continue to receive RISPERDAL CONSTA® as adjunctive therapy in an open-label manner, in addition to continuing their treatment as usual, for up to an additional 36 weeks as clinically indicated for a total period of up to 52 weeks; these patients (N=70) were also included in the evaluation of safety.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of RISPERDAL CONSTA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for RISPERDAL CONSTA® often cannot be reliably established in individual cases. Further, 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 the rates observed in clinical practice.

The majority of all adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials - Schizophrenia

Table 4 lists the adverse reactions reported in 2% or more of RISPERDAL CONSTA®-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial.

Table 4. Adverse Reactions in ≥2% of RISPERDAL CONSTA®-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

	Percentage of Patients Reporting Event		
	RISPERDAL CONSTA®		Placebo
System/Organ Class Adverse Reaction	25 mg (N=99)	50 mg (N=103)	(N=98)
Eye disorders			
Vision blurred	2	3	0
Gastrointestinal disorders			
Constipation	5	7	1
Dry mouth	0	7	1
Dyspepsia	6	6	0
Nausea	3	4	5
Toothache	1	3	0
Salivary hypersecretion	4	1	0
General disorders and administration site conditions			
Fatigue*	3	9	0
Edema peripheral	2	3	1
Pain	4	1	0
Pyrexia	2	1	0
Infections and infestations			
Upper respiratory tract infection	2	0	1
Investigations			
Weight increased	5	4	2
Weight decreased	4	1	1
Musculoskeletal and connective tissue disorders			
Pain in extremity	6	2	1
Nervous system disorders			
Headache	15	21	12
Parkinsonism*	8	15	9
Dizziness	7	11	6
Akathisia*	4	11	6
Sedation*	5	6	3
Tremor	0	3	0
Syncope	2	1	0
Hypoesthesia	2	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	4	2	3
Sinus congestion	2	0	0
Skin and subcutaneous tissue disorders			
Acne	2	2	0
Dry skin	2	0	0

* Fatigue includes fatigue and asthenia. Parkinsonism includes extrapyramidal disorder, musculoskeletal stiffness, muscle rigidity, and bradykinesia. Akathisia includes akathisia and restlessness. Sedation includes sedation and somnolence.

6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Bipolar Disorder

Table 5 lists the treatment-emergent adverse reactions reported in 2% or more of RISPERDAL CONSTA®-treated patients in the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with Bipolar I Disorder.

Table 5. Adverse Reactions in ≥2% of Patients with Bipolar I Disorder Treated with RISPERDAL CONSTA® as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial

	Percentage of Patients Reporting Event	
System/Organ Class	**RISPERDAL CONSTA®**	**Placebo**
Adverse Reaction	**(N=154)**	**(N=149)**
Investigations		
Weight increased	5	1
Nervous system disorders		
Dizziness	3	1
Vascular disorders		
Hypertension	3	1

Table 6 lists the treatment-emergent adverse reactions reported in 4% or more of patients in the 52-week double-blind, placebo-controlled treatment phase of a trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as adjunctive maintenance treatment in patients with bipolar disorder.

Table 6. Adverse Reactions in ≥ 4% of Patients with Bipolar Disorder Treated with RISPERDAL CONSTA® as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial

	Percentage of Patients Reporting Event	
System/Organ Class Adverse Reaction	RISPERDAL CONSTA® + Treatment as Usual[a] (N=72)	Placebo + Treatment as Usual[a] (N=67)
General disorders and administration site conditions		
Gait abnormal	4	0
Infections and infestations		
Upper respiratory tract infection	6	3
Investigations		
Weight increased	7	1
Metabolism and nutrition disorders		
Decreased appetite	6	1
Increased appetite	4	0
Musculoskeletal and connective tissue disorders		
Arthralgia	4	3
Nervous system disorders		
Tremor	24	16
Parkinsonism[b]	15	6
Dyskinesia[b]	6	3
Sedation[c]	7	1
Disturbance in attention	4	0
Reproductive system and breast disorders		
Amenorrhea	4	1
Respiratory, thoracic and mediastinal disorders		
Cough	4	1

[a] Patients received double-blind RISPERDAL CONSTA® or placebo in addition to continuing their treatment as usual, which included mood stabilizers, antidepressants, and/or anxiolytics.

[b] Parkinsonism includes muscle rigidity, hypokinesia, cogwheel rigidity, and bradykinesia. Dyskinesia includes muscle twitching and dyskinesia.

[c] Sedation includes sedation and somnolence.

6.3 Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone

The following additional adverse reactions occurred in < 2% of the RISPERDAL CONSTA®-treated patients in the above schizophrenia double-blind, placebo-controlled trial dataset, in < 2% of the RISPERDAL CONSTA®-treated patients in the above double-blind, placebo-controlled period of the monotherapy bipolar disorder trial dataset, or in < 4% of the RISPERDAL CONSTA®-treated patients in the above double-blind, placebo-controlled period of the adjunctive treatment bipolar disorder trial dataset. The following also includes additional adverse reactions reported at any frequency in RISPERDAL CONSTA®-treated patients who participated in the open-label phases of the above bipolar disorder studies and in other studies, including double-blind, active controlled and open-label studies in schizophrenia and bipolar disorder.

Blood and lymphatic system disorders: anemia, neutropenia

Cardiac disorders: tachycardia, atrioventricular block first degree, palpitations, sinus bradycardia, bundle branch block left, bradycardia, sinus tachycardia, bundle branch block right

Ear and labyrinth disorders: ear pain, vertigo

Endocrine disorders: hyperprolactinemia

Eye disorders: conjunctivitis, visual acuity reduced

Gastrointestinal disorders: diarrhea, vomiting, abdominal pain upper, abdominal pain, stomach discomfort, gastritis

General disorders and administration site conditions: injection site pain, chest discomfort, chest pain, influenza like illness, sluggishness, malaise, induration, injection site induration, injection site swelling, injection site reaction, face edema

Immune system disorders: hypersensitivity

Infections and infestations: nasopharyngitis, influenza, bronchitis, urinary tract infection, rhinitis, respiratory tract infection, ear infection, pneumonia, lower respiratory tract infection, pharyngitis, sinusitis, viral infection, infection, localized infection, cystitis, gastroenteritis, subcutaneous abscess

Injury and poisoning: fall, procedural pain

Investigations: blood prolactin increased, alanine aminotransferase increased, electrocardiogram abnormal, gamma-glutamyl transferase increased, blood glucose increased, hepatic enzyme increased, aspartate aminotransferase increased, electrocardiogram QT prolonged, glucose urine present

Metabolism and nutritional disorders: anorexia, hyperglycemia

Musculoskeletal, connective tissue and bone disorders: posture abnormal, myalgia, back pain, buttock pain, muscular weakness, neck pain, musculoskeletal chest pain

Nervous system disorders: coordination abnormal, dystonia, tardive dyskinesia, drooling, paresthesia, dizziness postural, convulsion, akinesia, hypokinesia, dysarthria

Psychiatric disorders: insomnia, agitation, anxiety, sleep disorder, depression, initial insomnia, libido decreased, nervousness

Renal and urinary disorders: urinary incontinence

Reproductive system and breast disorders: galactorrhea, oligomenorrhea, erectile dysfunction, sexual dysfunction, ejaculation disorder, gynecomastia, breast discomfort, menstruation irregular, menstruation delayed, menstrual disorder, ejaculation delayed

Respiratory, thoracic and mediastinal disorders: nasal congestion, pharyngolaryngeal pain, dyspnea, rhinorrhea

Skin and subcutaneous tissue disorders: rash, eczema, pruritus generalized, pruritus

Vascular disorders: hypotension, orthostatic hypotension

Additional Adverse Reactions Reported with Oral RISPERDAL®

The following is a list of additional adverse reactions that have been reported during the clinical trial evaluation of oral RISPERDAL®, regardless of frequency of occurrence:

Blood and Lymphatic Disorders: granulocytopenia

Cardiac Disorders: atrioventricular block

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: ocular hyperemia, eye discharge, eye rolling, eyelid edema, eye swelling, eyelid margin crusting, dry eye, lacrimation increased, photophobia, glaucoma

Gastrointestinal Disorders: abdominal pain upper, dysphagia, fecaloma, abdominal discomfort, fecal incontinence, lip swelling, cheilitis, aptyalism

General Disorders: thirst, feeling abnormal, gait disturbance, pitting edema, edema, chills, discomfort, generalized edema, drug withdrawal syndrome, peripheral coldness

Immune System Disorders: drug hypersensitivity

Infections and Infestations: tonsillitis, eye infection, cellulitis, otitis media, onychomycosis, acarodermatitis, bronchopneumonia, respiratory tract infection, tracheobronchitis, otitis media chronic

Investigations: body temperature increased, heart rate increased, eosinophil count increased, white blood cell count decreased, hemoglobin decreased, blood creatine phosphokinase increased, hematocrit decreased, body temperature decreased, blood pressure decreased, transaminases increased

Metabolism and Nutrition Disorders: polydipsia

Musculoskeletal, Connective Tissue, and Bone Disorders: joint swelling, joint stiffness, rhabdomyolysis, torticollis

Nervous System Disorders: hypertonia, balance disorder, dysarthria, unresponsive to stimuli, depressed level of consciousness, movement disorder, hypokinesia, parkinsonian rest tremor, transient ischemic attack, cerebrovascular accident, masked facies, speech disorder, loss of consciousness, muscle contractions involuntary, akinesia, cerebral ischemia, cerebrovascular disorder, neuroleptic malignant syndrome, diabetic coma, head titubation

Psychiatric Disorders: blunted affect, confusional state, middle insomnia, listlessness, anorgasmia

Renal and Urinary Disorders: enuresis, dysuria, pollakiuria

Reproductive System and Breast Disorders: vaginal discharge, retrograde ejaculation, ejaculation disorder, ejaculation failure, breast enlargement

Respiratory, Thoracic, and Mediastinal Disorders: epistaxis, wheezing, pneumonia aspiration, dysphonia, productive cough, pulmonary congestion, respiratory tract congestion, rales, respiratory disorder, hyperventilation, nasal edema

Skin and Subcutaneous Tissue Disorders: erythema, skin discoloration, skin lesion, skin disorder, rash erythematous, rash papular, hyperkeratosis, dandruff, seborrheic dermatitis, rash generalized, rash maculopapular

Vascular Disorders: flushing

6.4 Discontinuations Due to Adverse Reactions

Schizophrenia

Approximately 11% (22/202) of RISPERDAL CONSTA®-treated patients in the 12-week double-blind, placebo-controlled schizophrenia trial discontinued treatment due to an adverse event, compared with 13% (13/98) who received placebo. The adverse reactions associated with discontinuation in two or more RISPERDAL CONSTA®-treated patients were: agitation (3%), depression (2%), anxiety (1%), and akathisia (1%).

Bipolar Disorder

In the 24-month double-blind, placebo-controlled treatment period of the trial assessing the efficacy and safety of RISPERDAL CONSTA® when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 1 (0.6%) of 154 RISPERDAL CONSTA®-treated patients discontinued due to an adverse reaction (hyperglycemia).

In the 52-week double-blind phase of the placebo-controlled trial in which RISPERDAL CONSTA® was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing with their treatment as usual, approximately 4% (3/72) of RISPERDAL CONSTA®-treated patients discontinued treatment due to an adverse event, compared with 1.5% (1/67) of placebo-treated patients. Adverse reactions associated with discontinuation in RISPERDAL CONSTA®-treated patients were: hypokinesia (one patient) and tardive dyskinesia (one patient).

6.5 Dose Dependency of Adverse Reactions in Clinical Trials

Extrapyramidal Symptoms:

Two methods were used to measure extrapyramidal symptoms (EPS) in the 12-week double-blind, placebo-controlled trial comparing three doses of RISPERDAL CONSTA® (25 mg, 50 mg, and 75 mg) with placebo in patients with schizophrenia, including: (1) the incidence of spontaneous reports of EPS symptoms; and (2) the change from baseline to endpoint on the total score (sum of the subscale scores for parkinsonism, dystonia, and dyskinesia) of the Extrapyramidal Symptom Rating Scale (ESRS).

As shown in Table 1, the overall incidence of EPS-related adverse reactions (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse reactions was higher in patients treated with 50 mg RISPERDAL CONSTA®.

The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with RISPERDAL CONSTA® compared with patients treated with placebo: 0 (placebo group); -1 (25-mg group, significantly less than the placebo group); and 0 (50-mg group).

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.

6.6 Changes in ECG

The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL CONSTA® and 98 schizophrenic patients treated with placebo in the 12-week double-blind,

placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA®.

The electrocardiograms of 227 patients with Bipolar I Disorder were evaluated in the 24-month double-blind, placebo-controlled period. There were no clinically relevant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA® compared to placebo.

The electrocardiograms of 85 patients with bipolar disorder were evaluated in the 52-week double-blind, placebo-controlled trial. There were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL CONSTA® 25 mg, 37.5 mg, or 50 mg when administered as adjunctive treatment in addition to continuing treatment as usual compared to placebo.

6.7 Pain Assessment and Local Injection Site Reactions

The mean intensity of injection pain reported by patients with schizophrenia using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL CONSTA® experienced redness, swelling, or induration at the injection site.

In a separate study to observe local-site tolerability in which RISPERDAL CONSTA® was administered into the deltoid muscle every 2 weeks over a period of 8 weeks, no patient discontinued treatment due to local injection site pain or reaction. Clinician ratings indicated that only mild redness, swelling, or induration at the injection site was observed in subjects treated with 37.5 mg or 50 mg RISPERDAL CONSTA® at 2 hours after deltoid injection. All ratings returned to baseline at the predose assessment of the next injection 2 weeks later. No moderate or severe reactions were observed in any subject.

6.8 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of risperidone; because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency: agranulocytosis, alopecia, anaphylactic reaction, angioedema, atrial fibrillation, blood cholesterol increased, blood triglycerides increased, diabetes mellitus, diabetic ketoacidosis in patients with impaired glucose metabolism, drug withdrawal syndrome neonatal, dysgeusia, hypoglycemia, hypothermia, ileus, inappropriate antidiuretic hormone secretion, intestinal obstruction, jaundice, mania, pancreatitis, priapism, QT

prolongation, sleep apnea syndrome, thrombocytopenia, urinary retention, and water intoxication. In addition, the following adverse reactions have been observed during postapproval use of RISPERDAL CONSTA®: cerebrovascular disorders, including cerebrovascular accidents, and diabetes mellitus aggravated.

Retinal artery occlusion after injection of RISPERDAL CONSTA® has been reported during postmarketing surveillance. This has been reported in the presence of abnormal arteriovenous anastomosis.

