CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021346Orig1s052

Trade Name:	RISPERDAL CONSTA
Generic or Proper Name:	(risperidone)
Sponsor:	Janssen Pharmaceuticals Inc.
Approval Date:	June 5, 2014
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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Clinical Review(s)	X
Product Quality Review(s)	X
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Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21346/S-052

APPROVAL LETTER

Janssen Pharmaceuticals, Inc.
Attention: Timothy Dring, Associate Director
Global CMC Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Mr. Dring:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 7, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Risperdal Consta (risperidone) 12.5 mg, 25 mg, 37.5 mg, 50 mg intramuscular injection.

We acknowledge receipt of your amendments dated May 15, 2014 and May 29, 2014.

In your June 3, 2014 email from Jacqueline Brown, you agreed to the following:

1) Submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, given the high failure rate observed in the usability study.
2) Submit your plans for introducing the new Risperdal Consta kits into the marketplace.
3) Submit your plans for tracking medication errors and product complaints involving the new kits and clarify how you will address the challenges of differentiating reports for the new kits from reports involving the currently marketed kits.
4) Submit product quality and use-related serious adverse events in expedited fashion to the Agency.

This prior approval supplemental new drug application proposes changes to the drug product kit device components and associated labeling.

We have completed our review of this supplemental new drug application, as amended. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 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, M.D.
CAPT USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

MITCHELL V Mathis
06/05/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s052

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

Dosage and Administration *(2.8)* 6/2014

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. *(5.15)*
- 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 the product *(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.*(5.8)*
- Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. *(5.9)*
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. *(5.10)*
- Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. *(5.11)*
- Priapism: has been reported. Severe priapism may require surgical intervention. *(5.12)*
- Thrombotic Thrombocytopenic Purpura (TTP): has been reported.*(5.13)*
- Avoid inadvertent administration into a blood vessel *(5.15)*
- Suicide: There is increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. *(5.17)*
- 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———————

- 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)*
- Nursing Mothers: should not breast feed. *(8.3)*
- 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: 6/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 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 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

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.

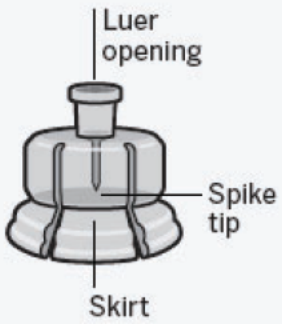
Proper dosing
The entire contents of the vial must be administered to ensure intended dose of RISPERDAL® CONSTA® is delivered.

SINGLE-USE DEVICE

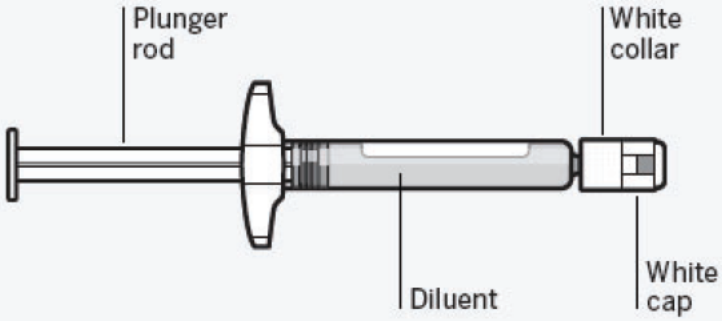
Do not reuse. Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single use only. Any attempt to re-process the device for subsequent re-use may adversely affect the integrity of the device or lead to deterioration in performance.

Dose pack contents

West-Medimop Vial Adapter®

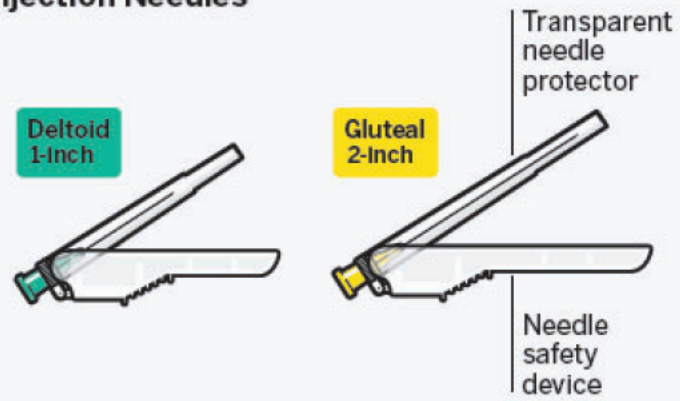


Prefilled Syringe



Vial

Terumo SurGuard® 3 Injection Needles



Step 1 Assemble components

Take out dose pack **Connect vial adapter to vial**

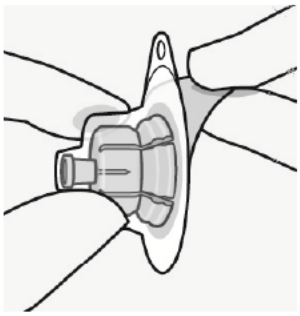
Wait 30 minutes
Remove dose pack from the refrigerator and allow to sit at room temperature for at least **30 minutes** before reconstituting.

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.

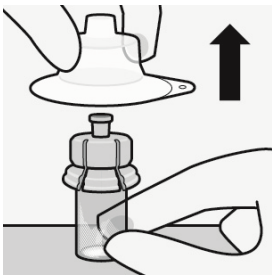
Do not remove vial adapter from blister.

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



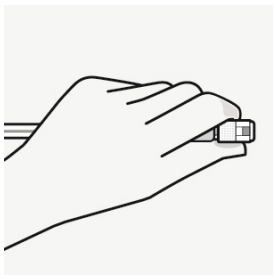
Remove sterile blister

> Remove vial adaptor from sterile blister only when you are ready to remove the white cap from the prefilled syringe.

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

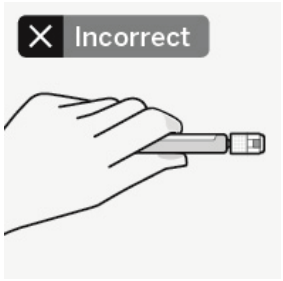
Do not shake.

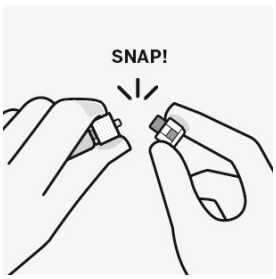
Do not touch exposed luer opening on vial adapter.
This will result in contamination.



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

Do not hold syringe by the glass barrel during assembly.

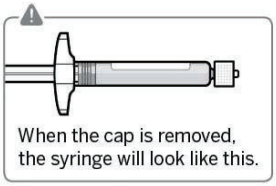




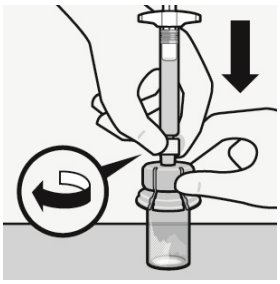
Remove cap
Holding the white collar, snap off the white cap.

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.

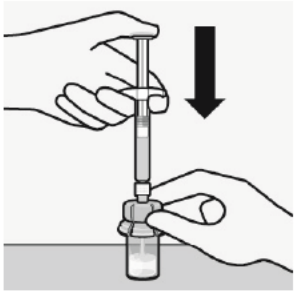
Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

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



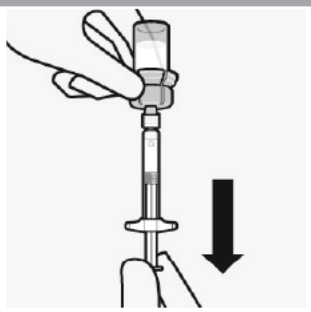
Inject diluent
Inject entire amount of diluent from syringe into the vial.

⚠ 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.



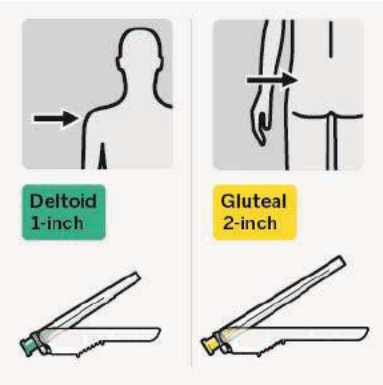
Transfer suspension to syringe
Invert vial completely. Slowly pull plunger rod down to withdraw entire contents from the vial into the syringe.

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

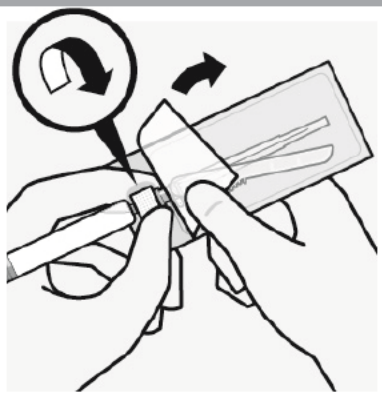
Tear section of the vial label at the perforation. Apply detached label to the syringe for identification purposes.