Serious injection site reactions including abscess, cellulitis, cyst, hematoma, necrosis, nodule, and ulcer have been reported with RISPERDAL CONSTA® during postmarketing surveillance. Isolated cases required surgical intervention.

Very rarely, cases of anaphylactic reaction after injection with RISPERDAL CONSTA® have been reported during postmarketing experience in patients who have previously tolerated oral risperidone.

7 DRUG INTERACTIONS

The interactions of RISPERDAL CONSTA® with coadministration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral RISPERDAL®.

7.1 Centrally-Acting Drugs and Alcohol

Given the primary CNS effects of risperidone, caution should be used when RISPERDAL CONSTA® is administered in combination with other centrally-acting drugs or alcohol.

7.2 Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, RISPERDAL CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential.

7.3 Levodopa and Dopamine Agonists

RISPERDAL CONSTA® may antagonize the effects of levodopa and dopamine agonists.

7.4 Amitriptyline

Amitriptyline did not affect the pharmacokinetics of risperidone or of risperidone and 9-hydroxyrisperidone combined following concomitant administration with oral RISPERDAL®.

7.5 Cimetidine and Ranitidine

Cimetidine and ranitidine increased the bioavailability of oral risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of risperidone and

9-hydroxyrisperidone combined, whereas ranitidine increased the AUC of risperidone and 9-hydroxyrisperidone combined by 20%.

7.6 Clozapine

Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

7.7 Lithium

Repeated doses of oral RISPERDAL® (3 mg twice daily) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (N=13).

7.8 Valproate

Repeated doses of oral RISPERDAL® (4 mg once daily) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (N=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of oral RISPERDAL®.

7.9 Digoxin

Oral RISPERDAL® (0.25 mg twice daily) did not show a clinically relevant effect on the pharmacokinetics of digoxin.

7.10 Topiramate

Oral RISPERDAL® administered at doses from 1-6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone C_{max} and a 33% decrease in risperidone $AUC_{0\text{-}12\ hour}$ at steady state. Minimal reductions in the exposure to risperidone and 9-hydroxyrisperidone combined, and no change for 9-hydroxyrisperidone were observed. This interaction is unlikely to be of clinical significance. There was no clinically relevant effect of oral RISPERDAL® on the pharmacokinetics of topiramate.

7.11 Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

Risperidone is metabolized to 9-hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs *[see Clinical Pharmacology (12.3)]*. Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≅70 patients) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism.

Fluoxetine and Paroxetine

Fluoxetine (20 mg once daily) and paroxetine (20 mg once daily), CYP 2D6 inhibitors, have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9-hydroxyrisperidone. Paroxetine lowered the concentration of 9-hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of RISPERDAL CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. When fluoxetine or paroxetine is initiated in patients receiving the recommended dose of 25 mg RISPERDAL CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL CONSTA® treatment. When RISPERDAL CONSTA® is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[see also Dosage and Administration (2.5)]*. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied.

Erythromycin

There were no significant interactions between oral RISPERDAL® and erythromycin.

7.12 Carbamazepine and Other CYP 3A4 Enzyme Inducers

Carbamazepine co-administration with oral RISPERDAL® decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Co-administration of other known CYP 3A4 enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9-hydroxyrisperidone, which could lead to decreased efficacy of RISPERDAL CONSTA® treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of RISPERDAL CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL CONSTA®

between 2 to 4 weeks before the planned discontinuation of carbamazepine or other CYP 3A4 enzyme inducers to adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone. For patients treated with the recommended dose of 25 mg RISPERDAL CONSTA® and discontinuing from carbamazepine or other CYP 3A4 enzyme inducers, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates lowering the RISPERDAL CONSTA® dose to 12.5 mg or necessitates interruption of RISPERDAL CONSTA® treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. *[see also Dosage and Administration (2.5)]*

7.13 Drugs Metabolized by CYP 2D6

In vitro studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL CONSTA® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral RISPERDAL® did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including RISPERDAL CONSTA®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at *http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/*.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including RISPERDAL CONSTA®, during pregnancy *(see Clinical Considerations)*. Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® *[see Clinical Pharmacology (12.3)]*. The clinical significance of RISPERDAL CONSTA® administered before pregnancy or anytime during pregnancy is not known.

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3 to 4 times the maximum recommended human dose (MRHD) with maternal toxicity observed at 4-times the MRHD based on mg/m^2 body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the MRHD based on mg/m^2 body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the MRHD based on mg/m^2 body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the MRHD and offspring mortality increased at doses 0.1 to 3 times the MRHD based on mg/m^2 body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including RISPERDAL CONSTA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk major of birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of

pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3 times the MRHD of 16 mg/day based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6 times the MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6 and 1.2 times the MRHD based on mg/m^2 body surface area; postnatal development and growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1 to 3 times the MRHD of 16 mg/day based on mg/m^2 body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5 times the MRHD based on mg/m^2 body surface area.

In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) were reduced in offspring born to control but reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3 times the MRHD based on mg/m^2 and the only dose tested in the study.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone *(see Clinical Considerations).* Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® *[see Clinical Pharmacology (12.3)]*, and the clinical significance on

the breastfed infant is not known. There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RISPERDAL CONSTA® and any potential adverse effects on the breastfed child from RISPERDAL CONSTA® or from the mother's underlying condition.

Clinical Considerations

Infants exposed to RISPERDAL CONSTA® through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of risperidone (D2 receptor antagonism), treatment with RISPERDAL CONSTA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.6)]*.

8.4 Pediatric Use

Safety and effectiveness of RISPERDAL CONSTA® in pediatric patients have not been established. However, juvenile animal toxicology studies have been conducted with oral risperidone.

Juvenile Animal Studies

Juvenile dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.31, 1.25, or 5 mg/kg/day, which are 1.2, 3.4 and 13.5 times the MRHD of 6 mg/day for children, based on mg/m^2 body surface area. Bone length and density were decreased with a no-effect dose of 0.31 mg/kg/day; this dose produced plasma AUC of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) that were similar to those in children and adolescents receiving the MRHD of 6 mg/day. In addition, sexual maturation was delayed at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period. Juvenile rats, treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the MRHD of 6 mg/day for children, based on mg/m^2 body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the

MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the MRHD of 6 mg/day for children.

8.5 Geriatric Use

In an open-label study, 57 clinically stable, elderly patients (≥ 65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL CONSTA® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern *[see Warnings and Precautions (5.7)]*.

Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis

In two of four placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus oral risperidone when compared to patients treated with oral risperidone alone or with oral placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of oral risperidone regardless of concomitant use with furosemide. RISPERDAL CONSTA® is not approved for the treatment of patients with dementia-related psychosis. *[see Boxed Warning* and *Warnings and Precautions (5.1)]*

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

RISPERDAL CONSTA® (risperidone) is not a controlled substance.

9.2 Abuse

RISPERDAL CONSTA® has not been systematically studied in animals or humans for its potential for abuse. Because RISPERDAL CONSTA® is to be administered by health care professionals, the potential for misuse or abuse by patients is low.

9.3 Dependence

RISPERDAL CONSTA® has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

10 OVERDOSAGE

10.1 Human Experience

No cases of overdose were reported in premarketing studies with RISPERDAL CONSTA®. Because RISPERDAL CONSTA® is to be administered by health care professionals, the potential for overdosage by patients is low.

In premarketing experience with oral RISPERDAL®, there were eight reports of acute RISPERDAL® overdosage, with estimated doses ranging from 20 to 300 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. One case, involving an estimated overdose of 240 mg, was associated with hyponatremia, hypokalemia, prolonged QT, and widened QRS. Another case, involving an estimated overdose of 36 mg, was associated with a seizure.

Postmarketing experience with oral RISPERDAL® includes reports of acute overdose, with estimated doses of up to 360 mg. In general, the most frequently reported signs and symptoms are those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and extrapyramidal symptoms. Other adverse reactions reported since market introduction related to oral RISPERDAL® overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of oral RISPERDAL® and paroxetine.

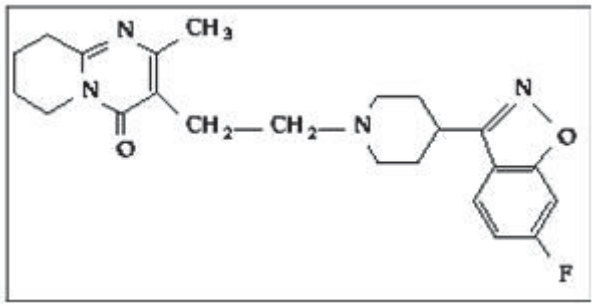
10.2 Management of Overdosage

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT prolonging effects that might be additive to those of risperidone. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of risperidone, resulting in problematic hypotension.

There is no specific antidote to risperidone. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of risperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

11 DESCRIPTION

RISPERDAL CONSTA® contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 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. Its molecular formula is $C_{23}H_{27}FN_4O_2$ and its molecular weight is 410.49. The structural formula is:



Risperidone is practically insoluble in water, freely soluble in methylene chloride, and soluble in methanol and 0.1 N HCl.

RISPERDAL CONSTA® (risperidone) Long-Acting Injection is a combination of extended-release microspheres for injection and diluent for parenteral use.

The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres.

The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes citric acid anhydrous, disodium hydrogen phosphate dihydrate, polysorbate 20, sodium carboxymethyl cellulose, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

RISPERDAL CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a West-Medimop Vial Adapter®, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of risperidone in schizophrenia is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major active metabolite, 9-hydroxyrisperidone (paliperidone) *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$ may explain some of the other effects of risperidone *[see Clinical Pharmacology (12.1)]*.

12.2 Pharmacodynamics

Risperidone is a monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D_2), α1 and α2 adrenergic, and H_1 histaminergic receptors. Risperidone showed low to moderate affinity (Ki of 47 to 253 nM) for the serotonin $5HT_{1C}$, $5HT_{1D}$, and $5HT_{1A}$ receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D_1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations $>10^{-5}$ M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

12.3 Pharmacokinetics

Absorption

After a single intramuscular (gluteal) injection of RISPERDAL CONSTA®, there is a small initial release of the drug (< 1% of the dose), followed by a lag time of 3 weeks. The main release of the drug starts from 3 weeks onward, is maintained from 4 to 6 weeks, and subsides by 7 weeks following the intramuscular (IM) injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with RISPERDAL CONSTA® to maintain therapeutic levels until the main release of risperidone from the injection site has begun *[see Dosage and Administration (2)]*. Following single doses of RISPERDAL CONSTA®, the pharmacokinetics of risperidone, 9-hydroxyrisperidone (the major metabolite), and risperidone plus 9-hydroxyrisperidone were linear in the dosing range of 12.5 mg to 50 mg.

The combination of the release profile and the dosage regimen (IM injections every 2 weeks) of RISPERDAL CONSTA® results in sustained therapeutic concentrations. Steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection. Following multiple doses of 25 mg and 50 mg RISPERDAL CONSTA®, plasma concentrations of risperidone, 9-hydroxyrisperidone, and risperidone plus 9-hydroxyrisperidone were linear.

Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.

Distribution

Once absorbed, risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α1-acid glycoprotein. The plasma protein binding of risperidone is approximately 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/mL), warfarin (10 mcg/mL), and carbamazepine (10 mcg/mL) caused only a slight increase in the free fraction of risperidone at 10 ng/mL and of 9-hydroxyrisperidone at 50 ng/mL, changes of unknown clinical significance.

Metabolism and Drug Interactions

Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through N-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar pharmacological activity as risperidone. Consequently, the clinical effect of the drug results from the combined concentrations of risperidone plus 9-hydroxyrisperidone.

CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6%-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of risperidone and 9-hydroxyrisperidone combined, after single and multiple doses, are similar in extensive and poor metabolizers.

The interactions of RISPERDAL CONSTA® with coadministration of other drugs have not been systematically evaluated in human subjects. Drug interactions are based primarily on experience with oral RISPERDAL®. Risperidone could be subject to two kinds of drug-drug interactions. First, inhibitors of CYP 2D6 interfere with conversion of risperidone to 9-hydroxyrisperidone *[see Drug Interactions (7.11)]*. This occurs with quinidine, giving essentially all recipients a risperidone pharmacokinetic profile typical of poor metabolizers. The therapeutic benefits and adverse effects of RISPERDAL® in patients receiving quinidine have not been evaluated, but observations in a modest number (n≅70) of poor metabolizers given oral RISPERDAL® do not suggest important differences between poor and extensive metabolizers. Second, co-administration of carbamazepine and other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with oral RISPERDAL® cause a decrease in the combined plasma

concentrations of risperidone and 9-hydroxyrisperidone *[see Drug Interactions (7.12)]*. It would also be possible for risperidone to interfere with metabolism of other drugs metabolized by CYP 2D6. Relatively weak binding of risperidone to the enzyme suggests this is unlikely *[see Drug Interactions (7.11)]*.

Excretion

Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. As illustrated by a mass balance study of a single 1 mg oral dose of ^{14}C-risperidone administered as solution to three healthy male volunteers, total recovery of radioactivity at 1 week was 84%, including 70% in the urine and 14% in the feces.

The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA® administration is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone. The clearance of risperidone and risperidone plus 9-hydroxyrisperidone was 13.7 L/h and 5.0 L/h in extensive CYP 2D6 metabolizers, and 3.3 L/h and 3.2 L/h in poor CYP 2D6 metabolizers, respectively. No accumulation of risperidone was observed during long-term use (up to 12 months) in patients treated every 2 weeks with 25 mg or 50 mg RISPERDAL CONSTA®. The elimination phase is complete approximately 7 to 8 weeks after the last injection.

Renal Impairment

In patients with moderate to severe renal disease treated with oral RISPERDAL®, clearance of the sum of risperidone and its active metabolite decreased by 60% compared with young healthy subjects. Although patients with renal impairment were not studied with RISPERDAL CONSTA®, it is recommended that patients with renal impairment be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with renal impairment *[see Dosage and Administration (2.4)]*.

Hepatic Impairment

While the pharmacokinetics of oral RISPERDAL® in subjects with liver disease were comparable to those in young healthy subjects, the mean free fraction of risperidone in plasma was increased by about 35% because of the diminished concentration of both albumin and α1-acid glycoprotein. Although patients with hepatic impairment were not studied with RISPERDAL CONSTA®, it is recommended that patients with hepatic impairment be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL CONSTA® is initiated at a dose of 25 mg. A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant

dose adjustment, such as in patients with hepatic impairment *[see Dosage and Administration (2.4)]*.

Elderly

In an open-label trial, steady-state concentrations of risperidone plus 9-hydroxyrisperidone in otherwise healthy elderly patients (≥ 65 years old) treated with RISPERDAL CONSTA® for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. Dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients *[see Dosage and Administration (2)]*.