Discard both vial and vial adapter appropriately.

Step 3 Attach needle



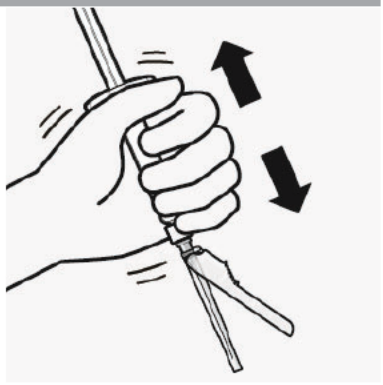
Select appropriate needle
Choose needle based on injection location (gluteal or deltoid).



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.

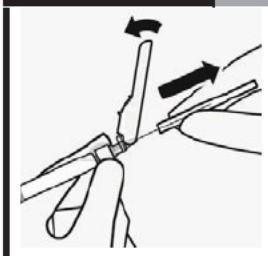
Do not touch needle luer opening. This will result in contamination.



Resuspend microspheres
Fully remove the blister pouch.

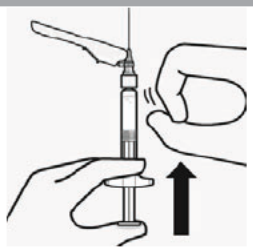
Just before injection, shake syringe vigorously again, as some settling will have occurred.

Step 4 Inject dose

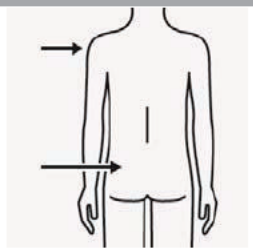


Remove transparent needle protector
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

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



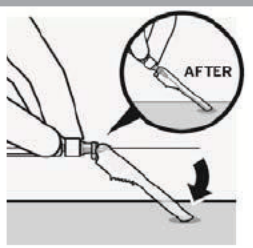
Remove air bubbles
Hold needle upright and tap gently to make any air bubbles rise to the top. Slowly and carefully press plunger rod upward to remove air.



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 <u>one hand</u>, 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 SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety 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® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

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. 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 (NMS)

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.

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

Given these considerations, 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 D2 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 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.

5.9 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.

5.10 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.

5.11 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)]*

5.12 Priapism

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

5.13 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.

5.14 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.

5.15 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)]*

5.16 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.

5.17 Suicide

There is an increased risk of suicide attempt in patients with schizophrenia or bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. RISPERDAL® CONSTA® is to be administered by a health care professional *[see Dosage and Administration (2)]*; therefore, suicide due to an overdose is unlikely.

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.

5.20 Monitoring: Laboratory Tests

No specific laboratory tests are recommended.

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)]*
- Leukopenia/Neutropenia and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Dysphagia *[see Warnings and Precautions (5.11)]*
- Priapism *[see Warnings and Precautions (5.12)]*
- Thrombotic Thrombocytopenic Purpura (TTP) *[see Warnings and Precautions (5.13)]*
- Disruption of body temperature regulation *[see Warnings and Precautions (5.14)]*
- Avoidance of inadvertent injection into a blood vessel *[see Warnings and Precautions (5.15)]*
- Antiemetic effect *[see Warnings and Precautions (5.16)]*
- Suicide *[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 Cmax and a 33% decrease in risperidone AUC_{0-12} 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 Category C.

The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post-natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.

There was no no-effect dose for increased rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to

impair maternal behavior in that pup body weight gain and survival (from Days 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the oral MRHD on a mg/m^2 basis.

No studies were conducted with RISPERDAL® CONSTA®.

Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to oral RISPERDAL® therapy is unknown.

Non-Teratogenic Effects

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

RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of RISPERDAL® CONSTA® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection.

8.4 Pediatric Use

RISPERDAL® CONSTA® has not been studied in children younger than 18 years old. However, juvenile animal toxicology studies have been conducted with oral risperidone.

Juvenile dogs were treated for 40 weeks with oral risperidone doses of 0.31, 1.25, or 5 mg/kg/day. Decreased bone length and density were seen, with a no-effect dose of 0.31 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) which were similar to those in children and adolescents receiving the maximum recommended human dose (MRHD) of 6 mg/day. In addition, a delay

in sexual maturation was seen 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.

In a study in which juvenile rats were treated with oral risperidone from days 12 to 50 of age, a reversible impairment of performance in a test of learning and memory was seen, in females only, with a no-effect dose of 0.63 mg/kg/day. This dose produced plasma levels (AUC) of risperidone plus paliperidone about half those observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest testable dose (1.25 mg/kg/day). This dose produced plasma levels (AUC) of risperidone plus paliperidone which were about two thirds of those observed in humans at the MRHD.

The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated in children and adolescents.

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

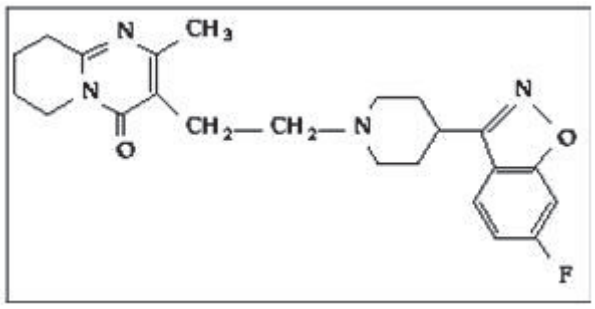
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic

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

Risperidone is a psychotropic agent 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 polysorbate 20, sodium carboxymethyl cellulose, disodium hydrogen phosphate dihydrate,

citric acid anhydrous, 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 SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety 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 RISPERDAL® CONSTA®, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_2$) receptor antagonism.

RISPERDAL® is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 ($5HT_2$), dopamine Type 2 (D2), α1 and α2 adrenergic, and H_1 histaminergic receptors. RISPERDAL® acts as an antagonist at other receptors, but with lower potency. RISPERDAL® has 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.

12.2 Pharmacodynamics

The clinical effect from RISPERDAL® CONSTA® results from the combined concentrations of risperidone and its major metabolite, 9-hydroxyrisperidone *[see Clinical Pharmacology (12.3)]*. Antagonism at receptors other than D_2 and $5HT_2$*[see Clinical Pharmacology (12.1)]* may explain some of the other effects of RISPERDAL® CONSTA®.

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

Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. 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 2.4, 9.4, and 37.5 times the oral maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic

adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis.

Carcinogenesis - Intramuscular

RISPERDAL® CONSTA® 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 RISPERDAL® CONSTA® every 2 weeks. 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 potential for oral risperidone was found in the in vitro Ames reverse mutation test, in vitro mouse lymphoma assay, in vitro rat hepatocyte DNA-repair assay, in vivo oral micronucleus test in mice, the sex-linked recessive lethal test in Drosophila, or the in vitro chromosomal aberration test in human lymphocytes or in Chinese hamster cells.

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) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies (two mating and fertility studies and a multigenerational study) at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/m^2 basis. The effect appeared to be in females, since impaired mating behavior was not noted in the mating and fertility study in which males only were treated. 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 a mg/m^2 basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm values partially recovered, but remained decreased after treatment was discontinued. No no-effect doses were noted in either rat or dog.

No mating and fertility studies were conducted with RISPERDAL® CONSTA®.

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®.

17.1 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)]*.

17.2 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 (5.9)]*.

17.3 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy and for at least 12 weeks after the last injection of RISPERDAL® CONSTA®*[see Use in Specific Populations (8.1)]*.

17.4 Nursing

Patients should be advised not to breast-feed an infant during treatment and for at least 12 weeks after the last injection of RISPERDAL® CONSTA®*[see Use in Specific Populations (8.3)]*.

17.5 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)]*.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s052

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	28 May 2014
From	Mark Ritter, MD RPh.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 21-346 S-52
Applicant	Janssen Pharmaceuticals
Date of Submission	07 February 2014
PDUFA Goal Date	07 June 2014
Proprietary Name / Established (USAN) names	Risperdal Consta/ risperidone
Dosage forms / Strength	Intramuscular injection: 12.5, 25, 37.5 and 50mg
Proposed Indication(s)	1. Schizophrenia
Recommended:	APPROVAL

Cross Discipline Team Leader Review

1. Introduction

The sponsor submitted this prior approval chemistry supplement on 7 February 2014 for Risperdal Consta which contained a change in the pre-packaged syringe that is contained with the Risperdal Consta kit, allowing clinicians to administer the product intramuscularly. The main purpose for this change was to correct errors with syringe function that had been noted from post-marketing reports with the previous Risperdal Consta product.

Specifically, errors have been reported whereby the prepacked needles had become disconnected from the prepackaged syringe during intramuscular administration of the Risperdal Consta product. In response to such errors, the sponsor had tested and selected a replacement for the original adapter device and conducted a human factors study to examine the use of the new device product.

2. Background

The background regulatory history was provided by the clinical reviewer, Lucas Kempf, MD and is provided below:

The proposed changes to the Risperdal Consta injection kit were the subject of a Type C meeting held on 9 December 2013, and were summarized in a pre-meeting briefing document filed to FDA on 6 November 2013.
Since a replacement for the Alaris™ SMARTSITE® Needle-Free vial adapter device component had been selected, a similar vial adapter manufactured and supplied by

West/Medimop. As the replacements for the current Smiths Medical 1-inch deltoid and 2-inch gluteal injection needles with safety shields, similar but improved 1-inch deltoid and 2-inch gluteal injection needles with safety shields, manufactured and supplied by Terumo, were selected. In addition, the exterior surface of the conus (i.e., luer tip) surface of the diluent glass syringe barrel had been roughed.
The following were done to validate these changes:
-On 6 October 2011, the Company provided to FDA a drug product kit device quality risk mitigation plan.
-On 9 November 2011 and on 11 January 2012, the Company provided FDA with a draft protocol for a summative human factors study (HFS), for which agreement was reached with FDA on 26 April 2012.
-On 23 December 2011, the Company filed a prior-approval NDA supplement (S-047) for a change in the supplier of the glass syringe barrel primary container for diluent from the previous Becton-Dickinson supplied glass syringe barrel to one supplied by Nuova OMPI (Agency approval of this supplement was granted on 10 October 2013; both had a smooth finish luer tip/conus).
-In February 2012, two formative type HFS were completed to validate the overall design approach to be used in the summative HFS.
-In September 2012, an initial summative HFS was completed using finished drug product kits that included new injection needle and vial adapter device components, in addition to the new glass syringe barrel.
-Based on the results of the initial summative HFS, the new OMPI glass syringe barrel was changed to slightly roughen the exterior luer tip/conus surface and then conduct a follow-up summative HFS.
-In May 2013, a follow-up summative HFS was completed, the results from which indicated improvements in device performance compared to the initial summative HFS results.
-In September of 2013, an additional HFS was completed to validate an improved IFU leaflet.
-Preliminary and final design verification testing of the new devices at the laboratory scale has been completed.
-The 510(k) (K113422) for Terumo's SurGuard®3 (abbreviated herein as SG3) deltoid and gluteal injection needles received FDA premarket clearance on 5 March 2012.

The completed tests and activities described above were intended to ensure that the drug product kit device components (vial adapter and injection needles), along with the modified glass syringe barrel conus, function as designed to reduce the risk of inadvertent disconnections during use and do not pose any additional risks.

3. CMC/Device

The primary CMC reviewer for this supplement was Gupreet Gill-Sangha, PhD. The following changes to the kit were submitted as part of this supplement:

Component	Currently Approved	Proposed	Location in Supplement of Descriptive and Supportive Documentation
(b) (4) glass syringe barrel container for diluent	Becton-Dickinson or Nuova OMPI supplied with luer tip conus having smooth exterior surface	Nuova OMPI supplied with luer tip conus having roughened exterior surface	CTD Modules 3.2.P.2.4, and 3.2.P.7-Container/Closure System Description for Diluent
2-inch gluteal injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo	CTD Modules 3.2.P.2.4, and 3.2.P.7-Medical Device Components
1-inch deltoid injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo	CTD Modules 3.2.P.2.4, and 3.2.P.7-Medical Device Components
Vial adapter	Alaris type supplied by CareFusion	Supplied by West/Medimop	CTD Modules 3.2.P.2.4, and 3.2.P.7-Medical Device Components
Instructions-for-Use (IFU) leaflet, and physician's prescribing information	Originally-approved format for the IFU	Improved format and layout for the IFU	CTD Module 1 and Module 3.2.P.2.4-Pharmaceutical Development-Medical Device Components

- General product quality considerations
  Dr. Gill-Sangha recommended approval of the supplement. There were no additional product quality concerns or considerations noted.
- Facilities review/inspection
  CMC consulted the Office of Compliance based on the changes instituted by the sponsor. A review from Jennifer Kelly of the Office of Compliance dated 21 May 2014 was found to be acceptable and noted that no facilities need to be inspected with regards to Medical Device Regulations prior to approval of this supplement.
- Other notable issues (resolved or outstanding)
  CMC consulted the Center for Devices and Radiological Health (CDRH) to review the proposed sponsor changes to the kit. Kathleen Fitzgerald of CDRH reviewed the changes proposed by the sponsor. After receiving additional information from the sponsor, Ms. Fitzgerald has stated all deficiencies have been addressed by the sponsor, thus recommending approval of this supplement. The following is from her 28 May 2014 review:

  The Sponsor was asked to provide the following for the propose (b) (4) *glass barrel syringe supplied by Nuovo OMPI, Stevanato Group in the RISPERDAL® CONSTA® new device kit:*
  1. Please provide the certificate of conformance to ISO 11040. If you do not have a certificate of conformance, please provide your complete bench performance testing on your syringe that demonstrates the safety and effectiveness of your device.

Sponsor's Response: The Sponsor has provided a signed certificate of conformance to ISO 11040-4:2007 for the (b) (4) glass syringe supplied by Nuovo OMPI, Stevanato Group.
2. Please provide complete test reports that show the 2-inch gluteal injection needle 1-inch deltoid injection needle ,both supplied by Terumo (K113422 & K122249), is compatible with the (b) (4) glass syringe (no leakage, doesn't fall off, doesn't damage syringe tip, etc).
Sponsor's Response: In response to No. 2, the full design verification report was located in CTD Section 32P24 Appendix D, but I have attached another copy of it for your reviewer's convenience.
3. Please provide complete test reports for break loose, glide force and dose accuracy for the syringe when used with the drug.
Sponsor's Response: Break loose and glide force are not tests that have been performed for Risperdal CONSTA, since it does not use an autoinjector, for which such tests are standard. Same with dosing accuracy, since the volume of the syringe, the amount of drug in suspension, and the injection needle dimensions associated with the new device components are not changing from what they were at the time of original NDA approval.

CDRH's Response: The Sponsor has adequately addressed all deficiencies. I have no additional recommendations at this time.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical or toxicological data was submitted as part of this application.

5. Clinical Pharmacology/Biopharmaceutics

There were no new clinical pharmacology data submitted with this supplement, nor new issues identified.

6. Clinical Microbiology

There was no new clinical microbiological data submitted as part of this supplement.

7. Clinical/Statistical- Efficacy

There was no new efficacy data submitted as part of this efficacy supplement. Lucas Kempf, MD was the primary medical reviewer for this supplement. Based on his review of the recommendations from CMC and consultants, he has recommended approval of this supplement. I concur with his recommendation.

8. Safety

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted by the Division of Psychiatry Products to review results from a usability study that used the new syringe and needle system. Loretta Holmes, RN, PharmD. From DMEPA reviewed the usability study results and updated labeling for Information For Use (IFU) of this product. Dr. Holmes has stated the following from her 19 May 2014 review:

The Division of Psychiatry Products (DPP) asked DMEPA to review the Risperdal Consta Usability Study results (version date October 22, 2013). This is the third of three Risperdal Consta validation usability studies conducted. The previous two studies resulted in additional changes to the kit and/or labeling that required revalidation. DPP also requested a review of the revised kit and labeling to determine if the revised product is at risk for medication errors.

...Janssen has proposed several changes to the Risperdal Consta kit components (see Appendix F.1) in order to address concerns with the currently marketed kits. These concerns relate to detachments or loosening of kit components occurring before, during, or after drug administration and leakage or clogging of the vial adaptors. Some of these detachments and loosening have resulted in needle stick injuries to healthcare providers, the needle being retained in the patient after injection, and leakage during drug preparation and administration.
Thus, Janssen has proposed the following changes to the kit components:
- *Replacing the current Beckton Dickinson glass syringe barrel with Nuovo OMPI glass syringe barrels with roughened conus surface*
- *Replacing the current Smiths Medical needles with Terumo needles*
- *Replacing the current Alaris vial adapters with West vial adapters*
- *Updates to the IFU and Full Prescribing Information*

To validate the proposed changes, Janssen conducted three usability studies. After each of the first two studies, additional changes to the kit and/or labeling were introduced, requiring revalidation.

...In the third usability validation study, each participant was asked to conduct four trials, with the first trial being conducted without training. The trials' success rates increased after participants received training on the use of the kit and with each successive trial as compared to using the IFU alone. However, the overall success rate was only 76% for both the naïve and experienced user groups on the final trial (see Appendix D.2 for the list of user tasks and use errors). This is less than expected given the fact that all participants were ultimately allowed to use the IFU and given training. Furthermore, a significant amount of failures and errors continued to occur despite the training received. Use errors that persisted included handling the kit components in a way that risked needle sticks or jeopardized sterility and included: use of two hands to engage the needle safety device, neglect to swab the vial with alcohol, not fully reconstituting the medication (because of not shaking the vial for at least 10 seconds), and accidentally touching the luer connection of the vial adapter or needle. Additionally, participants persisted in neglecting to hold the syringe by the white collar while making or breaking luer connections and neglecting to mention to allow the kit to warm to room

temperature before use. Directions for these user tasks are part of the currently approved IFU, and they are also addressed in the proposed IFU. However, it is not clear why these types of errors continued to occur despite participants' use of the IFU and training since the participants were not specifically probed on each error committed to determine the root cause.