Race and Gender Effects

No specific pharmacokinetic study was conducted to investigate race and gender effects, but a population pharmacokinetic analysis did not identify important differences in the disposition of risperidone due to gender (whether or not corrected for body weight) or race.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Oral

Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to approximately 0.2, 0.75, and 3 times (mice) and 0.4, 1.5, and 6 times (rats) the MRHD of 16 mg/day, based on mg/m^2 body surface area. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas, endocrine pancreatic adenomas, and mammary gland adenocarcinomas. The table below summarizes the multiples of the human dose on mg/m^2 (mg/kg) basis at which these tumors occurred.

Tumor Type	Species	Sex	Multiples of Maximum Human Dose in mg/m^2 (mg/kg)	
			Lowest Effect Level	Highest No-Effect Level
Pituitary adenomas	mouse	Female	0.75 (9.4)	0.2 (2.4)
Endocrine pancreas adenomas	rat	Male	1.5 (9.4)	0.4 (2.4)
Mammary gland adenocarcinomas	mouse	Female	0.2 (2.4)	none
	rat	Female	0.4 (2.4)	none
	rat	Male	6.0 (37.5)	1.5 (9.4)
Mammary gland neoplasm, Total	rat	Male	1.5 (9.4)	0.4 (2.4)

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the risperidone carcinogenicity studies; however, measurements during subchronic toxicity studies showed that risperidone elevated serum prolactin levels 5-6 fold in mice and rats at the same doses used in the carcinogenicity studies.

An increase in mammary, pituitary, and endocrine pancreas neoplasms has 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 findings of prolactin-mediated endocrine tumors in rodents is unclear *[see Warnings and Precautions (5.6)]*.

Carcinogenesis - Intramuscular

Risperidone was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular (IM) injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD.

Dopamine D_2 receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone every 2 weeks IM. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis

No evidence of mutagenic or clastogenic potential for risperidone was found in the *in vitro* tests of Ames gene mutation, the mouse lymphoma assay, rat hepatocyte DNA-repair assay, the chromosomal aberration test in human lymphocytes, Chinese hamster ovary cells, or in the *in vivo* micronucleus test in mice, and the sex-linked recessive lethal test in *Drosophila*.

In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for RISPERDAL CONSTA®.

Impairment of Fertility

Oral risperidone (0.16 to 5 mg/kg) impaired mating, but not fertility, in rat reproductive studies at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD of 16 mg/day) based on mg/m^2 body surface area. The effect appeared to be in females, since impaired mating behavior was not noted in the male fertility study. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the oral MRHD on mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

14 CLINICAL STUDIES

14.1 Schizophrenia

The effectiveness of RISPERDAL CONSTA® in the treatment of schizophrenia was established, in part, on the basis of extrapolation from the established effectiveness of the oral formulation of risperidone. In addition, the effectiveness of RISPERDAL CONSTA® in the treatment of schizophrenia was established in a 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

Efficacy data were obtained from 400 patients with schizophrenia who were randomized to receive injections of 25 mg, 50 mg, or 75 mg RISPERDAL CONSTA® or placebo every 2 weeks. During a 1-week run-in period, patients were discontinued from other antipsychotics and were titrated to a dose of 4 mg oral RISPERDAL®. Patients who received RISPERDAL CONSTA® were given doses of oral RISPERDAL® (2 mg for patients in the 25-mg group, 4 mg for patients in the 50-mg group, and 6 mg for patients in the 75-mg group) for the 3 weeks after the first injection to provide therapeutic plasma concentrations until the main release phase of risperidone from the injection site had begun. Patients who received placebo injections were given placebo tablets.

Efficacy was evaluated using the Positive and Negative Syndrome Scale (PANSS), a validated, multi-item inventory, composed of five subscales to evaluate positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The primary efficacy variable in this trial was change from baseline to endpoint in the total PANSS score. The mean total PANSS score at baseline for schizophrenic patients in this study was 81.5.

Total PANSS scores showed significant improvement in the change from baseline to endpoint in schizophrenic patients treated with each dose of RISPERDAL CONSTA® (25 mg, 50 mg, or 75

mg) compared with patients treated with placebo. While there were no statistically significant differences between the treatment effects for the three dose groups, the effect size for the 75 mg dose group was actually numerically less than that observed for the 50 mg dose group.

Subgroup analyses did not indicate any differences in treatment outcome as a function of age, race, or gender.

14.2 Bipolar Disorder - Monotherapy

The effectiveness of RISPERDAL CONSTA® for the maintenance treatment of Bipolar I Disorder was established in a multicenter, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I, who were stable on medications or experiencing an acute manic or mixed episode.

A total of 501 patients were treated during a 26-week open-label period with RISPERDAL CONSTA® (starting dose of 25 mg, and titrated, if deemed clinically desirable, to 37.5 mg or 50 mg; in patients not tolerating the 25 mg dose, the dose could be reduced to 12.5 mg). In the open-label phase, 303 (60%) patients were judged to be stable and were randomized to double-blind treatment with either the same dose of RISPERDAL CONSTA® or placebo and monitored for relapse. The primary endpoint was time to relapse to any mood episode (depression, mania, hypomania, or mixed).

Time to relapse was delayed in patients receiving RISPERDAL CONSTA® monotherapy as compared to placebo. The majority of relapses were due to manic rather than depressive symptoms. Based on their bipolar disorder history, subjects entering this study had had, on average, more manic episodes than depressive episodes.

14.3 Bipolar Disorder - Adjunctive Therapy

The effectiveness of RISPERDAL CONSTA® as an adjunct to treatment with lithium or valproate for the maintenance treatment of Bipolar Disorder was established in a multi-center, randomized, double-blind, placebo-controlled study of adult patients who met DSM-IV criteria for Bipolar Disorder Type I and who experienced at least 4 episodes of mood disorder requiring psychiatric/clinical intervention in the previous 12 months, including at least 2 episodes in the 6 months prior to the start of the study.

A total of 240 patients were treated during a 16-week open-label period with RISPERDAL CONSTA® (starting dose of 25 mg, and titrated, if deemed clinically desirable, to 37.5 mg or 50 mg), as adjunctive therapy in addition to continuing their treatment as usual for their bipolar disorder, which consisted of mood stabilizers (primarily lithium and valproate), antidepressants, and/or anxiolytics. All oral antipsychotics were discontinued after the first three weeks of the

initial RISPERDAL CONSTA® injection. In the open-label phase, 124 (51.7%) were judged to be stable for at least the last 4 weeks and were randomized to double-blind treatment with either the same dose of RISPERDAL CONSTA® or placebo in addition to continuing their treatment as usual and monitored for relapse during a 52-week period. The primary endpoint was time to relapse to any new mood episode (depression, mania, hypomania, or mixed).

Time to relapse was delayed in patients receiving adjunctive therapy with RISPERDAL CONSTA® as compared to placebo. The relapse types were about half depressive and half manic or mixed episodes.

16 HOW SUPPLIED/STORAGE AND HANDLING

RISPERDAL CONSTA® (risperidone) is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone. It is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL CONSTA®, a West-Medimop Vial Adapter®, and two Terumo SurGuard® 3 Needles for intramuscular injection (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

12.5-mg vial/kit (NDC 50458-309-11): 41 mg (equivalent to 12.5 mg of risperidone) of a white to off-white powder provided in a vial with a violet flip-off cap (NDC 50458-309-01).

25-mg vial/kit (NDC 50458-306-11): 78 mg (equivalent to 25 mg of risperidone) of a white to off-white powder provided in a vial with a pink flip-off cap (NDC 50458-306-01).

37.5-mg vial/kit (NDC 50458-307-11): 116 mg (equivalent to 37.5 mg of risperidone) of a white to off-white powder provided in a vial with a green flip-off cap (NDC 50458-307-01).

50-mg vial/kit (NDC 50458-308-11): 152 mg (equivalent to 50 mg of risperidone) of a white to off-white powder provided in a vial with a blue flip-off cap (NDC 50458-308-01).

Storage and Handling

The entire dose pack should be stored in the refrigerator (36°-46°F; 2°-8°C) and protected from light.

If refrigeration is unavailable, RISPERDAL CONSTA® can be stored at temperatures not exceeding 77°F (25°C) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 77°F (25°C).

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL CONSTA®.

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension and instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position) *[see Warnings and Precautions (5.7)]*.

Interference with Cognitive and Motor Performance

Because RISPERDAL CONSTA® 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 treatment with RISPERDAL CONSTA® does not affect them adversely *[see Warnings and Precautions (5.10)]*.

Concomitant Medication

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 *[see Drug Interactions (7)]*.

Alcohol

Patients should be advised to avoid alcohol during treatment with RISPERDAL CONSTA® *[see Drug Interactions (7.1)]*.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with RISPERDAL CONSTA®. Advise patients that RISPERDAL CONSTA® may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to RISPERDAL CONSTA® during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise breastfeeding women using RISPERDAL CONSTA® to monitor infants for somnolence, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential that RISPERDAL CONSTA® may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Product of Ireland

Risperidone active ingredient is manufactured by:
Janssen Pharmaceutical
Wallingstown, Little Island, County Cork, Ireland
Microspheres are manufactured by:
Alkermes, Inc.
Wilmington, Ohio
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Langenargen, Germany
or
Cilag AG
Schaffhausen, Switzerland

RISPERDAL CONSTA® is manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s058

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG/NDA: Invega (paliperidone) Extended Release (ER) Tablets 1.5 mg, 3 mg, 6 mg, 9 mg, 12 mg (NDA 021999)
Invega Sustenna (paliperidone palmitate) extended-release injectable suspension, 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg (NDA 022264)
Invega Trinza (paliperidone palmitate) extended-release injectable suspension 273 mg, 410 mg, 546 mg, 819 mg (NDA 207946)

Risperdal (risperidone) Tablets 0.25mg, 0.5mg, 1mg, 2mg, 3mg, 4 mg (NDA 020272)
Risperdal (risperidone) Oral Solution 1 mg/mL (NDA 020588)
Risperdal M-Tabs (risperidone) Orally Disintegrating Tablets 0.5mg, 1mg, 2mg, 3mg, 4mg (NDA 021444)
Risperdal Consta (risperidone) Long-Acting Injection 12.5 mg, 25 mg, 37.5 mg and 50 mg (NDA 021346)

Sponsor: Janssen Pharmaceuticals, Inc.

Indication: Schizophrenia, schizoaffective disorder (Invega) & schizophrenia (Risperdal)

Supplements:

NDA	Supplement	Dated	Type	Provides for	Status
021999 Invega ER Tabs	S-034	8/3/17	CBE	Revisions to Management of Overdosage section (10.2)	Approved on 8/11/17
	S-035	11/17/17	PA	PLLR Conversion	Pending
	S-036	3/20/18	CBE	Addition of "somnambulism" to Postmarketing Experience section	Pending
022264 Invega Sustenna					
	S-015	7/11/14	PA	ES - Delay time to treatment failure in adults with schizophrenia	Approved 12/20/17
	S-027	11/17/17	PA	PLLR Conversion	Pending
	S-029	3/20/18	CBE	Addition of "somnambulism" to Postmarketing Experience section	Pending
207946 Invega Trinza	S-003	12/9/16	PA	Addition of Falls to the Warnings section as requested in 11/10/16 SLC letter	Approved on 2/23/17
	S-006	11/17/17	PA	PLLR Conversion	Pending
	S-008	3/20/18	CBE	Addition of "somnambulism" to Postmarketing Experience section	Pending

NDA	Supplement	Dated	Type	Provides for	Status
020272 Risperdal (risperidone) Tablets	S-078	12/9/16	PA	Addition of Falls to the Warnings section as requested in 11/10/16 SLC letter	Approved on 2/23/17
	S-080	11/17/17	PA	PLLR Conversion	Pending
	S-082	3/20/18	CBE	Addition of (b) (4) (b) (4)	Pending

				somnambulism" to Postmarketing Experience section	
020588 Risperdal (risperidone) Oral Solution	S-066	12/9/16	PA	Addition of Falls to the Warnings section as requested in 11/10/16 SLC letter	Approved on 2/23/17
	S-068	11/17/17	PA	PLLR Conversion	Pending
	S-070	3/20/18	CBE	Addition of (b) (4) (b) (4) somnambulism" to Postmarketing Experience section	Pending
021444 Risperdal M-Tabs (risperidone) Orally Disintegrating Tablets	S-052	12/9/16	PA	Addition of Falls to the Warnings section as requested in 11/10/16 SLC letter	Approved on 2/23/17
	S-054	11/17/17	PA	PLLR Conversion	Pending
	S-056	3/20/18	CBE	Addition of (b) (4) (b) (4) somnambulism" to Postmarketing Experience section	Pending
021346 Risperdal Consta	S-056	12/9/16	PA	Addition of Falls to the Warnings section as requested in 11/10/16 SLC letter	Approved on 2/23/17
	S-058	11/17/17	PA	PLLR Conversion	Pending
	S-060	3/20/18	CBE	Addition of (b) (4) (b) (4) somnambulism" to Postmarketing Experience section	Pending

BACKGROUND

- The three Invega formulations each have their own USPI. Whereas, Risperdal tablets (NDA 20272), Risperdal solution (NDA 20588), & Risperdal M-Tab ODT (NDA 21444) share the same labeling and Risperdal Consta injection (NDA 21346) has a standalone USPI.
- The last approved labeling (approval letter dated 2/23/17 for NDAs 020272/S-078, 020588/S-066, 021444/S-052, 021346/S-056, & 207946/S-003, approval letter dated 12/20/17 for 022264/S-015, and approval letter dated 8/11/17 for NDA 021999/S-034) was used to delineate all the changes to labeling.
- The CBE supplement revisions submitted on 3/30/18 (NDAs 020272/S-082, 020588/S-070, 021444/S-056, 021346/S-060, 022264/S-029, & 207946/S-008, & 021999/S-036) were not incorporated into this labeling nor will they be included in the labeling attached to the action letter since they are still under review.

REVIEW

021999/S-035
022264/S-027
207946/S-006
020272/S-080
020588/S-068
021444/S-054
021346/S-058
Dated: 11/17/17
CBE: No
Reviews (DARRTS):

- DPMH – 4/17/17

These supplements propose the following changes to the PI for Invega and Risperdal:

- Revisions to the US Prescribing Information (USPI) as required according to *Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*, referred to as the "Pregnancy and Lactation Labeling Rule" (PLLR, or final rule).