We realize that some of the use errors committed, such as failure to swab the top of the vial with alcohol, recapping the needle, and closing the needle protection device with both hands instead of using one, may not be new for Risperdal Consta or unique to this kit and may occur with kits containing similar types of components. Therefore, it is unlikely that all of these use errors can be eliminated. While our analysis did not determine that the revised IFU and kit components are more vulnerable to medication errors compared to what is currently marketed, the fact that the number of user failures were high in the final trial by participants despite use of the revised IFU and training is concerning. Thus, we will closely monitor for any post marketing reports of medication errors or confusion involving the use of Risperdal Consta.

Additionally, we recommend DPP consider whether a post market commitment (PMC) to have the company submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, may be reasonable given the high failure rate observed in the usability study. If a PMC is imposed, the Applicant should determine an appropriate means to ensure that these reports are easily identifiable as relating to the new kits versus the currently marketed kits.

In addition, Dr. Holmes has made the following recommendations to DPP:

1. We recommend DPP consider whether a post market commitment (PMC) to have the company submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, may be reasonable given the high failure rate observed in the usability study.
2. We recommend Janssen submit their plans for introducing the new Risperdal Consta kits into the marketplace.
3. We recommend Janssen submit their plans for tracking medication errors and product complaints involving the new kits and clarify how they will address the challenges of differentiating reports for the new kits from reports involving the currently marketed kits.

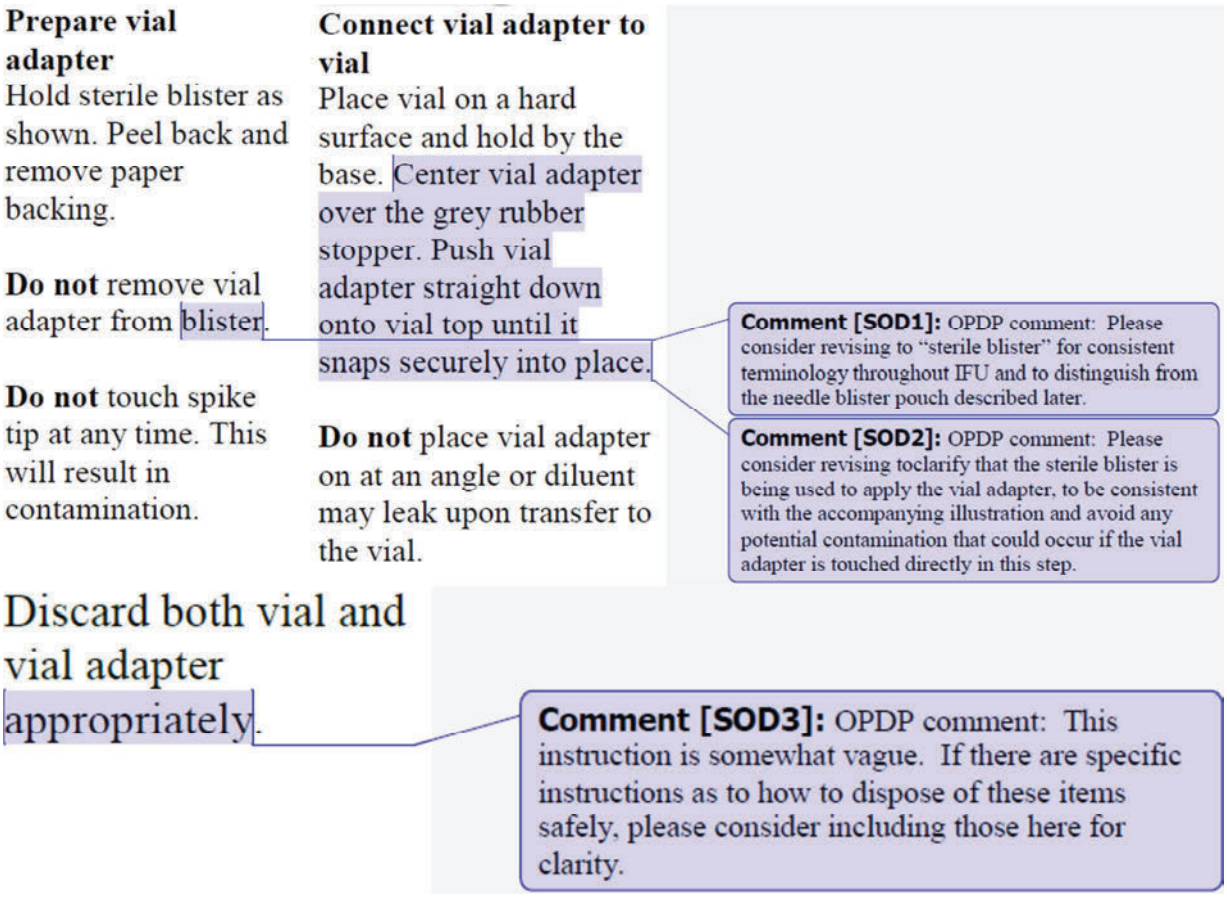
In review of previous communications with the sponsor, the sponsor has committed to provide the Agency bi-monthly report of device failures as stated on page 8 in a 6 Oct 2011 Quality improvement, monitoring and Risk Remediation Plan:"

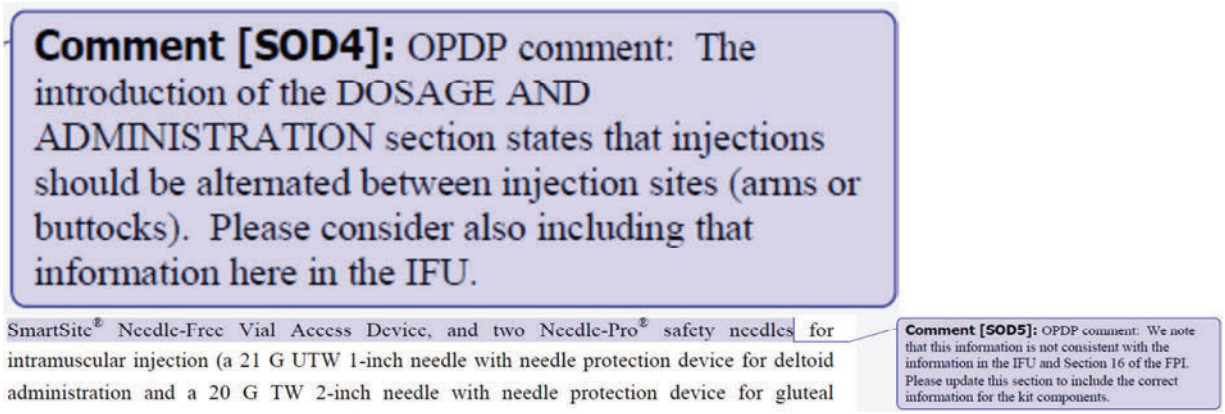
As was done previously, the Company commits to providing FDA with updated data and information on RISPERDAL® CONSTA® drug product quality improvement actions (including updated complaint data) in the form of bi-monthly (alternating months) reports to be submitted to the NDA's primary FDA review division in CDER, with a copy to FDA CDRH.

This reviewer agrees with Dr. Holmes' recommendation. However, I feel that a risk management plan is a more appropriate strategy to ensure product quality and reduce product errors. In addition, expedited reports of serious adverse events related to product quality and use of product be included as part of the risk management plan.

This reviewer also agrees with recommending to the sponsor to submit their plans for introducing and tracking medication errors and product complaints as part of the approval letter.

Also, the Office of Prescription Drug Promotion (OPDP) was consulted by the division on 11 March 2014 to review the Information for Use provided by the sponsor. Susannah O'Donnell, MPH reviewed the IFU. Several recommended comments were made regarding the IFU as listed below:





These recommendations were considered by the division. Since the labeling recommendations provided by OPDP contained recommendations found in other parts of the labeling, in my opinion these labeling recommendations are not critical to be adopted by the sponsor, but rather duplicative of labeling already in place in the label. Therefore I recommend that these recommendations not be included into the IFU at this time.

9. Advisory Committee Meeting

An advisory committee meeting was not held to discuss finding from this application.

10. Pediatrics

No preclinical or clinical juvenile or pediatric data was submitted to the Agency with this submission.

11. Other Relevant Regulatory Issues

There are no outstanding regulatory issues at this time with this product.

12. Labeling

Dr. Holmes made the following labeling recommendations to the sponsor. All of these recommendations were adopted by the sponsor:

A. Instructions for Use:

1. Risperdal Consta should be allowed to sit at room temperature for 30 minutes before reconstituting. To help mitigate the user errors identified with this task, we recommend moving the instruction for waiting so it immediately precedes instructions for assembling components. Additionally, the instruction for waiting could be marked as "Step 1", with step 1 consisting of tasks required to prepare for injection. Subsequent steps should then be renumbered accordingly.

2. Under Step 1 and Step 3, we recommend bolding the statement "clockwise twisting motion" for added prominence.
3. Under Step 1: "Connect syringe to vial adaptor", consider bolding, changing font color, or some other means to highlight the sentence portion "Hold syringe by white collar" to bring prominence to this instruction
4. Under Step 2, we recommend bringing more prominence to the 10 second timer graphic and/or the instruction about shaking for at least 10 seconds. Consider the use of color or some other means to bring attention to this since there were user errors with completing this task.
5. Under Step 3: "Attach needle", consider bolding, changing font color, or some other means to highlight the sentence portion "Holding the white collar on the syringe" to bring prominence to this instruction.

B. Dosage and Administration, Full Prescribing Information:

Ensure that under Dosage and Administration section 2.8 of the Full Prescribing Information, the instructions are updated for consistency with changes made to the IFU.

C. How Supplied/Storage and Handling, Full Prescribing Information:

Update this section with accurate information about the newly proposed kit components.

13. Recommendations/Risk Benefit Assessment

This reviewer recommends APPROVAL of this chemistry supplement.

A. Risk Benefit Assessment

The re-designed kit appears to reduce the risk of inadvertent needle detachments and possibly needle injuries with use when compared to the original Consta kit. However the high failure rates seen in the third usability study reviewed by Dr. Holmes indicates that a high number of product quality and use errors may still occur with the newly-designed product.

B. Recommendation for Post marketing Risk Evaluation and Management Strategies

The following Risk Management strategies have been agreed-upon with the sponsor and are recommended to be sent to the sponsor as part of the approval letter:

1. **We request that you submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, given the high failure rate observed in the usability study.**
2. **We request that you submit your plans for introducing the new Risperdal Consta kits into the marketplace.**

3. **We request that you submit your plans for tracking medication errors and product complaints involving the new kits and clarify how you will address the challenges of differentiating reports for the new kits from reports involving the currently marketed kits.**

4. **We request that you submit product quality and use-related serious adverse events in expedited fashion to the Agency.**

C. Recommendation for other Post marketing Requirements and Commitments

There are no recommendations for other post marketing requirements of commitments at this time.

D. Recommended Comments to Applicant

The comments bolded under section B in this section of the review as reviewed above are recommended to be conveyed to the sponsor with the approval letter as agreed-upon risk management strategies.

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/s/

MARK A RITTER
06/05/2014

MITCHELL V Mathis
06/05/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s052

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Prior approval NDA supplement
Application Number(s)	NDA 21346/S-052
Priority or Standard	4 month review
Submit Date(s)	2/7/14
Received Date(s)	2/7/14
PDUFA Goal Date	6/7/14
Division / Office	DPP/CDER
Reviewer Name(s)	Lucas Kempf, MD
Review Completion Date	5/2/14
Established Name	Risperdal Consta
(Proposed) Trade Name	Risperdal Consta
Therapeutic Class	Antipsychotic
Applicant	Janssen Pharmaceuticals
Formulation(s)	Injection Kit device
Dosing Regimen	Every 2 weeks
Indication(s)	Antipsychotic
Intended Population(s)	Schizophrenia and Bipolar Disorder

Template Version: March 6, 2009

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APPEARS THIS WAY ON ORIGINAL

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Risperdal Consta is a long acting injectable antipsychotic with indications for the treatment of schizophrenia and the maintenance of bipolar disorder. The finished product kit contains risperidone microspheres in a stoppered glass vial, diluent in a pre-filled glass syringe (b) (4) a vial adaptor, and two different length and gage needles. There were changes to the Instruction for Use (IFU) leaflet to reflect the changes in the products. I recommend that the new kit be approved. The redesigned product in an improvement on previous designs and pose no additional risk to the existing device. IFU changes showed no difference in user errors.

1.2 Risk Benefit Assessment

The redesign was done to overcome several safety issues. These hazards were assessed via a hazard analysis and a Failure Mode and Effects Analysis (FMEA). The results of the analyses are documented in DS-TEC-15122, *Risperdal® Consta® Hazard Identification;* DS-TEC-8066, *Risperdal Consta User Failure Modes and Effects Analysis (FMEA)*; and DS-TEC-8584, *Risperdal Consta Preparation and Administration Kit Design Failure Mode and Effect Analysis.* The foremost safety issue was failure due to syringe component disconnections. The high rate of comorbid HIV and infectious hepatitis in this population is a concern for practitioner safety in addition to the distress in this psychiatrically vulnerable population. Additionally, this product is used primarily for treatment non-adherent patients that partial dosage delivery is a concern for efficacy of the product.

The device components appear to fit better together and lock when properly assembled. The major difficulty with disconnections lies in the fact that when assembling the device the health professional needs to hold a small plastic ring at the tip of the syringe rather than the standard grip of the barrel to attach the needle with a Luar locked needle. This leads to the syringe only nesting in the needle and relying on friction to not disconnect during injections and while mixing the components. Roughing the conus of the syringe tip helped with the mechanical tightness due to increased friction of the fit but even with the redesign of the label the end users continued to assemble it improperly and will continue to have disconnections when injecting against resistance and when removing the needle from the patient. The needles were also change and also show an improved fit with the roughened conus.

Broader issues of ease of administration are revealed in their user studies that were not improved by label design of their IFU. Redesign of the label did not seem to improve the rate of other user errors in novel or experienced practitioners though it appears clearer and removes distracting trade name component parts. Practitioners

continued to not use sterile technique, warm the product properly, handle the needle properly, inject properly and shake the product sufficiently. It is encouraging that after the Dear Health provider letter and field calls in February 2012 the rate of complaints decreased. The difficulties with the non-standard injection protocol continue to be a problem with this product that has been on the market since 2003. It was the first injectable *atypical* antipsychotic but now has several competitors on the market with greater ease of administration. The need for reeducation is evident with a recent post marketing reports bare evidence of this fact with a report of a practitioner attempting to inject the diluent into a patient.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I would suggest further targeted and continuing education of end users if a better designed product is not being pursued. Continued reporting on events need to continue due determine the effects of the change in the kit. A tracking procedure for the new kits needs to be proposed due to the likelihood that both kits will be in circulation for a limited time and it will be difficult to ascertain the which kit is failing in the reports.

1.4 Recommendations for Postmarket Requirements and Commitments

Due to the relatively small number of persons in the user studies, I recommend continued averse event reporting in regards to kit failures.

2 Introduction and Regulatory Background

2.1 Products for replacement

Table 1.

Component	Currently Approved	Proposed
(b) (4) I glass syringe barrel container for diluent	Becton-Dickinson or Nuova OMPI supplied with luer tip conus having smooth exterior surface	Nuova OMPI supplied with luer tip conus having roughened exterior surface
2-inch gluteal injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo
1-inch deltoid injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo

Vial adapter	Alaris type supplied by CareFusion	Supplied by West/Medimop

2.2 Summary of Presubmission Regulatory Activity Related to Submission

The proposed changes to the Risperdal Consta injection kit were the subject of a Type C meeting held on 9 December 2013, and were summarized in a pre-meeting briefing document filed to FDA on 6 November 2013.

Since a replacement for the Alaris™ SMARTSITE® Needle-Free vial adapter device component had been selected, a similar vial adapter manufactured and supplied by West/Medimop. As the replacements for the current Smiths Medical 1-inch deltoid and 2-inch gluteal injection needles with safety shields, similar but improved 1-inch deltoid and 2-inch gluteal injection needles with safety shields, manufactured and supplied by Terumo, were selected. In addition, the exterior surface of the conus (i.e., luer tip) surface of the diluent glass syringe barrel had been roughed.

The following were done to validate these changes:

-On 6 October 2011, the Company provided to FDA a drug product kit device quality risk mitigation plan.
-On 9 November 2011 and on 11 January 2012, the Company provided FDA with a draft protocol for a summative human factors study (HFS), for which agreement was reached with FDA on 26 April 2012.
-On 23 December 2011, the Company filed a prior-approval NDA supplement (S-047) for a change in the supplier of the glass syringe barrel primary container for diluent from the previous Becton-Dickinson supplied glass syringe barrel to one supplied by Nuova OMPI (Agency approval of this supplement was granted on 10 October 2013; both had a smooth finish luer tip/conus).
-In February 2012, two formative type HFS were completed to validate the overall design approach to be used in the summative HFS.
-In September 2012, an initial summative HFS was completed using finished drug product kits that included new injection needle and vial adapter device components, in addition to the new glass syringe barrel.
-Based on the results of the initial summative HFS, the new OMPI glass syringe barrel was changed to slightly roughen the exterior luer tip/conus surface and then conduct a follow-up summative HFS.
-In May 2013, a follow-up summative HFS was completed, the results from which indicated improvements in device performance compared to the initial summative HFS results.
-In September of 2013, an additional HFS was completed to validate an improved IFU leaflet.
-Preliminary and final design verification testing of the new devices at the laboratory scale has been completed.
-The 510(k) (K113422) for Terumo's SurGuard®3 (abbreviated herein as SG3) deltoid and gluteal injection needles received FDA premarket clearance on 5 March 2012.