DISCUSSION

- Per DPP protocol for PLLR supplements, DPMH was consulted and provided a written review. Other disciplines, clinical and nonclinical in this case, also reviewed the labeling and provided language directly in the labeling document. The labeling review (and attached annotated labeling) captures the clinical and nonclinical review of the PLLR supplements.
- Labeling was edited by DPMH, the clinical team, the nonclinical team, and the Associate Director for Labeling (ADL). Labeling comments were sent to the sponsor and several rounds of negotiation occurred prior to final agreement. The review team (which included DPP management, the ADL, DPMH representatives, and the clinical and nonclinical teams) met multiple times to discuss labeling prior to initiation of and during labeling negotiation. Differences between the final agreed upon language and that found in the original DPMH review, were discussed and agreed upon by team members.
- Beyond the PLLR revisions, other revisions were requested to ensure consistency throughout the class and consistency with PLR formatting requirements (see below):
    - Revisions to the Patient Counseling Information –
        - Removal of numbering throughout the section (e.g., removed 17.1, 17.2 … etc.),
        - Removal of existing Pregnancy and Nursing subsections,
        - Addition of the following subsections: Pregnancy, Lactation, and Infertility;
    - Removal of Recent Major Changes (RMC) in Highlights that are greater than one year old;

- Revised the Warnings and Precautions – Tardive Dyskinesia section (section 5.5 for Invega, Invega Sustenna, Invega Trinza and section 5.4 for Risperdal, Risperdal Consta) based upon recent drug approvals;
- Revised revision date in Highlights;
- For Risperdal Consta and Invega, the Boxed Warning (BW) in the Full Prescribing Information (FPI) and the corresponding Warnings and Precautions (section 5.1) was switched for consistency with other labels in the class (i.e., the language in the BW was placed in section 5.1 and the language in section 5.1 was placed in the FPI BW). It should be noted that the language was not altered. Thus, the change was not considered a "substantive change," and not listed under Recent Major Changes (RMC);
- In the Patient Package Inserts (PPIs) for Invega Sustenna and Invega Trinza, the "**What should I tell my healthcare provider before receiving …"** section, was updated to include pertinent information from sections 8.1 and 8.2.

- There was additional discussion about the withdrawal terms in the parenthetical under Risk Summary (i.e., the terms did not align with the withdrawal symptoms listed under Clinical Considerations - Fetal/Neonatal Adverse Reactions). This also applied to Section 17 under Pregnancy, and the adverse event terms were not listed in the Highlights-Pregnancy section. Although the sponsor agreed that the adverse event terms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) should be consistent, they argued that the terms should only be listed in section 8.1 under the Clinical Considerations-Fetal Neonatal Adverse Reactions section with only a cross reference in Pregnancy-Risk Summary (8.1), and Pregnancy (17) sections. This was based upon other atypical antipsychotic drug labels such as Vraylar, Rexulti, and Saphris which are already in PLLR format. The Agency agreed that where applicable, there should consistency across the class.

CONCLUSIONS

1. These PA labeling supplements only provide for the revisions as stated above when compared to the last approved labeling (see Background section above). This review does not encompass CBE labeling supplement, noted above, since they are still under review.
2. The sponsor agreed to labeling revisions in an e-mail dated 7/27/18.
3. Given that the sponsor has adequately revised their labeling to encompass our requested revisions, I recommend that an approval letter for these pending supplemental applications.

{See appended electronic signature page}

Paul David, RPh
Chief, Project Management Staff

{See appended electronic signature page}

Kimberly Updegraff, RPh, MS, RAC
Associate Director for Labeling

Attachment: 1) Annotated Labeling denoting differences between last approved labeling and final, agreed upon, labeling, and 2) labeling e-mail agreement from the Sponsor

290 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

David, Paul A

From: Updegraff, Kimberly
Sent: Friday, July 27, 2018 1:39 PM
To: David, Paul A
Subject: Risperdal and Invega PLLR labeling

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Friday, July 27, 2018 12:41 PM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>
Subject: RE: Risperdal and Invega PLLR labeling

Hi Kim,

We are in agreement with the labeling text provided in my email of Thursday that you referenced below and with the new highlighted text that you provided in the evening.

Best,
Beth

From: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Sent: Friday, July 27, 2018 12:24 PM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Subject: RE: Risperdal and Invega PLLR labeling

Thank you, Beth. A response by 1:00 pm would be appreciated. Kim

---

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Friday, July 27, 2018 10:31 AM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: RE: Risperdal and Invega PLLR labeling

Hi Kim,

Yes, I did. I will get back to you shortly with our final response.

Beth

From: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Sent: Friday, July 27, 2018 10:27 AM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: Risperdal and Invega PLLR labeling

Dear Beth,

I wanted to confirm that you received the email below.

Thank you,

Kim

From: Updegraff, Kimberly
Sent: Thursday, July 26, 2018 6:10 PM
To: 'Geter-Douglass, Beth [JRDUS]' <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>; Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Subject: Risperdal and Invega PLLR labeling

Hi Beth,

I discussed with the team and we are in agreement with the labeling included with the email below.

Please note that the Risperdal and Invega Sustenna labels do not include the phrase highlighted below in section 8.1. We plan to include the phrase a part of the labeling agreement. Risperdal Consta, Invega, and Invega Trinza appropriately include the phrase.

Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including RISPERDAL CONSTA®, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
Risk Summary
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including RISPERDAL CONSTA®, during pregnancy *(see Clinical Considerations)*. Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® *[see Clinical Pharmacology (12.3)]*. The clinical significance of RISPERDAL CONSTA® administered before pregnancy or anytime during pregnancy is not known.

Please let me know if you have any questions.

Best regards,

Kim

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Thursday, July 26, 2018 9:48 AM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: RE: Risperdal and Invega PLLR labeling

Hi Kim,

Attached is our response to the Division's latest comments. I have included both Clean and Marked versions of all of the labels.

Beth

From: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Sent: Wednesday, July 25, 2018 5:28 PM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: RE: Risperdal and Invega PLLR labeling

Okay, Beth. I discussed briefly with the team and they prefer to keep the language currently found in Invega Trinza – "Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder …"

I also should of noted in my previous email that the change applies to HL and section 17.

I look forward to your response.

Kim

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Wednesday, July 25, 2018 5:22 PM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: RE: Risperdal and Invega PLLR labeling

Hi Kim,

Please disregard my last e-mail. The team is looking into the Division's response in more depth and we will have a formal response for you in the morning as requested.

Regards,
Beth

From: Geter-Douglass, Beth [JRDUS]
Sent: Wednesday, July 25, 2018 3:45 PM
To: 'Updegraff, Kimberly' <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>
Subject: RE: Risperdal and Invega PLLR labeling

Hi Kim,

This issue was discussed within our Team and it was decided to include (b) (4), in the parenthetical where it is (across all 5 USPIs) because it is a symptom of withdrawal. Based on this reasoning, does the Division agree with assessment?

Beth

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Wednesday, July 25, 2018 3:25 PM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; David, Paul A <Paul.David@fda.hhs.gov>; Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>

Subject: Risperdal and Invega PLLR labeling
Importance: High

Dear Beth,

Thank you for providing the labels for the Risperdal and Invega products. As we reviewed the documents, we found a discrepancy in section 8.1. The withdrawal terms in the parenthetical under Risk Summary should align with the withdrawal symptoms listed under Clinical Considerations - Fetal/Neonatal Adverse Reactions.

The same applies to section 17 under Pregnancy.

Please see the attached Risperdal label for the annotated change and comments.

If your team is amendable to the changes, we will make the edits to the documents (across the 5 labels) you sent in your email dated 7/24/18. There is no need to send additional labeling in your response.

We request a response as soon as possible but no later than 10:00 AM tomorrow (Thursday, July 7/25/18).

Thank you,

Kim

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Tuesday, July 24, 2018 11:27 PM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>
Subject: RE: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Hi Kim,

As requested, attached are the Clean and Marked versions of the agreed upon PLLR labels for risperidone and paliperidone. Please note that these are Word .doc files and not .docx files.

Best,
Beth

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Tuesday, July 24, 2018 4:45 PM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>; Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Subject: RE: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Dear Beth,

Please see the attached labels for Risperdal Consta and Invega. Our changes are tracked and are accompanied by highlighted comments. As discussed earlier, our proposed formatting change is shown under RMC in HL and section 5.1.

We do not have any further changes to the Risperdal, Invega Sustenna, or Invega Trinza labels included in your 7/23/18 email.

We ask that you confirm labeling agreement for the 5 labels and include clean labeling in your response.

Let me know if you have any questions.

Best regards,

Kim

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Monday, July 23, 2018 5:33 PM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>
Subject: RE: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Hi Kim,

Thanks for your patience. Attached are our latest responses to the PLLR labeling text.

Best,
Beth

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Monday, July 23, 2018 5:20 PM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>
Cc: Tan, James [JRDUS] <JTan7@its.jnj.com>
Subject: RE: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Hi Beth,

Just checking to see if you are planning to respond to the labeling proposal this evening.

Thank you,

Kim

From: Geter-Douglass, Beth [JRDUS] [mailto:BGeterdo@its.jnj.com]
Sent: Thursday, July 19, 2018 9:52 AM
To: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>; Tan, James [JRDUS] <JTan7@its.jnj.com>
Subject: RE: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Thank you Kim. I will alert the Team.

Beth

From: Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]
Sent: Thursday, July 19, 2018 9:47 AM
To: Geter-Douglass, Beth [JRDUS] <BGeterdo@its.jnj.com>; Tan, James [JRDUS] <JTan7@its.jnj.com>
Cc: Updegraff, Kimberly <Kimberly.Updegraff@fda.hhs.gov>
Subject: NDAs 20272/S080; 20588/S068; 21444/S054 - Risperdal Tablets/Solution/ODT- PLLR labeling

Dear Drs. Geter-Douglass and Tan,

Please refer to your supplemental New Drug Applications for Risperdal (Tablets/Solution/ODT) and Risperdal Consta submitted and received on November 17, 2017.

Please review the attached labeling that contains our edits and comments to your 6/18/18 response.

We request a response (i.e., agreement with the proposed labeling or comments), as soon as possible, but no later than Monday, July 23, 2018.

Best regards,

Kim

Kimberly Updegraff, RPh, MS, RAC
……..
Associate Director for Labeling
Division of Psychiatry Products
Office of Drug Evaluation I
Food and Drug Administration
301-796-2201

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PAUL A DAVID
07/27/2018

KIMBERLY S UPDEGRAFF
07/27/2018

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Review

Date: 4/16/2018 **Date consulted:** 1/29/2018

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, D.O., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products

Drug: RISPERDAL (risperidone)
RISPERDAL Solution (risperidone)
RISPERDAL Orally Disintegrating Tablet (risperidone)
RISPERDAL CONSTA (risperidone)
INVEGA (paliperidone)
INVEGA SUSTENNA (paliperidone palmitate)
INVEGA TRINZA (paliperidone palmitate)

NDA: 20272/S-080, 20588/S-068, 21444/S-054, NDA 21346/S-058, 21999/S-035, 22264/S-027, 207946/SS-006

Applicant: Jansen Pharmaceuticals

Subject: Pregnancy and Lactation Labeling

Indication: *Risperdal NDA 20272; Risperdal Oral Solution NDA 20588; Risperdal Orally Disintegrating tablet NDA 21444*

- Treatment of schizophrenia
- As monotherapy or adjunctive therapy with lithium or valproate for the treatment of acute mania or mixed episodes associated with Bipolar I Disorder
- Treatment of irritability associated with autistic disorder

Risperdal Consta NDA 21346

- Treatment of schizophrenia
- As monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder

Invega NDA 21999

- Treatment of schizophrenia adults and adolescents (12-17)
- Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and antidepressants in adults

Invega Sustenna NDA 22264

- Treatment of schizophrenia in adults
- Treatment of schizoaffective disorder in adults as an adjunct to mood stabilizers or antidepressants

Invega Trinza NDA 207946

- Treatment of schizophrenia in patients after they have been adequately treated with Invega Sustenna for at least 4 months

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 20272/S-080, 20588/S-068, NDA 21444/S-054, NDA 21346/S-058, NDA 21999/S-035, NDA 22264/S-027, NDA 207946/SS-006.
- DPMH review of INVEGA TRINZA (paliperidone palmitate) NDA 2079461, Leyla Sahin, M.D., April 17, 2015. DARRTS Reference ID 3741973
- DPMH consult request dated January 29, 2018, DARRTS Reference ID 4214923

Consult Question: "The Division is seeking DPMH input to confirm that the language the Sponsor provided is accurate and appropriate, as well as assistance in aligning PLLR format across the risperidone/paliperidone product line."

INTRODUCTION

The Division of Psychiatry Products consulted the Division of Pediatric and Maternal Health (DPMH) on January 29, 2018, to review the Pregnancy and Lactation sections of RISPERDAL CONSTA (risperidone), RISPERDAL (risperidone), RISPERDAL Oral Solution (risperidone), RISPERDAL Orally Disintegrating Tablets, INVEGA TRINZA (paliperidone), INVEGA (paliperidone), and INVEGA SUSTENNA (paliperidone) labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule (PLLR) formatting requirements.

REGULATORY HISTORY

- On November 17, 2017, the applicant, Jansen Pharmaceuticals submitted prior approval labeling supplements for conversion to PLLR formatting for the following products: RISPERDAL NDA 20272, RISPERDAL Oral Solution NDA 20588, RISPERDAL ODT NDA 21444, RISPERDAL CONSTA NDA 21346, INVEGA NDA 21999, INVEGA SUSTENNA NDA 22264, and INVEGA TRINZA NDA 207946.

BACKGROUND

Drug Characteristics[1,2,3,4,5]

- Risperidone and paliperidone are atypical antipsychotic agents and are also known as second-generation antipsychotics (SGAs).
- The exact mechanism of action is unknown; however, it has been proposed that the therapeutic activity in schizophrenia is mediated through dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) receptor antagonism.

NDA 20272 Risperdal, 20588 Risperdal solution, 21444 Risperdal ODT

- The molecular weight for risperidone is 410.49 Daltons.
- The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%.
- The overall mean elimination half-life for risperidone is approximately 20 hours.
- The absolute oral bioavailability of risperidone is 70%.
- Known serious adverse events for risperidone include cerebrovascular events, including stroke, neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, including hyperglycemia, dyslipidemia and weight gain, hyperprolactinemia, orthostatic hypertension, leukopenia, potential for cognitive and motor impairment and seizures.

NDA 21346 Risperdal Consta

- The molecular weight for risperidone is 410.49 Daltons.
- The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone, is 77%.
- The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA administration is 3-6 days.
- Known serious adverse events for RISPERDAL CONSTA include all of those listed for Risperdal (above) with the following additional serious adverse events: dysphagia, priapism, thrombotic thrombocytopenic purpura (TTP), suicide, increased sensitivity in patients with Parkinson's disease or Lewy bodies, use with caution in patients with recent myocardial infarction or unstable cardiac disease.