The completed tests and activities described above were intended to ensure that the drug product kit device components (vial adapter and injection needles), along with the modified glass syringe barrel conus, function as designed to reduce the risk of inadvertent disconnections during use and do not pose any additional risks.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

All the submitted documents appear in order.

3.2 Compliance with Good Manufacturing Practices

Manufacturing sites need to be inspected for compliance.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Due to the fact that the product change was for the injection kit that majority of the review is covered in the devices are reviewed by CDRH Office of Compliance and CDRH/ODE/DAGRID/GHDB by Chemistry. Please refer to their reviews for details. They report no further deficiencies.

5 Review of Safety

Safety Summary

5.1 Methods

All new components were tested >10 times for verification that they conform to the mechanical properties requirements. With one exception, the number of tests was determined by the distribution of the variance of the mechanical properties being studied. The case of the shear force for breaking the syringe cap which has a high variance and was tested well in the clinic. If the components met or exceeded the expectations they were included in the new test kit for human factor studies.

Additionally, the test kits were tested using Human Factor Studies (HFS) in two formative and three summative studies. They were examining the performance of the system of device components used to prepare and administer a dose of the drug product, and to validate the use of an improved Instructions-For-Use (IFU) leaflet. These studies were designed following the principles outlined in FDA's draft guidance ***Applying Human Factors and Usability Engineering to Optimize Medical Device Design***, and used a protocol that was reviewed by FDA prior to the conduct of the pivotal summative studies. Each study was conducted by the same contract research organization (b) (4).

5.1.1 Studies/Clinical Trials Used to Evaluate Safety

The studies conducted are of two categories. The first being the mechanical testing of the component parts and the second being the Human facto studies. They are listed below.

Medical Device Component Design Testing Results
Table 2 digitally copied below:

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5.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Table 5 Percent Incidences in HFS 1, 2, and 3.

Errors	HFS 1	HFS 2	HFS 3
Device component disconnections	5.2%	2.1%,	2.2%.
Needle detachments	1%	0.6%,	1.4%
Not holding the collar by the white ring	34%	41%	52%

5.2 Adequacy of Safety Assessments

The HFSs were adequate to define the user errors. No previously unidentified device failure modes/effects, or new patterns of use failures, were observed in these studies.

Future studies could use a mannequin that would have resistance with injecting similar to real tissue since this is a reported failure type reported in post marketing reports.

5.3 Major Safety Results

The results from summative HFS Study No. 2 demonstrated that the roughening of the glass syringe barrel conus luer tip provides improved connections between the syringe and either the vial adapter or the injection needles, particularly in terms of device component-attributable disconnects, as well as either vial adapter or injection needle detachments. These results confirmed the improvement in connection security demonstrated in the design verification tests described above, even when the observed connections were made using the syringe barrel to tighten the connections (i.e., not using the luer locking method as described in the IFU). Since this user error is a major source of kit failures that is important improvement but the occurrence in the field is low frequency and true estimates could not be obtained in the HFS.

The purpose of HFS Study No. 3 was to validate a reformatted IFU, including improved illustrations, that was developed as single-page labeling that would allow for easier reference by users performing the dose reconstitution and administration tasks. The goal of this study was to show that the revised IFU had no discernible negative impact on the usability and safety of the devices, and that overall the IFU continues to supply the necessary instructions for use of the product. In addition, the study solicited participant preferences for either the IFU used in Study No. 2, or the reformatted IFU

used in Study No. 3. From the Study No. 3 data presented above, the reformatted IFU did improve the overall performance. There was no improvement in subject holding the white ring properly and perhaps it even got worse with the new IFU but the small number of participants makes generalizations difficult.

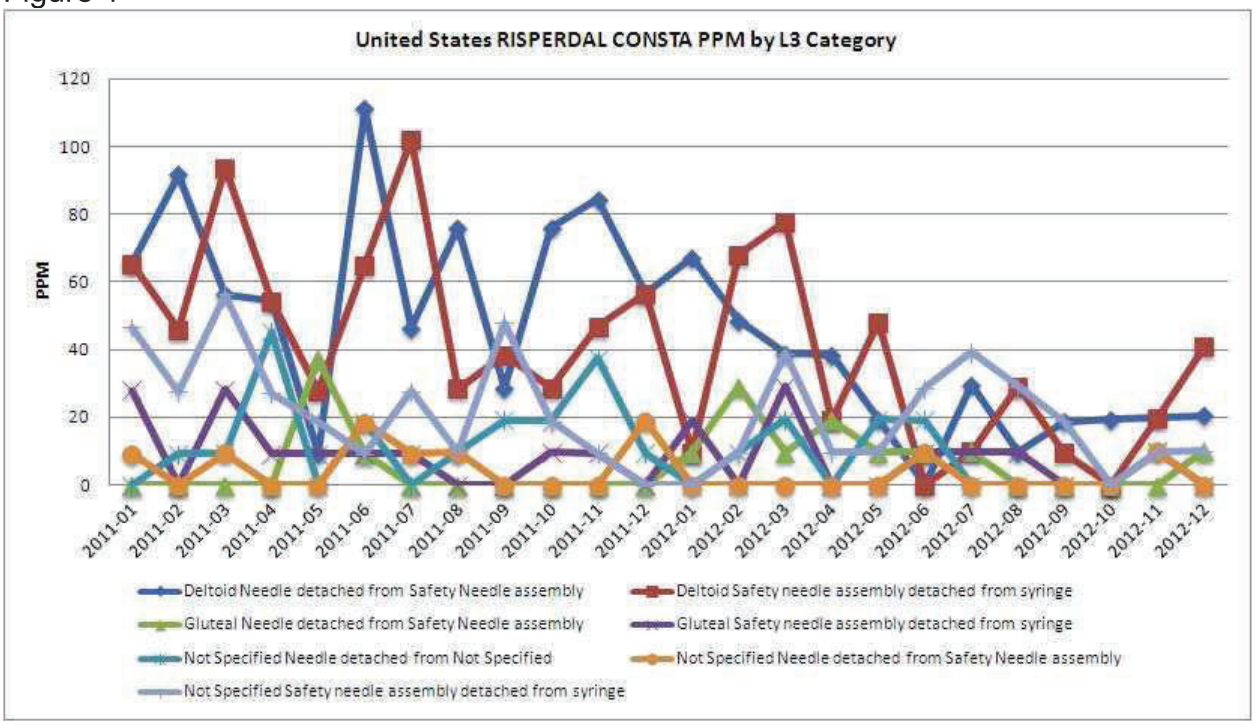
Participants were generally able to answer almost all of the IFU comprehension test questions correctly when using either the original IFU version used in Study No. 2, or the reformatted IFU used in Study No. 3. Despite the apparent lack of performance improvement for the reformatted IFU in Study No. 3 compared to Study No. 2, participants generally indicated a preference for the reformatted IFU, citing its improved layout, increased readability, and more concise wording.

Some of the observations in the HFS also reflect user errors that deviate from the expected professional training and practices for injection devices, aseptic techniques, and/or occupational safety-related precautions of which general training in school seem to have been neglected.

6 Postmarket Experience

The digitally copied below graph demonstrates the improvement of the health provider conduct after Janssen provided a Dear Health Provider Letter and targets field education in 2/2012 with their previous product. Provider education appears to successfully impact user errors but does not eliminate the problem.

Figure 1



The new kits and IFU have not yet been used on the market.

7 Appendices

7.1 Labeling Recommendations

Bolding the “hold white collar” and “Wipe top of the grey stopper with an alcohol swab” may improve compliance with these steps.

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/s/

LUCAS B KEMPF
06/02/2014

MARK A RITTER
06/02/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s052

PRODUCT QUALITY REVIEW(S)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA number: 21346**

2. **Submission(s) Being Reviewed: S052**

Supplement Number	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
PAS	776	2/7/14	2/7/14	3/5/14	6/7/14	5/29/14

3. **Proposed Changes: Supplement provides for changes to drug product kit components and associated labeling.**

4. **Review #: 1**

5. **Clinical Review Division:** CDER/ODE1/DPP

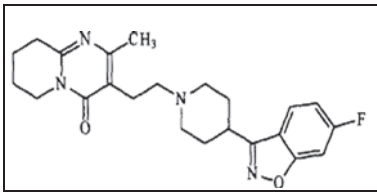
6. **Name and Address of Applicant:**
Janssen Pharmaceuticals, Inc.
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560-0200
(b) (6)

7. **Drug Product:**

Proprietary Name	Nonproprietary Name (USAN) of Drug Substance	Indication	Dosage Form	Strength	Route of Administration
Risperdal Consta (Risperidone)	Risperidone	Treatment of schizophrenia and as monotherapy or adjunct therapy to lithium or valproate for maintenance of bipolar I disorder	Dose pack of vial containing risperidone microspheres and a pre-filled syringe with diluent	12.5, 25, 37.5 and 50 mg	Deltoid or gluteal IM injection

Rx or OTC	Special Product?
Rx	-

8. **Chemical name and structure of drug substance:**



Chemical name: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-a]pyrimidin-4-one

Molecular formula: $C_{23}H_{27}FN_4O_2$
MW: 410.48

9. Supporting/Relating Document: NA

10. Consults:

- **DMEPA review by Loretta Holmes dated 5/19/14 is acceptable.**
- **CDRH Office of Compliance review is acceptable dated 5/21/14 by Jennifer Kelly**
- **CDRH review by Kathleen Fitzgerald dated 5/21/14 requested additional information. Follow-up memo dated May 28, 2014 evaluated all the responses to FDA requests and found them adequate.**

11. Summary/Remarks: None

12. Conclusions & Recommendations: Recommend Approval from CMC perspective.

13. Comments/Deficiencies to be Conveyed to Applicant: None

14. Primary Reviewer: Gurpreet Gill-Sangha, Ph.D., CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

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3. Please provide complete test reports for break loose, glide force and dose accuracy for the syringe when used with the drug.

A follow-up review dated May 28, 2014 was able to evaluate responses to all these deficiencies and found the responses from the sponsor adequate.

Labeling:

There are no changes to the package insert for **Dosage Forms and Strengths, Description and How Supplied** sections of the label. The changes include an updated "**Instructions for Use"** section.

Evaluation: Acceptable as there are no changes to the quality components of the package insert. Please note that Loretta Holmes from DMPEA has reviewed the changes to "Instructions for Use" information and provided some recommendations to the clinical division and the applicant as well. Refer to Loretta Homes review dated 5/19/14 for details on recommendations.

RECOMMEND APPROVAL

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/s/

GURPREET K GILL SANGHA
05/29/2014
N21346-S52-AP-cmc-ggs

HASMUKH B PATEL
05/29/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021346Orig1s052

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: June 3, 2014

To: Ann Sohn, PharmD
Regulatory Project Manager
Division of Psychiatry Products (DPP)

From: Susannah K. O'Donnell, MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA #021346**
Risperdal® Consta® (risperadone) Long-Acting Injection

OPDP has reviewed the draft instructions for use (IFU) for Risperdal® Consta® (risperadone) Long-Acting Injection as requested in the consult from DPP dated March 11, 2014.

OPDP's review of the draft IFU is based on the version provided by Ann Sohn via email on June 2, 2014. Comments are provided directly on the attached label below.

If you have any questions, please feel free to contact me by phone at 301-796-3245 or by email at Susannah.ODonnell@fda.hhs.gov.

OPDP appreciates the opportunity to provide comments on these materials. Thank you!

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/s/

SUSANNAH O'DONNELL
06/03/2014

REGULATORY PROJECT MANAGER

LABELING REVIEW

Division of Psychiatry Products

Date: June 4, 2014

Application Numbers: NDA 21346/S-052

Name of Drug: Risperdal Consta (risperidone) long-acting injection

Applicant: Janssen Pharmaceuticals, Inc.

Material Reviewed:

NDA	Supplement #	Submission Date	Receipt Date	Supplement Type	Status
21346	S-051 Resubmission	4-30-13 11-12-13	4-30-13 11-12-13	PA	CR 9-25-13 AP 4-28-14
21346	S-052	2-7-14	2-7-14	PA	Pending

Background and Summary

1. For last approved labeling see table above.
2. The sponsor submitted a prior approval CMC supplement proposing new device components and changes to the instructions for use.

Review

A new Instructions for Use section was added to replace old section for the new device components:

Instructions for Use

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.

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The same information is repeated in the stand alone IFU (attached).

Recommendations

1. This supplement only provides for the above labeling changes when compared to the last approved labeling supplement (see table above).
2. The clinical reviewer agrees with the sponsor's proposed changes.
3. I recommend that an approval letter issue for these pending applications.

{See appended electronic signature page}

Ann Sohn, Pharm.D.
Regulatory Project Manager

{See appended electronic signature page}

cc: annotated labeling

Paul David, R.Ph.

Chief, Project Management Staff

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/s/

ANN J SOHN
06/05/2014

PAUL A DAVID
06/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: May 28, 2014
From: Kathleen FitzGerald, Nurse consultant WO66, RM2560
CDRH/ODE/DAGRID/GHDB
To: Robert Levin
CDER, Division of Psychiatry Products
Subject: CDRH Device review for NDA 21346-Janssen Pharmaceuticals, Inc

1. Issue:

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH) regarding NDA 21346. CDRH has been consulted to review the new device kit components that include a glass barrel syringe, safety needle and vial adapter

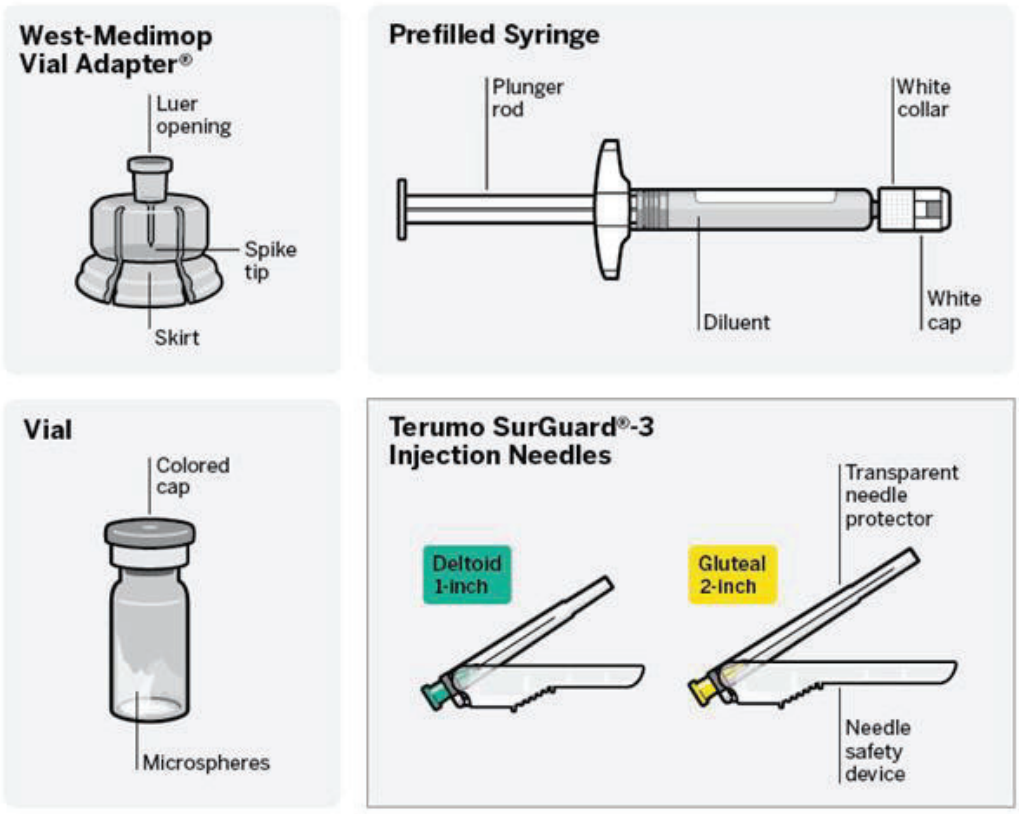
The Sponsor is replacing the device components currently included in RISPERDAL® CONSTA® finished drug product kits. The proposed changes to the drug device kit are as follows:

As the replacement for the current Alaris™ SMARTSITE® Needle-Free vial adapter device component, a similar but improved vial adapter manufactured and supplied by West/Medimop has been selected. As the replacements for the current Smiths Medical 1-inch deltoid and 2-inchgluteal injection needles with safety shields, similar but improved 1-inch deltoid and 2-inchgluteal injection needles with safety shields, manufactured and supplied by Terumo, have been selected. In addition, an improvement to the exterior surface of the conus (i.e., luer tip) surface of the diluent glass syringe barrel has been developed.

2. **Device Description:**

As the replacement for the current Alaris™ SMARTSITE® Needle-Free vial adapter device component, a similar but improved vial adapter manufactured and supplied by West/Medimop has been selected. As the replacements for the current Smiths Medical 1-inch deltoid and 2-inchgluteal injection needles with safety shields, similar but improved 1-inch deltoid and 2-inchgluteal injection needles with safety shields, manufactured and supplied by Terumo, have been selected. In addition, an improvement to the exterior surface of the conus (i.e., luer tip) surface of the diluent glass syringe barrel has been developed.