NDA 21999 Invega Tablets

- The molecular weight for paliperidone is 426.49 Daltons.
- The plasma protein binding of racemic paliperidone is 74%.
- The terminal elimination half-life for paliperidone is approximately 23 hours.
- The absolute oral bioavailability of paliperidone following Invega administration is 28%.
- Known serious adverse events for paliperidone include cerebrovascular adverse reactions, neuroleptic malignant syndrome, QT prolongation, tardive dyskinesia, metabolic changes, including hyperglycemia, dyslipidemia and weight gain, hyperprolactinemia, gastrointestinal narrowing, orthostatic hypertension and syncope, leukopenia, potential for cognitive impairment, seizures, and suicide.

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[1] Risperdal Proposed Package Insert
[2] Risperdal Consta Proposed Package Insert
[3] Invega Proposed Package Insert
[4] Invega Sustenna Proposed Package Insert
[5] Invega Trinza Proposed Package Insert

NDA 22264 Invega Sustenna and NDA 207946 Invega Trinza

- The molecular weight of paliperidone palmitate is 664.89 Daltons.
- The plasma protein binding of racemic paliperidone is 74%.
- The median apparent half-life of paliperidone following Invega Sustenna administration over the dose range of 39mg to 234 mg ranged from 25 – 49 days.
- The mean apparent half-life of paliperidone following Invega Trinza administration over the dose range of 273-819 mg ranged from 84-95 days following deltoid injections and 118-139 days following gluteal injections.
- Known serious adverse events include those listed for Invega (above) without the following serious adverse event, gastrointestinal narrowing.

Schizophrenia and Pregnancy

- Schizophrenia is seen in less than 1 % of the adult population. Women generally have a later age of onset (twenties to thirties) than men do (late teens to early twenties). It is slightly more prevalent in men compared to women (1.4:1).[6]
- Untreated schizophrenia is associated with increased all-cause mortality, hospitalization, and risk of suicide.[7,8]
- Schizophrenia is commonly comorbid with cigarette use and substance abuse; approximately 62% of patients with schizophrenia smoke.[9]
- Pregnancy and schizophrenia are associated with the following adverse obstetrical outcomes: prematurity, low birth weight, small-for-gestational age, still birth, and low APGAR scores. It is not known if the adverse obstetrical outcomes are due to the disease itself or due to the social circumstances (lack of prenatal care, poor eating habits, smoking, use of illicit drugs) of pregnant women with schizophrenia.[10,11]

Bipolar Disorder and Pregnancy

- The lifetime prevalence of bipolar I disorder in the U.S. is 1.0%, and is approximately equally prevalent in men and women.[12]
- Average age of onset is 21 years of age.[13]
- Untreated bipolar disorder is associated with increased risk of substance abuse, suicide and all-cause mortality.[14]

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[6] McGrath J, et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.

[7] Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. J Psychopharmacol. 2010;24(4Suppl):81-90.

[8] Kane JM, et al. Comprehensive versus usual community care for first episode psychosis: 2 year outcomes from the NIMH RAISE early treatment program. Am J Psychiatry. 2016; 173(4):362-72.

[9] Dickerson F, et al. Cigarette smoking by patients with serious mental illness, 1999-2016: an increasing disparity. Psychitr Serv. 2018;69(2):147-153.

[10] Robinson, G. (2012). Treatment of Schizophrenia in Pregnancy and Postpartum. J Popul Ther Clin Pharmcol, 19 (3):e380-e386.

[11] Einarson, A and Boskovic, R. Use and safety of antipsychotic drugs during pregnancy. J Psychiatr Pract. 2009. 15 (3): 183-92.

[12] Harvard Medical School 2007. National Comorbidity Survey (NCS) Retrieved from https://www.hcp.med.harvard.edu/ncs/index.php. Lifetime prevalence DSM-IV/WMH-CIDI disorders by sex and cohort. Accessed 3/19/2018

[13] Merikangas KR, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2007;64:543-552.

- Women with bipolar disorder are at high risk for relapse during pregnancy. A prospective observational clinical cohort study followed 89 women with bipolar disorder who either maintained or discontinued treatment during pregnancy. The overall risk of recurrence was 71%. Among women who discontinued versus continued treatment with a mood stabilizer, recurrence risk was two-fold greater, the time to recurrence was four-fold shorter, and the number of weeks ill was five times greater.[15]
- Women with Bipolar I disorder are at increased risk for adverse perinatal outcomes, including: preterm birth, low birth weight, gestational hypertension, antepartum hemorrhage, small for gestational age infants and large for gestational age (LGA) infants.[16,17] It is not known if these adverse outcomes are from the illness itself or comorbid conditions (poor eating habits, smoking, use of illicit drugs.)

Current State of the Labeling

These products have various labeling formats as describe below. All of the products have a boxed warning for increased mortality in elderly patients with dementia-related psychosis, and no boxed warning for embryofetotoxicity. There are no listed pregnancy testing/contraception recommendations or listed drug-drug interactions with hormonal contraceptives for any of these products.

Drug name/NDA #	Year of Approval	Labeling Format	Highlights	Pregnancy info.	Lactation info.
RISPERDAL NDA20272[18]	December 29, 1993	PLLR-hybrid	-Pregnancy- Based on animal data, may cause fetal harm Nursing mothers- discontinue drug or nursing	Category C Human data presented	- risperidone and 9-hydroxyrisperidone are present in human breast milk.
RISPERDAL Solution NDA 20588[19]	June 10, 1996	PLLR-hybrid	Pregnancy- Based on animal data, may cause fetal harm Nursing mothers- discontinue drug or nursing	Category C Human data presented	- risperidone and 9-hydroxyrisperidone are present in human breast milk.

[14] Hayes JF, et al. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. Br J Psychiatry. 2017;211(3_:175-181.
[15] Viguera A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry. 2007;162:1817-1824.
[16] Rusner M, et al. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. BMC Pregnancy Childbirth. 2016;16(1):331.
[17] Mei-Dan E, et al. Perinatal outcomes among women with bipolar disorder: a population-based cohort study. Am J Obstet Gynecol. 2015;212(3):367.
[18] RISPERDAL (risperidone) approved package insert. Drugs@FDA, accessed 2/15/2018
[19] RISPERDAL Solution (risperidone) approved package insert. Drugs@FDA, accessed 2/15/2018

RISPERDAL ODT 21444[20]	April 2, 2003	PLLR-hybrid	Pregnancy- Based on animal data, may cause fetal harm Nursing mothers- discontinue drug or nursing	Category C Human data presented	- risperidone and 9-hydroxyrisperidone are present in human breast milk.
RISPERDAL CONSTA/NDA21 346[21]	October 29, 2003	PLR	Nursing mothers- should not breastfeed	-Pregnancy Category C -statement that neonates exposed to antipsychotics during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms	- risperidone and 9-hydroxyrisperidone are present in human breast milk - women should not breastfeed during treatment with RISPERDAL CONSTA and for at least 12 weeks after the last injection.
INVEGA/NDA 21999[22]	December 19, 2006	PLR	-Nursing Mothers: Benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone	Pregnancy Category C -The first generation of antipsychotic drugs has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is unknown whether paliperidone when taken near the end of pregnancy will lead to similar signs and symptoms.	Paliperidone is excreted in human breastmilk

[20] RISPERDAL ODT (risperidone) approved package insert. Drugs@FDA, accessed 2/15/2018
[21] RISPERDAL CONSTA (risperidone) approved package insert. Drugs@FDA, accessed 2/15/2018
[22] INVEGA (paliperidone) approved package insert, Drugs@FDA, accessed 2/15/2018

INVEGA SUSTENNA NDA 22264	July 31, 2009	PLLR-hybrid	Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure	Category C Clinical Considerations and Human Data subheadings related to neonatal extrapyramidal symptoms	-in animal studies, paliperidone was excreted in milk -discontinue nursing or discontinue the drug
INVEGA TRINZA NDA 207946	May 18, 2015	PLLR	Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.	-Pregnancy Registry information -Clinical Considerations and Human Data subheadings related to neonatal extrapyramidal	Paliperidone is present in human breast milk, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant or the effects on milk production.

REVIEW

PREGNANCY

Nonclinical Experience

Risperidone (b) (4) at doses up to 6-times the MRHD of 16 mg/day risperidone on a mg/m2 basis (b) (4) (b) (4), learning was impaired. (b) (4) neuronal cell death (b) (4) in the fetal brains o (b) (4) offspring o (b) (4) rat (b) (4) (b) (4) postnatal development and growth of the offspring was delayed.

Paliperidone- No increases in fetal abnormalities (b) (4) when (b) (4) (b) (4) pregnant rats and rabbits (b) (4) up to 8-times the MRHD of 12 mg/day (b) (4)

The reader is referred to the Pharmacology/Toxicology review by Sonia Tabacova Ph.D., and Aisar Atrakchi, Ph.D.

Applicant's Review of Literature

The applicant conducted a search using MEDLINE, Embase, Derwent Drug File, and BIOSIS databases through February 9, 2017. Search terms included risperidone and paliperidone formulations and "pregnancy," "lactation," and "reproductive potential" terms.

First Trimester Exposure and Congenital Malformations

The applicant referred to a previous search of the literature[23] through November 22, 2016 of thirty publications related to risperidone and paliperidone and congenital malformations that was triggered by the publication of Huybrechts, et al.[24] The Huybrechts' study is a cohort study of pregnancies from the US Medicaid Analytic Extract Database, 9258 of whom filled a prescription for an atypical antipsychotic during the first trimester (risperidone n=1566). Huybrechts did not indicate an increased risk of birth defects overall, but did find a small, but significant increase in birth defects with risperidone. Details of this study and other large cohort studies reviewed by the applicant are in Appendix B.

The applicant also reported on results of two meta-analyses.

- Ennis et al. performed a meta-analysis of SGA exposure and congenital anomalies based on 12 cohort studies, 25 case reports, and data from the Swedish Birth Registry. Eight studies included exposures to risperidone. Twenty-two malformations were seen in 432 exposed pregnancies, for a malformation rate of 5.1%. The relative risk estimate was 1.4 (0.9-2.2). The data did not allow for estimates of specific anomalies.[25]
- Terrano et al. reported on 12 studies published in the literature from January 1990 to December 2014 with a total of 1782 cases of SGA exposure (including 314 risperidone exposures) and 1,322,749 controls. The odds ratio for major congenital anomalies was higher for infants exposed to SGAs that controls (OR=2.03, 95%CI=1.41-2.93). There was no specific pattern of malformations. Risperidone was not analyzed separately. Limitations of the studies reviewed include lack of adequate controls, lack of assessment of severity of illness, and other comorbid diagnoses or concomitant medications.[26]

The applicant concluded that the findings of the studies were inconsistent due to a wide variation in study design, inclusion of different antipsychotic medications, and presence of confounding factors, and that no labeling changes were necessary.

The applicant also supplied information regarding the cumulative post-marketing exposure to risperidone and paliperidone in person-years from inception to October 31, 2016, which was (b) (4) and (b) (4) person-years, respectively.

Reviewer comment:
This reviewer agrees with the applicant that there are methodological limitations with most of the studies reviewed above; most are underpowered, and do not have adequate comparison groups to minimize confounding by diagnosis, severity, comorbid medical and psychiatric illness, smoking and concomitant medications. Huybrechts et al., provides the best estimate of birth defects associated with risperidone, given the large sample size and efforts to minimize error due to confounding. The authors stated that the results of the study are not conclusive and require further study, but it is information that might be helpful in labeling under Human Data. Given the many

[23] Risk of congenital malformations after first trimester exposure to risperidone or paliperidone. Janssen Research and Development. January 23, 2017.
[24] Huybrechts KF, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry. 2016.73(9):938-46.
[25] Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole, and the risk of congenital malformations. A systematic review. Basic Clin Pharmacol Toxicol. 2015. 116(4):315-20.
[26] Terrana N, et al. Pregnancy outcomes following in utero exposure to second generation antipsychotics: a systematic review and meta-analysis. J Clin Psychopharmacol. 2015. 35(5):559-65.

years of exposure, particularly to risperidone, a major teratogen signal would likely have been detected.

Neonatal extrapyramidal and/or withdrawal symptoms.
The applicant reports on a paper published by their research and development group in 2007,[27] that describes twenty–one cases of jitteriness, irritability, feeding problems, seizures, or somnolence that the authors describe as a "withdrawal emergent syndrome" occurring after third trimester exposure to risperidone. The cases are described as usually resolving within a few days without intervention. No other references were described by the applicant. The applicant noted that there is already a statement about the risk of extrapyramidal and/or withdrawal symptoms in risperidone and paliperidone labeling, and concluded that no changes are needed in labeling.

Reviewer comment:
Current labeling for antipsychotics as a class has language regarding the risk for "neonatal extrapyramidal and/or withdrawal symptoms" with third trimester use of antipsychotics. A more recent study comparing 133 SGA exposed mother-infant pairs with a comparison group of 133 unexposed pairs found poor neonatal adaptation (CNS symptoms, irritability, respiratory problem) and NICU admissions were more common (p=0.002) in the exposed group. However, the majority of these cases were exposed to multiple psychotropic medications; it is not known whether these symptoms are due to toxicity or withdrawal from antipsychotics. Consideration may be given to changing the terminology from withdrawal to poor neonatal adaptation, similar to antidepressants.

Gestational Diabetes
The applicant performed a search related to metabolic changes in pregnancy, since risperidone and paliperidone use may result in hyperglycemia, weight gain, diabetes, and dyslipidemia. Two articles were found.

- A study using administrative health databases in Canada, studied women with infants born between April 1, 2003 and December 31, 2012. Women had to have ≥ 2 antipsychotic prescriptions during pregnancy. Women on antipsychotic medication (n=1021) were matched with non-users. Diabetes was documented in 4.1% of non-users and 3.8% of antipsychotic users. The risk of gestational diabetes was not different between the groups (RR=1.10, 95%CI=0.77-1.57). A sub-analysis with risperidone users specifically was also not significant. This paper also reported that there was no increased risk of hypertensive disorder of pregnancy with the use of antipsychotics (the number of risperidone users was too small for a relative risk calculation).[28]
- A study using data from the Swedish Medical Birth Register, the Register of Congenital Malformations, and the Hospital Discharge Register examined women and infants with early pregnancy exposure to antipsychotics (n=570) versus all births (973,767). There was a higher risk for gestational diabetes in the antipsychotics group (OR=1.78, 95%CI=1.04=3.01). Only one case was related to risperidone use.[29]

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[27] Coppola D, et al. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Safety. 2007. 30(3):247-264.
[28] Vigod SN, et al. Antipsychotic use during pregnancy: high dimensional, propensity matched, population-based cohort study. BMJ. 2015;350:h2298.
[29] Reis M, Kallen B. Maternal use of antipsychotics in early pregnancy and delivery outcome. J Clin Psychopharmacol. 2008;28:279-288.

The applicant concluded there was no strong evidence for increased risk of gestational diabetes with risperidone or paliperidone use.

Reviewer comment:
An additional reference from the National Pregnancy Registry for Atypical Antipsychotics (see DPMH literature review) does not show an increased risk for gestational diabetes in women exposed to SGAs during pregnancy. This reviewer agrees with the applicant; the results of these studies do not provide a clear drug-associated risk for gestational diabetes. Metabolic changes, including an increased risk for developing diabetes, are already included in the Warnings and Precautions section of labeling.

Spontaneous abortion and stillbirth
The applicant reported on one article related to risperidone and stillbirth/spontaneous abortion, but some of the previously mentioned papers from the applicant's search also provide rates related to spontaneous abortion and are listed below.

- A study examined all clinically recognized pregnancies in the Danish registries from February 1 1997- December 31, 2008 (n=1,005,319). Exposure to antipsychotics was defined as any prescription given the 30 days prior to conception to the day of the spontaneous abortion or stillbirth. Unexposed women were defined as those who did not redeem any prescription during the exposure window. Women in the antipsychotic group had a higher risk of spontaneous abortion than unexposed women (adjusted RR=1.34, (95%CI=1.22-1.46), but similar to women exposed to antipsychotics prior to but not during pregnancy (adjusted RR=1.04, 95%CI=0.93-1.17). Risperidone exposure occurred in 116 cases, with 25 (21.6%) spontaneous abortions. There was a two-fold increase in stillbirth with exposure to any antipsychotic. The authors concluded that the increase in spontaneous abortion and stillbirth might have been due to confounding factors, since underlying health issues, severity of illness, and dose of medication, were not considered in the analysis and because in a previous study the risk of stillbirth and spontaneous abortion was greater in women with psychiatric diagnoses.[30]
- The paper by Coppola, previously referenced, reported a spontaneous abortion rate of 16.9% in pregnancies exposed to risperidone.[31]
- A prospective cohort study of women taking SGAs (n=151), including 49 women taking risperidone, had an overall spontaneous abortion rate of 14.5%.[32] A specific analysis for risperidone was not performed.

Reviewer Comment:
While these studies often have confounding issues related to severity of illness, concomitant medications and other factors, the risk of spontaneous abortion with risperidone appears within the background risk of 15-20%.

Preterm Birth
The applicant reported on studies related to preterm birth and risperidone use.

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[30] Sorensen MJ, et al. Risk of fetal death after treatment with antipsychotic medications during pregnancy. PLoS One. 2015;10(7):e0132280.
[31] Coppola D, et al. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Safety. 2007. 30(3):247-264.
[32] McKenna K, et al. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective cohort study. J Clin Psychiatry. 2005;66:444-449.

- Terrana, et al, (previously reported on under the subheading *Congenital Anomalies*) found an increased risk of preterm birth in women exposed to SGAs compared to women not exposed to SGAs (odds ratio, 1.85; 95% CI 1.20–2.86).[29]
- A high dimensional propensity matched population-based cohort study of women from an administrative health database in Canada taking SGAs during pregnancy (n=1021) and women not taking SGAs matched for diagnoses, age, hospitalization, procedures, and other factors (n=1021) did not find an increased risk of preterm birth between the groups.[33]

Neurodevelopmental Outcomes

- A study by Shao[34], et al. followed the developmental progress of thirty-three infants who had exposure to either clozapine (n=33) or other SGAs (risperidone, olanzapine or quetiapine) throughout pregnancy (risperidone n=16). Infants were assessed at 2, 5, and 12 months of age with the Bayley-III instrument for cognitive, language, motor, social, and emotional development. More clozapine-exposed infants had lower adaptive behavior scores at 2 and 6 months of age compared to the other SGA group. This difference was not apparent at 12 months.

Placental Passage

- A study by Newport, et al. describes a study of 54 pregnant women taking a stable daily dose of antipsychotics (minimum of 2 weeks) prior to delivery who had maternal and umbilical cord blood collected and assayed for the medication used. For the six patients taking risperidone, the placental passage was calculated to be an average of 49.2%.[35]

<u>DPMH Review of Literature</u>

DPMH conducted a search of the literature using PubMed, Embase, Reprotox, and Micromedex[36] using the search terms, "risperidone" or "paliperidone" and "pregnancy," "pregnancy outcomes," "congenital anomalies," "stillbirth," and "spontaneous abortion."

Reprotox[36] states, "Based on experimental animal studies and limited human experience, therapy with risperidone during pregnancy is not anticipated to increase the risk of congenital anomalies."

Briggs[37] states, "Although no structural malformations attributable to risperidone have been reported, the number of exposures is too low to fully assess the embryo-fetal risk. In addition, there is a risk of extrapyramidal and/or withdrawal symptoms in the newborn if the drug is used in the 3rd trimester. Nevertheless, risperidone is indicated for severe debilitating mental disease and the benefits to the mother appear to outweigh the potential embryo-fetal risks. The Pregnancy recommendation is Compatible- Maternal Benefit >> Embryo-Fetal Risk."

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[33] Vigod SN, et al. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. BMJ. 2015;350:h2298.

[34] Shao P, et al. Effects of clozapine and other atypical antipsychotics on infants development who were exposed to as fetus: a post-hoc analysis. PLoS One. 2015;10(4):e0123373.

[35] Newport DJ, et al. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. Am J Psychiatry. 2007;164:1214-1220.

[36] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 1/14/2018

[37] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Chapter on Risperidone. 10th Ed. 2015. Online, accessed 3/16/2018

For paliperidone, Briggs[38] states, "No reports describing the use of paliperidone, the active metabolite of risperidone, in human pregnancy have been located. Developmental toxicity, in the absence of maternal toxicity, was not observed in two animal species. Risperidone was carcinogenic in rodents, but the relationship of this effect to humans has not been studied. Although there are no human pregnancy data with paliperidone, there are limited data for risperidone. The Pregnancy recommendation is No human data- Animal data suggest low risk."

A search of the published literature revealed the following additional reports:

- A report from the National Pregnancy Registry for Atypical Antipsychotics describing 214 women with first trimester exposure to SGAs during pregnancy and 89 comparison women. There were three congenital anomalies in the exposed group and one in the unexposed group. None of the three cases had exposure to risperidone. The odds ratio of major malformations in infants exposed to SGAs in this sample was 1.25 (95% CI=0.13-12.9).[39]
- A report from the National Pregnancy Registry for Atypical Antipsychotics examined the risk of gestational diabetes in 303 women exposed to SGAs compared to 149 unexposed women. After adjustment for maternal age, race, marital status, employment status, level of education, smoking and primary psychiatric diagnosis, there was no increased risk of gestational diabetes for SGA exposure (adj OR 0.79 (0.40-1.56).[40]
- An abstract of a retrospective review of 56 pregnant women who took antipsychotics or mood stabilizers at some point during pregnancy (risperidone n=5). No correlation was found between medications studied and adverse outcomes.[41]
- A systematic review of studies examining the neurodevelopmental outcomes in infants exposed *in utero* to antipsychotics, including risperidone. The authors reported that the studies were of limited clinical relevance due to their small sample size and that no conclusions could be drawn from the data.[42]

Review of Pharmacovigilance Database

Risperidone

The applicant provided a cumulative review of its Global Medical Safety database through November 1, 2016, to examine the risk of congenital malformations following first trimester exposure to risperidone or paliperidone. Sixty-three cases with a total of 105 congenital malformations were reported by the applicant. Of the 63 cases, 17 were reported to have limited information; thirty-five had concomitant medication use and/or maternal medical conditions.

[38] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Chapter on Paliperidone. 10th Ed. 2015. Online, accessed 3/16/2018

[39] Cohen LS, et al. Reproductive safety of second –generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Am J Psychiatry. 2016;173:263-270.

[40] Panchaud A, et al. Use of atypical antipsychotics in pregnancy and maternal gestational diabetes. J Psychiatr Res. 2017;95:84-90.

[41] Moller-Olsen C, et al. Mood stabilizer and antipsychotic utilization among maternal mental health service users in pregnancy. Australian and New Zealand J Psychiatry. 2016;Suppl 1:161-162.

[42] Gentile S and Fusco ML. Neurodevelopmental outcomes in infants exposed in utero to antipsychotics: a systematic review of the published data. CNS Spectrums. 2017;22(3):273-281.

Distribution of Preferred Terms for Cases of Risperidone Reporting Congenital Malformations Received Cumulatively Through 01 November 2016 (n=63)[43]

Congenital Malformations PTs[a]	Number of Cases[b]
Atrial septal defect[c]	7
Ventricular septal defect	6
Talipes	5
Congenital anomaly	4
Congenital central nervous system anomaly	4
Patent ductus arteriosus	4
Oesophageal atresia	3
Anal atresia	2
Cleft lip and palate	2
Congenital foot malformation	2
Cryptorchism	2
Developmental hip dysplasia	2
Dysmorphism	2
Facial paralysis	2
Foetal alcohol syndrome	2
Pierre Robin syndrome	2
Pulmonary artery stenosis congenital	2

[43] Cumulative review of congenital malformation cases with use of risperidone, paliperidone palmitate and paliperidone. Janssen Research and Development, LLC. February 6, 2017.

Table 2: Distribution of Preferred Terms for Cases of Risperidone Reporting Congenital Malformations Received Cumulatively Through 01 November 2016 (n=63)

Congenital Malformations PTs[a]	Number of Cases[b]

Key: CIOMS= Council for International Organizations of Medical Sciences;
MedDRA= Medical Dictionary for Regulatory Activities; n= Number; PT= Preferred Term.

a: MedDRA PTs with ≥2 frequency has been reported. MedDRA PTs reported once include: Anomaly of external ear congenital, Aortic stenosis, Arachnoid cyst, Atrioventricular septal defect, Brain malformation, Cardiac aneurysm, Cardiomyopathy, Cerebral palsy, Chondrodystrophy, Cleft lip, Cleft palate, Coarctation of the aorta, Congenital brain damage, Congenital heart valve disorder, Congenital hydronephrosis, Congenital musculoskeletal anomaly, Congenital neurological disorder, Congenital ureteric anomaly, Deafness, Dextrocardia, Ear malformation, Ebstein's anomaly, Fallot's tetralogy, Gastroschisis, Glossoptosis, Haemangioma congenital, Heart disease congenital, Heterotaxia, High arched palate, Hydrocele, Hydrocephalus, Hypoplastic left heart syndrome, Hypospadias, Laryngomalacia, Meningomyelocele, Multiple congenital abnormalities, Neonatal respiratory distress syndrome, Nervous system disorder, Parachute mitral valve, Phalangeal agenesis, Plagiocephaly, Pulmonary malformation, Pulmonary valve stenosis, Pyloric stenosis, Renal tubular disorder, Retrognathia, Single umbilical artery, Spina bifida, Tracheo-oesophageal fistula, Turner's syndrome, Ventricular hypoplasia, Visual impairment.

b: A single case may report more than 1 MedDRA PT of interest.

c: MedDRA PT of interest in case JAFRA40440 is coded as Atrial septal defect. However, as per CIOMS the event of interest is tricuspid atresia.

Paliperidone

The search of the Global Medical Safety database yielded one case each related to paliperidone and paliperidone palmitate.

- One infant exposed to paliperidone palmitate (trimester not reported) born with trisomy 21
- One infant exposed to paliperidone and perphenazine during the first trimester (paliperidone was discontinued after a positive pregnancy test at week 8) had esophageal atresia.

Postmarketing reporting frequency of congenital malformations (total) compared to total exposure of the product (person-years) is reported in the following sponsor-generated table.[44]

[44] Cumulative review of congenital malformation cases with use of risperidone, paliperidone palmitate and paliperidone. Janssen Research and Development, LLC. February 6, 2017.

Post-Marketing Reporting Frequency of Congenital Malformation for With Risperidone, Paliperidone Palmitate or Paliperidone (Oral and LAI) Cumulatively Through 01 November 2016.

Drug	Number of Cases[a]	Exposure (Person-Years) Through 31 October 2016	RR per Person-Years	RR per 1000 Person-Years	Frequency Category
Risperidone	52	(b) (4)	0.0000010	0.0010	Very Rare
Paliperidone Palmitate	1		0.0000006	0.0006	Very Rare
Paliperidone[b]	1		0.0000004	0.0004	Very Rare

Key: RR= Reporting Rate; LAI= Long-Acting Injection. a: Spontaneous serious cases only.
b: Does not include generic.

Summary

Data from epidemiologic studies, registry studies and studies examining data from large healthcare databases regarding use of risperidone during pregnancy do not report consistent findings and have methodologic limitations, including many studies with insufficient sample size, inadequate comparison groups (confounding related to diagnosis), few studies that measure illness severity, comorbid conditions and concomitant medications. However, given the number of reported cases compared to the number of years of exposure to risperidone and paliperidone (see Post-Marketing Reporting table above), the likelihood of that these products are major teratogens appears to be low.

Data from Huybrechts et al. indicate a small increased risk of congenital malformations with SGAs with a slightly increased relative risk of congenital malformations (RR 1.26), in particular cardiac defects (RR 1.26), with first trimester risperidone use. Given the large sample size and efforts to minimize error due to confounding in the Huybrechts et al. study, DPMH recommends adding data from the National Pregnancy Registry for Atypical Antipsychotics and the Huybrechts study to subsection 8.1, under Human Data.

Data from published literature also indicate possible neonatal withdrawal or extrapyramidal symptoms (EPS) following third trimester exposure; this is already described in current labeling, but can be added to Clinical Considerations. In addition, a statement regarding the risk to the mother from untreated Schizophrenia or Bipolar disorder will be added to Clinical Considerations.

LACTATION

Nonclinical Experience

(b) (4)

The reader is referred to the Pharmacology/Toxicology review by Sonia Tabacova Ph.D., and Aisar Atrakchi, Ph.D.

Applicant's Review of Literature

The applicant performed a search of the literature published on or before February 9, 2017, using the MEDLINE, Embase, Derwent Drug File and BIOSIS databases using the terms, "risperidone," and "paliperidone" and terms relating to "lactation" or "breastfeeding."

The search identified five case reports[45,46,47,48,49] describing a total of eight cases related to risperidone or paliperidone and lactation (see summary table under DPMH Review of Literature) and reported no adverse effects were noted in the seven infants exposed to risperidone or paliperidone (two cases reported on milk/plasma levels, one was a case of galactorrhea, the other had no infant exposure). The applicant concluded that there was insufficient evidence to prompt changes in the package inserts.

DPMH Review of Literature

DPMH conducted a search of *Medications in Mother's Milk,* the Drugs and Lactation Database (LactMed),[50] Micromedex,[36] and of the published literature in PubMed and Embase using the search terms "risperidone" or "paliperidone" and "lactation" or "breastfeeding."

Micromedex[36] states, "Infant risk cannot be ruled out."

In *Medications and Mother's Milk*[51], Thomas Hale, a breastfeeding expert, states that risperidone is rated "L2- Limited Data-Probably Compatible." The relative infant dose (RID) is reported as ranging from 2.8% to 9.1%*, and infant monitoring for sedation or irritability, apnea, not waking to feed/poor feeding, extrapyramidal symptoms, and weight gain is listed. Paliperidone is rated as "L3-No Data- Probably Compatible."

**Reviewer's comment: Hale reports the upper range of the RID as 9.1%, however, in the cases referenced by Hale the maximum RID is listed as 4.7%.*

Risperidone and paliperidone are referenced in the LactMed database. The following is a summary from LactMed:

> *Risperidone*
> "Limited information indicates that maternal risperidone doses of up to 6 mg daily produce low levels in milk. Because there is little published experience with risperidone during breastfeeding and little long-term follow-up data, other agents may be preferred, especially while nursing a newborn or preterm infant. Systematic reviews of second-generation antipsychotics concluded that risperidone seemed to be a second-line agent

[45] Aichhorn W, et al. Risperidone and breast-feeding. J Psychophamacol. 2005;19:211-213.
[46] Hill RC, et al. Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast feeding. J Clin Psychopahrmacol. 2000;20:285-286.
[47] Ilett KF, et al. Transfer of risperidone and 9-hydroxyrisperidone into human milk. Ann Pharmacother. 2004;38:273-276.
[48] Ranayake T, Libretto SE. No complications with risperidone treatment before and throughout pregnancy and during the nursing period. J Clin Psychiatry. 2002;63:76-77.
[49] Weggelaar NM, et al. A case report of risperidone distribution and excretion into human milk: how to give good advice if you have not enough data available. J Clin Psychophamacol. 2011; 31:129-131.
[50] http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
[51] Hale, Thomas and Rowe, Hilary E. (2017). Medications and Mother's Milk. New York, NY. Springer Publishing.

during breastfeeding because of the limited data available and higher excretion into milk relative to other agents."[52,53]

Paliperidone

"Although no data are available for the use of paliperidone during breastfeeding, it is the active metabolite of risperidone. Risperidone data indicate that the concentrations of paliperidone (9-hydroxyrisperidone) in breastmilk are low, and amounts ingested by the infant are small. Because there is no published experience with paliperidone during breastfeeding and little long-term follow-up data, other agents may be preferred, especially while nursing a newborn or preterm infant. Because paliperidone is available only as a sustained-release product, timing of nursing with respect to doses would not be useful."

LactMed reports on the cases that are noted in the table below. LactMed also reports that both risperidone and paliperidone cause elevated prolactin and can cause galactorrhea and gynecomastia.[54,55,56]

A review of the published literature did not reveal any additional cases of risperidone, or paliperidone and breastfeeding other than what was reported by the applicant. A summary of these cases that was found in a review paper[57] is included below and notes the following:

TABLE 1. Characteristics of Reports Examining Safety of SGAs on the Infants During Breastfeeding

Report	n	Maternal Dose, mg/d	Infant Age at the Assessment	Follow-Up Period	M/P Ratio	RID, %	Infant Serum Levels, ng/mL	Adverse Events
Risperidone/paliperidone								
Ratnayake and Libretto,[35] 2002	2	4–6	NA	9–12 mo	NA	NA	NA	No
Weggelaar et al,[36] 2011	1	1 mg	3 mo	NA	0.88	4.7	Below the detection limits	No
Ilett et al,[37] 2004	3	1–3	0–3.3 mo	9–12 mo	0.1–0.5	2.3–4.7	Below the detection limits	Nursing was discontinued (n = 1); no adverse events in other infants
Aichhorn et al,[39] 2005	1	2	2 wk	3 mo	0.1–0.3	NA	Below the detection limits	No
Hill et al,[38] 2000	1	6	2.5 mo	NA	0.24–0.42	4.3	NA	Nursing was discontinued

[52] Uguz F. Second-generation antipsychotics during the lactation period: a comparative systematic review on infant safety. J Clin Psychopharmacol. 2016;36:244-252.
[53] Pacchiarotti I, Leon-Caballero J, Murru A et al. Mood stabilizers and antipsychotics during breastfeeding: Focus on bipolar disorder. Eur Neuropsychopharmacol. 2016;26:1562-78.
[54] Skopek M, Manoj P. Hyperprolactinemia during treatment with paliperidone. Australas Psychiat. 2010;18:261-3.
[55] Schreiber S, Segman RH. Risperidone-induced galactorrhea. Psychopharmacol. 1997;130:300-1.
[56] Benazzi F. Gynecomastia with risperidone-induced symptomatic hyperprolactinemia. Psychopharmacol. 199;32:41.
[57] Uguz F. Second-generation antipsychotics during the lactation period: a comparative systematic review on infant safety. J Clin Psychopharmacol. 2016;36:244-252.

Review of Pharmacovigilance Database
The applicant provided a cumulative review of lactation cases through May 31, 2017 for risperidone and through June 30, 2017 for paliperidone and paliperidone palmitate.

The applicant reported forty-six cases of infant exposure to risperidone through breastfeeding. Forty-four cases were reported as nonserious, but included one case each of somnolence, sedation, and vomiting . There are two cases of infant exposure through breastfeeding described as having serious events:

- one case of failure to thrive
- one case with extrapyramidal disorder

No further details were provided in any of the cases.

There were eight cases of infant exposure to paliperidone or paliperidone palmitate through breastfeeding. Seven of these cases were reported as nonserious. There was one case report of extrapyramidal disorder. No details were provided in any of the cases.

Summary
Risperidone and paliperidone are present in human milk. Limited published case reports indicate a relative infant dose of less than 10% for risperidone; no data on the relative infant dose of paliperidone are available. While the majority of reports do not indicate adverse effects on a breastfed infant, there are cases of reported sedation, failure to thrive and extrapyramidal symptoms in breastfed infants from the applicant's pharmacovigilance database. DPMH recommends the following language be included in 8.2, Lactation labeling:

> "The development and health benefits of breastfeeding should be considered along with the mother's clinical need for (risperidone or paliperidone product name) and any potential adverse effects on the breastfed infant with (risperidone or paliperidone product name) or from the underlying maternal condition."

In addition, DPMH proposes adding the following Clinical Consideration:

> Infants exposed to [TRADENAME] through breastmilk should be monitored for excess sedation, respiratory depression, failure to thrive, tremor, jitteriness and irritability..

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL
Nonclinical Experience
Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in (b) (4) rats (b) (4) (b) (4) reproductive studies (b) (4)) at doses 0.1 to 3 times the maximum recommended human dose (MRHD (b) (4). The effect appeared to be in females, since impaired mating behavior was not noted in the (b) (4) (b) (4) mal (b) (4) In a subchronic study in Beagle dogs in which risperidone was adm t doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the MRHD on a mg/m2 (b) (4) basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

[redacted] The fertility of male rats was not affected at oral doses of paliperidone of up [redacted] to 2 times the MRHD of 12 mg on mg/m2 [redacted] although sperm count and sperm viability studies were not conducted with paliperidone. In a sub-chronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested 0.31 to 5.0 mg/kg/day, which are 0.6 to 10 times the MRHD of 16 mg on mg/m2 basis [redacted] Serum testosterone and sperm parameters partially recovered, but remained decreased at the last observation two months after treatment was discontinued.

The reader is referred to the Pharmacology/Toxicology review by Sonia Tabacova Ph.D., and Aisar Atrakchi, Ph.D.

Applicant's Review of Literature

The applicant completed a review of the literature related to hyperprolactinemia and fertility for risperidone November 30, 2007 to February 9, 2017 and for paliperidone December 31, 2013 to February 9, 2017. (Previous literature searches had been submitted for the same topic for risperidone January 1, 1992 to November 30, 2007 and for paliperidone September 12, 2012 to December 31, 2013). Summary Tables from those reviews are in Appendix C. The current literature search reportedly found hundreds of articles related to risperidone and paliperidone and prolactin. For a complete listing of abstracts, the reader is referred to the applicant's Literature Summary.[58] The studies indicate that risperidone and paliperidone increase prolactin through dopamine type two (D2) receptor antagonism, and are associated with hyperprolactinemia-related side effects such as oligo- or amenorrhea, decreased testosterone levels, and gynecomastia.[59,60]

The applicant concluded that hyperprolactinemia and its potentially related adverse events and priapism were already represented in the labeling and that no further changes were needed.

Reviewer Comment:
While the applicant is correct, the risk of hyperprolactinemia and its effects are described in Warnings and Precautions, it might be helpful to include information on the effects of hyperprolactinemia on fertility in 8.3.

[58] Human and nonclinical studies of pregnancy, lactation, and reproductive potential associated with risperidone and paliperidone formulations: Risperidone, Paliperidone, and Paliperidone Palmitate. Janssen Research and Development LLC. June 29, 2017.
[59] Jerrell JM, et al. Hyperprolactinemia-related adverse event associated with antipsychotic treatment in children and adolescents. J Adolesc Health. 2009;45(1):70-76.
[60] Dickson RA, Seeman MV, Corenblum B. Hormonal side effects in women: typical versus atypical antipsychotic treatment. J Clin Psychiatry. 2000;61(Suppl 3):10-15.

DPMH Review of Literature

DPMH conducted a review of Micromedex, Embase, and PubMed using the terms, "risperidone" or "paliperidone" and "fertility," "contraception," "oral contraceptives," and "infertility."

Reprotox[61] states, "Hyperprolactinemia and related symptoms including galactorrhea, gynecomastia, and sexual dysfunction in males and females and amenorrhea or oligomenorrhea and infertility in females can occur as side effects.[62, 63,64,65,66,67] Hyperprolactinemia in women can be seen with very low dose exposure levels (<2 mg/day).[68] Some investigators have reported on the successful transition of patients from risperidone to "prolactin-sparing" antipsychotics, including olanzapine or quetiapine.[69, 70,71] Other investigators have reported conflicting results as to whether switching improves sexual dysfunction as prolactin concentrations decrease[72,73] Reversible retrograde ejaculation secondary to risperidone was reported in a 51 year old man who had no complaints of decreased libido, erectile dysfunction, or anorgasmia.[74] The authors attributed this symptom to the alpha-1 adrenergic blocking properties of risperidone. Prolactin concentrations were not reported."

A search of the published literature for paliperidone and infertility did not result in any additional references. A search of the published literature for risperidone and infertility resulted in a couple of additional reports.

- A study of 80 patients with schizophrenia with elevated serum prolactin levels (risperidone n=33) were treated with cabergoline to reduce their prolactin levels. Overall,

[61] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 3/14/2018
[62] Schreiber S, Segman RH: Risperidone-induced galactorrhea [letter]. Psychopharmacology Berl 1997; 130: 300-1.
[63] Popli A, Gupta S, Rangwani SR: Risperidone-induced galactorrhea associated with a prolactin elevation. Ann Clin Psychiatry 1998;10:31-3.
[64] Kleinberg DL, Davis JM, de Coster R, Van Baelen B, Brecher M: Prolactin levels and adverse events in patients treated with risperidone. J Clin Psychopharmacol 1999;19:57-61.
[65] Haddad PM, Wieck A: Antipsychotic-induced hyperprolactinemia: mechanisms, clinical features and management. Drugs 2004;64:2291
[66] Bobes J, Garc A-Portilla MP, Rejas J et al: Frequency of sexual dysfunction and other reproductive side-effects in patients with schizophrenia treated with risperidone, olanzapine, quetiapine, or haloperidol: the results of the EIRE study. J Sex Marital Ther 2003;29:125-47.
[67] Eberhard J, Lindstrom E, Holstad M, et al.: Prolactin level during 5 years of risperidone treatment in patients with psychotic disorders. Acta Psychiat Scand 2007;115:268-276.
[68] Lusskin SI, Cancro R, Chuang L, et al.: Prolactin elevation with ziprasidone. Am J Psychiatry 2004;161:1925.
[69] Lusskin SI, Cancro R, Chuang L, et al.: Prolactin elevation with ziprasidone. Am J Psychiatry 2004;161:1925.
[70] Kim KS, Pae CU, Chae JH, Bahk WM, Jun TY, Kim DJ, Dickson RA: Effects of olanzapine on prolactin levels of female patients with schizophrenia treated with risperidone. J Clin Psychiatry 2002;63:408-13.
[71] Halbreich U, Kahn LS: Hyperprolactinemia and schizophrenia: mechanisms and clinical aspects. J Psychiatr Pract 2003;9:344-53.
[72] Nakonezny PA, Byerly MJ, Rush AJ: The relationship between serum prolactin level and sexual functioning among male outpatients with schizophrenia or schizoaffective disorder: a randomized double-blind trial of risperidone vs. quetiapine. J Sex Marital Ther 33:203-216, 2007.
[73] Byerly MJ, Nakonezny PA, Rush AJ: Sexual functioning associated with quetiapine switch vs. risperidone continuation in outpatients with schizophrenia or schizoaffective disorder: a randomized double-blind pilot trial. Psychiatry Res 159:115-120, 2008.
[74] Loh C, Leckband SG, Meyer JM, et al.: Risperidone-induced retrograde ejaculation: case report and review of the literature. Int Clin Psychopharmacol 19:111-112, 2004.

sexual functioning was improved (as measured by questionnaire) and females reported improved menstrual cycle regularity.[75]

- A review of psychotropics and male reproduction that reports that antipsychotics, in particular risperidone, haloperidol, and thioridazine increase prolactin, decrease testosterone and increase ejaculatory problems.[76]

No references related to risperidone or paliperidone and interactions with hormonal contraception were found in the literature search.

Review of Pharmacovigilance Database

The applicant did not report cases related to infertility.

Summary

Risperidone and paliperidone increase prolactin, which can cause oligo-and amenorrhea, impacting fertility. There are insufficient data to establish a relationship between risperidone or paliperidone and adverse effects on sperm quality or quantity. There were no reports related to adverse effects of risperidone or paliperidone on hormonal contraception. DPMH recommends adding a statement to 8.3 regarding prolactin effects on fertility in females, referencing the Warnings and Precautions section on Hyperprolactinemia.

CONCLUSIONS

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of TRADENAME labeling were structured to be consistent with the PLLR, as follows:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of labeling was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" subheadings.
- **Lactation, Section 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: the "Risk Summary" and "Clinical Considerations," subheadings.
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential," section of labeling was formatted in the PLLR format to include: the "Infertility" subheading.
- **Patient Counseling Information, Section 17**
  The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1,8.2, and 8.3 of labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2, 8.3 and 17 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

[75] Michopoulos II, et al. Hyperprolactinemia, psychopathology and sexual functioning in schizophrenic patients. Eur Neuropsychopharmacol. 2014;24:S561-562.
[76] Drobnis EZ, Nangia AK. Psychotropics and male reproduction. Adv Experimental Med Biol. 2017;1034:63-101.

DPMH Proposed Pregnancy and Lactation Labeling for RISPERDAL NDA 20272; RISPERDAL Oral Solution NDA 20588; RISPERDAL Orally Disintegrating tablet NDA 21444

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------

(b) (4)

Risk Summary
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms (b) (4) (b) (4) following delivery *(see Clinical Considerations).* Overall available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder *(see Clinical Considerations)*.

(b) (4)

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
There is risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX B

Table 1: Key Parameters of the 6 Larger-scale Studies Describing Congenital Malformations After First-trimester Exposure to Antipsychotics

Publication[citation]	Risk Population Exposures: Total	Risk Population Exposures: Risperidone or Paliperidone	Reference Population Exposures	Congenital Malformation Risk, for Group Including Risperidone or Paliperidone	Risperidone or Paliperidone Exposures Among Malformation Cases
Registry Studies With Cohort Controls					
Habermann 2013[17]	561 pregnancies with atypical antipsychotics; 284 pregnancies with typical antipsychotics	64 risperidone, 0 paliperidone	Others in the same registry; 1,122 pregnancies exposed to medications known as not harmful to the unborn	• Major malformations: adjusted OR=2.17; 95%CI=1.20-3.91 (atypical versus reference)	• Malformation rates varied between 5 (3.59%) of 139 for quetiapine and 3 (6.81%) of 44 for aripiprazole, with risperidone falling at an unstated number within that range
Reis 2008[21]	570 women (576 infants) exposed to antipsychotics	51 risperidone, 0 paliperidone	Others in the same registries; total 958,729 women with 973,767 infants	• Any congenital malformation: adjusted OR=1.31; 95%CI=0.93-1.86 • Relatively severe malformations: OR=1.52; 95%CI=1.05-2.19	• 2 of 30 severe malformations were associated with risperidone; 1 was Turner syndrome (ie, not due to risperidone) and 1 was anal atresia plus lung malformation
McKenna 2005[13]	151 women exposed to atypical antipsychotics	49 risperidone, 0 paliperidone	Others in the same registries; matched 151 women exposed to nonteratogenic agents	• Major malformations: 1 (0.9%) in the atypical antipsychotic group, versus 2 (1.5%) in the reference group; p=1.0	• None; the 1 major malformation was associated with olanzapine, not risperidone
Healthcare Database Studies With Cohort Controls					
Petersen 2016[19]	290 women who were prescribed antipsychotics during pregnancy	70 risperidone, 0 paliperidone	Others in the same databases; 492 women who discontinued antipsychotic treatment before pregnancy, and 210,966 women who were not prescribed antipsychotics	Major malformations, active antipsychotic prescriptions versus reference groups: • Discontinued prescriptions, adjusted RR=1.79; 95%CI=0.72-4.47 • Without prescriptions, adjusted RR=1.59; 95%CI=0.84-3.00	• Not specified
Vigod 2015[26]	1,021 antipsychotic users	112 risperidone, not specified for paliperidone	Others matched from the same databases; 1,021 nonusers	• Malformations after first-trimester exposure: adjusted RR=1.37; 95%CI=0.82-2.29	• Not specified
Spontaneous Event/Exposure Reporting System Study					
Montastruc 2016[15]	1,235 cases of congenital, familial, and genetic disorders, among 351,028 cases exposed to antipsychotics	Not specified	16,508 cases of congenital malformations in a population of 9,014,653 exposed to other medications (excluding antipsychotics, antidepressants, antiepileptics, and direct-acting antivirals), and excluding cases related to movement disorders	• Palate disorders: PRR=2.1; 95%CI=1.6-2.9 • Anorectal disorders: PRR=3.0; 95%CI=1.6-5.6 • Esophageal disorders: PRR=2.5; 95%CI=1.3-4.7	• 4 of 41 cleft palates had exposure to risperidone • 2 of 11 anorectal disorders had exposure to risperidone • 4 of 10 esophageal disorders had exposure to risperidone or paliperidone

Key: CI = confidence interval; OR = odds ratio; PRR = proportional reporting ratio; RR = relative risk.

Publication; author/date/ country	Type of study	Population/control pop.; n and disease	Exposure during pregnancy or pre-conception; to what drug/dose	Pregnancy/infant outcomes	Comments/limitations
Huybrechts KF, et al.[77] 2016/US	Nested cohort study using Medicaid Analytic Extract Database	1,360,101 pregnant women enrolled in Medicaid (Jan. 1, 2000-Dec. 31, 2010), comparing women who took antipsychotics to those who did not take antipsychotics	Women filled at least one antipsychotic prescription during their first trimester. (Risperidone n=1,566)	Adjusted RR for risperidone (RR=1.26, 95%CI=1.02-1.56) for overall malformations; but no increased risk for cardiac defects	Adjusted for multiple confounders, overall no increased risk for congenital malformations with second generation antipsychotics. Authors concluded the slightly higher risk of overall malformations with risperidone be interpreted with caution, as there was no known biologic mechanism.

[77] Huybrechts KF, et al. Antipsychotic drug use in pregnancy and the risk of congenital malformations. JAMA Psychiatry. 2016. 73;938-946.

APPENDIX C

Table 1: Adverse Events Potentially Related to Prolactin and Reproductive Potential, Excerpted From the Table Entitled "Adverse Events Reported in the Articles Identified as Containing Original Clinical Data (Oral and Long-acting Injectable Risperidone)," 1 January 1992 to 30 November 2007

Adverse Events	Number of articles	Citations
Hyperprolactinemia/ prolactin increased	7	Cohen 2001; Fountoulakis 2004; Frazier 1999; Gutkovich 2007; Pavuluri 2004; Pavuluri 2006; Soutullo 2006
Amenorrhoea	5	Fountoulakis 2004; Raja 2007; Schweitzer 1999; Vasile 2006; Vieta 2003
Galactorrhea	4	Frazier 1999; Pavuluri 2004; Vieta 1998; Vieta 2004
Ejaculation disorder	2	Frazier 1999; Raja 2007
Impotence	2	Vieta 2001; Vieta 2004
Pituitary gland enlarged	1	Soutullo 2006
Sexual dysfunction	1	Vieta 2003

Note: The original table included information from a total of 28 articles that contained details regarding specific adverse events, from the overall 47 articles included in the literature summary.

Table 2: Adverse Events Potentially Related to Prolactin and Reproductive Potential, Excerpted From the Table Entitled "Brief Summary of Publications," Paliperidone and Paliperidone Palmitate, From 12 September 2012 to 31 December 2013

Reference	Type of Study	N	Patient Characteristics	Dosing	Relevant Safety Findings
Safety Data - Clinical Studies					
Albayrak 2013 abstract (conference publication)	Controlled study to compare the effect of risperidone and paliperidone on serum prolactin levels	78 (35 in the paliperidone extended-release group and 43 in the risperidone group)	Female patients with schizophrenia who were started on risperidone or paliperidone treatments	Not available	The increases in serum prolactin levels were significant in both groups with a higher increase in the paliperidone group. Discontinuation rates due to indirect effects of prolactin increase (galactorrhea and amenorrhea) were also higher in the paliperidone group compared with the risperidone group.
Montalvo 2013 (short communication)	Observational study to assess the effect of switching from risperidone LAI to paliperidone palmitate on sexual function and prolactin levels	11	Patients with psychosis who were switched from risperidone LAI to paliperidone palmitate after suffering from hyperprolactinaemia	Mean (SD) risperidone LAI dose was 54.5 (17.0) mg (at baseline) and paliperidone palmitate dose was 109.1 (34.0) mg equivalent (at 3 months)	A significant decrease in prolactin levels and 4-fold reduction in clinically significant sexual dysfunction was noted after switching from risperidone LAI to paliperidone palmitate.
Safety Data - Case Report					
Akkus 2013 abstract (conference publication)	Case report of sexual dysfunction due to hyperprolactinemia associated with increased paliperidone palmitate dose	1	22-year-old male with psychosis	Paliperidone palmitate 150 mg on Day 1, 100 mg on Day 8 followed by 100 mg/month for 3 months in deltoid muscle. Paliperidone palmitate 150 mg in gluteal region for 2 months.	Sexual dysfunction occurred after increasing the monthly dose of paliperidone palmitate.

Key: LAI = long-acting injection, N = number of subjects, SD = standard deviation.

References:

- Akkus M, Kok B, Karamustafalioglu N, Kalelioglu T. A case report of sexual dysfunction due to hyperprolactinemia associated with increased dose of paliperidone palmitate injection. Klinik Psikofarmakoloji Bulteni (Bulletin of Clinical Psychopharmacology). 2013;23:S173.
- Albayrak Y, Beyazyuz M, Ozturk N, Binbay Z, Kuloglu M. Comparison of serum prolactin levels between risperidone and paliperidone extended-release in female patients with schizophrenia. European Psychiatry. 2013;28:1, Article 1956.
- Montalvo I, Ortega L, Lopez X, et al. Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate. Int Clin Psychopharmacol. 2013;28:46-49.

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/s/

CATHERINE A ROCA
04/16/2018

MIRIAM C DINATALE
04/16/2018

LYNNE P YAO
04/17/2018

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s058

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**DIVISION OF PEDIATRIC AND MATERNAL HEALTH REQUEST FOR CONSULTATION**	
TO: CDER Division of Pediatric and Maternal Health *(please check appropriate box(es))* ☐ Pediatric Team ☒ Maternal Health Team			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Kim Updegraff, ODEI/DPP, 301-796-2201 OR Latrice Wilson, ODE1/DPP, 240-402-5317	
DATE OF CONSULT 1/29/18	IND NO.	NDA NO. **PDUFA NDA** 21346/S058 *Risperdal Consta* 20272/S080 *Risperdal* 20588/S068 *Risperdal Solution* 21444/S054 *Risperdal ODT* 207946/S006 *Invega Trinza* 21999/S035 *Invega* 22264/S027 *Invega Sustenna*	TYPE OF SUBMISSION PLLR Prior Approval Supplements	DATE OF SUBMISSION 11/17/17
NAME OF DRUG Risperdal and Invega supplements		NAME OF FIRM Jansen Pharmaceuticals	DRUG CLASS Antipsychotic	INDICATION(S) Treatment of Schizophrenia
PDUFA Goal Date: 5/17/18 **Please see the note below – DPP requests that the applications referenced above be reviewed alongside NDA 210655 Persaris**	**DPMH will work with you to establish a suitable due date for the completed consult. Please check one of the three boxes.**			
	☐ Urgent* (< 14 days)	☐ Priority (14-29 days)	☒ Routine (1 – 10 months)	
*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from DPMH team leaders.				

REASON FOR REQUEST (check all that apply)

Pediatrics:	Maternal Health Team:
☐ Labeling Review – non-PLLR ☐ Safety Labeling Supplement ☐ 505(b)(2)/ANDA Pediatric Labeling ☐ Industry Meeting Attendance (PDUFA or BSUFA) ☐ Other Industry Meeting Attendance ☐ BPCA-Related Questions or Documents for Review ☐ PREA-Related Questions or Documents for Review ☐ PeRC Preparation Assistance/iPSP Review ☐ SPA ☐ 30-day IND Review ☐ Other Protocol Review ☐ Tracked Safety Issue ☐ Advisory Committee Preparation ☐ Assistance with Guidance development ☐ Assistance with Citizen Petition Response ☐ Medical Necessity Determination ☐ Off-Patent BPCA/409i Related Questions	☒ Labeling Review – PLLR ☐ Labeling Review – non-PLLR ☐ Industry Meeting Attendance ☐ Pregnancy Exposure Registry (protocol or report) ☐ 30-day IND Review ☐ Evaluation of possible safety signal ☐ Risk Management – Pregnancy Prevention and Planning ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ Guidance development ☐ Advisory Committee Preparation ☐ Citizen Petition ☐ Other (please explain):

☐ Other (please explain):	
Link to electronic submission: EDR: **Risperdal tablets**: \\CDSESUB1\evsprod\NDA020272\0136 Oral solution: \\CDSESUB1\evsprod\NDA020588\0129 **Risperdal ODT:** \\CDSESUB1\evsprod\NDA021444\0130 **Risperdal Consta**: \\CDSESUB1\evsprod\NDA021346\0249 **Invega tablets:** \\CDSESUB1\evsprod\NDA021999\0193 **Invega Sustenna**: \\CDSESUB1\evsprod\NDA022264\0183 **Invega Trinza**: \\CDSESUB1\evsprod\NDA207946\0046	Materials to be reviewed: PLLR converted labeling and related literature. Risperdal (labeling) SP: Risperdal PLLR Invega (labeling) SP: Invega PLLR

1. **Please briefly describe the submission**:
DPP received 7 prior approval supplements proposing PLLR conversion of multiple risperidone and paliperidone products to include: Risperdal Consta, Risperdal, Risperdal Solution, Risperdal ODT, Invega, Invega Sustenna, and Invega Trinza (please note that Trinza is currently in PLLR format – the sponsor is proposing updates in this submission).

DPP would like to align labels for the risperidone and paliperidone products and is proposing that all the submissions be reviewed at the same time to ensure consistency.

Please cross reference our recent consult request for 210655 *Persaris.* Persaris (risperidone ER injection) is a new 505(b)(2) application with a PDUFA date of *7/28/18.* Consult Reference ID: 4214799

2. **Describe the reason for your consult. Include specific questions**:
The Division is seeking DPMH input to confirm that the language that the Sponsor provided is accurate and appropriate, as well as assistance in aligning PLLR format across the risperidone/paliperidone product line.

3. **Meeting dates requiring DPMH presence:**
Please note that the prior approval labeling supplements referenced in this consult will be review concurrently with NDA 210655 Persaris.

- Labeling Planning Meeting for Persaris: *Wednesday, March 14, 2018*

4. **Please list any prior Pediatric or Maternal Health consults for this product by date within the last 3 years that may be relevant to this consult**:

- Maternal Health review for INVEGA TRINZA (4/29/15) Reference ID: 3741973

Review team:
Project Manager: Kim Updegraff OR Latrice Wilson
Associate Director for Labeling: Kim Updegraff, MS
Clinical reviewer & Team Leader: Michael Davis, MD; Bernard Fischer, MD
Pharmacology/Toxicology reviewer & Team Leader: Sonia Tabacova, PhD; Aisar Atrakchi, PhD
Clinical Pharmacology reviewer & Team Leader: Praveen Balimane, PhD; Hao Zhu, PhD

PRINTED NAME or SIGNATURE OF REQUESTOR:
Kim Updegraff

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIMBERLY S UPDEGRAFF
01/31/2018