Device Component	Currently Approved	Proposed
Vial Adapter	Alaris SMARTSITE Needle-Free vial access device, supplied by Care Fusion	Vial Adapter Device, supplied by West-Medimop (K072511)
Injection Needles with Safety Shield	2-inch gluteal injection needle 1-inch deltoid injection needle Both supplied by Smiths medical	2-inch gluteal injection needle 1-inch deltoid injection needle Both supplied by Terumo (K113422 & K122249)
Diluent Primary Container Glass Syringe Barrel	(b) (4) glass syringe barrel, supplied by Becton-Dickinson with luer tip conus having smooth exterior surface.	(b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group, with luer tip conus having roughened exterior surface



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Plunger rod travel force-injection of drug product 1-inch deltoid injection needle 2-inch gluteal injection needle	(b) (4)	Pass Pass
Force to remove (b) (4) cap from syringe barrel conus		Pass
Insertion force of vial adapter spike into vial stopper		Pass
Vial adapter attachment force		Pass
Force to disconnect vial adapter from vial		Pass

3. Documents Reviewed:

- NDA 21346, briefing package device sections
- Meeting Request Information packet
- 510(k) submission K113422, Termuo Safety Needle
- Special 510(k) submission K122249, Termuo Safety Needle
- 510(k) submission K072511, Medimop Vial Adapter
- MAUDE-device adverse reporting for 510(k) cleared devices
- Appendix B-510(k) Reference Authorization Letter (Terumo)
- Appendix C-510(k) Reference Authorization Letter (West/Medimop)
- Stevanto group Authorization letter to review DMF (b) (4) for pharmaceutical usage, Annex 295
- DMF (b) (4)

4. CDRH Review and Comments:

This review was limited to the new device kit components which include (b) (4) glass barrel syringe, safety needle and vial adapter.

The following assessment and comments are based on the documents provided by the Sponsor and CDER regarding the proposed devices in RISPERDAL® CONSTA® new device kit:

The Terumo SurGuard 3 Safety Needle device has been cleared by ODE/CDRH/GHDB in 510(k) submissions K113422 and K122249. All relevant information and test reports are present in 510(k) submissions K113422 and K122249 for this device. There have

been no adverse events reported regarding the Terumo SurGuard 3 Safety Needle in the FDA MAUDE data base.

The Swabable Vial Adapter device has been cleared by ODE/CDRH/GHDB in 510(k) submission K072511. All relevant information and test reports are present in 510(k) submission K072511 for this device. There have been no adverse events reported regarding the Swabable Vial Adapter in the FDA MAUDE database.

The Sponsor has provided a summary of the performance test completed and device information regarding the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group, with added roughened-surface conus. The Sponsor provided an authorization letter from Stevanato Group for review of DMF (b) (4) (b) (4) No data on the performance testing could be located in DMF (b) (4) to be used in the new device kit. The Sponsor needs to provide complete information and test reports to assess the safety and effectiveness of the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group. The Sponsor should provide the following for the proposed (b) (4) glass barrel syringe in the RISPERDAL® CONSTA® new device kit:

1. Please provide the certificate of conformance to ISO 11040. If you do not have a certificate of conformance, please provide your complete bench performance testing on your syringe that demonstrates the safety and effectiveness of your device.
2. Please provide complete test reports that show the 2-inch gluteal injection needle 1-inch deltoid injection needle ,both supplied by Terumo (K113422 & K122249), is compatible with the 3ml glass syringe (no leakage, doesn't fall off, doesn't damage syringe tip, etc).
3. Please provide the break loose, glide force and dose accuracy for the syringe when used with the drug.

5. Recommendation:

The Sponsor has provided a summary of the performance test completed and device information regarding the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group, with added roughened-surface conus. The Sponsor provided an authorization letter from Stevanato Group for review of DMF (b) (4) fo (b) (4) glass syringes (b) (4) No data on the performance testing could be located in DMF (b) (4) for the (b) (4) glass syringe to be used in the new device kit. The Sponsor needs to provide complete information and test reports to assess the safety and effectiveness of the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group.

The Sponsor should provide the following for the propose (b) (4) glass barrel syringe supplied by Nuovo OMPI, Stevanato Group in the RISPERDAL® CONSTA® new device kit:

1. Please provide the certificate of conformance to ISO 11040. If you do not have a certificate of conformance, please provide your complete bench

performance testing on your syringe that demonstrates the safety and effectiveness of your device.

2. Please provide complete test reports that show the 2-inch gluteal injection needle 1-inch deltoid injection needle ,both supplied by Terumo (K113422 & K122249), is compatible with th (b) (4) glass syringe (no leakage, doesn't fall off, doesn't damage syringe tip, etc).
3. Please provide complete test reports for break loose, glide force and dose accuracy for the syringe when used with the drug.

6. **Sponsor's Responses to CDRH's Recommendations:**

The Sponsor was asked to provide the following for the proposed (b) (4) glass barrel syringe supplied by Nuovo OMPI, Stevanato Group in the RISPERDAL® CONSTA® new device kit:

1. Please provide the certificate of conformance to ISO 11040. If you do not have a certificate of conformance, please provide your complete bench performance testing on your syringe that demonstrates the safety and effectiveness of your device.
   Sponsor's Response: The Sponsor has provided a signed certificate of conformance to ISO 11040-4:2007 for the (b) (4) glass syringe supplied by Nuovo OMPI, Stevanato Group.
2. Please provide complete test reports that show the 2-inch gluteal injection needle 1-inch deltoid injection needle ,both supplied by Terumo (K113422 & K122249), is compatible with the (b) (4) glass syringe (no leakage, doesn't fall off, doesn't damage syringe tip, etc).
   Sponsor's Response: In response to No. 2, the full design verification report was located in CTD Section 32P24 Appendix D, but I have attached another copy of it for your reviewer's convenience.
3. Please provide complete test reports for break loose, glide force and dose accuracy for the syringe when used with the drug.
   Sponsor's Response: Break loose and glide force are not tests that have been performed for Risperdal CONSTA, since it does not use an autoinjector, for which such tests are standard. Same with dosing accuracy, since the volume of the syringe, the amount of drug in suspension, and the injection needle dimensions associated with the new device components are not changing from what they were at the time of original NDA approval.

CDRH's Response: The Sponsor has adequately addressed all deficiencies. I have no additional recommendations at this time.

Please contact Kathleen FitzGerald at (301) 796 – 6292, if you have any questions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Kathleen E. Fitzgerald -S Digitally signed by Kathleen E. Fitzgerald -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -S Date: 2014.05.28 13:11:30 -04'00'
Branch Chief Sign-Off	
Division Sign-Off	

APPEARS THIS WAY ON ORIGINAL

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/s/

TESHARA G BOUIE
05/28/2014
On behalf of Kathleen Fitzgerald (CDRH ODE).

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: May 21, 2014
From: Kathleen FitzGerald, Nurse consultant WO66, RM2560
CDRH/ODE/DAGRID/GHDB
To: Robert Levin
CDER, Division of Psychiatry Products
Subject: CDRH Device review for NDA 21346-Janssen Pharmaceuticals, Inc

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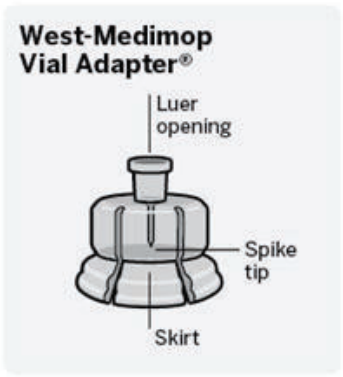
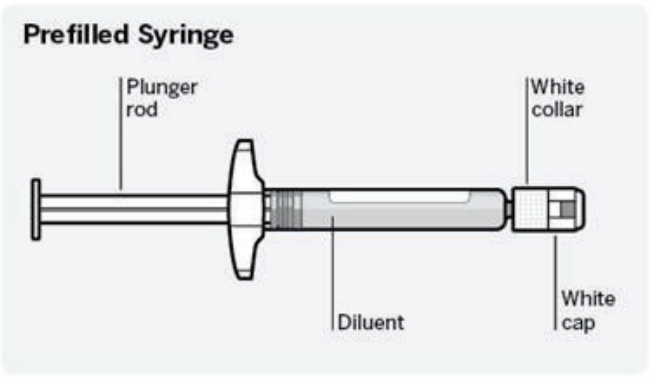
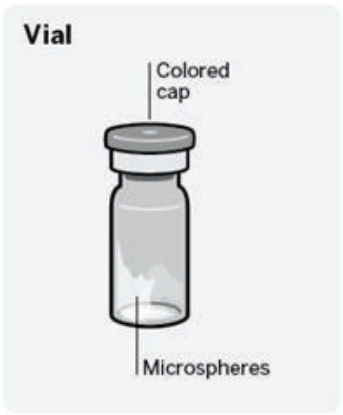
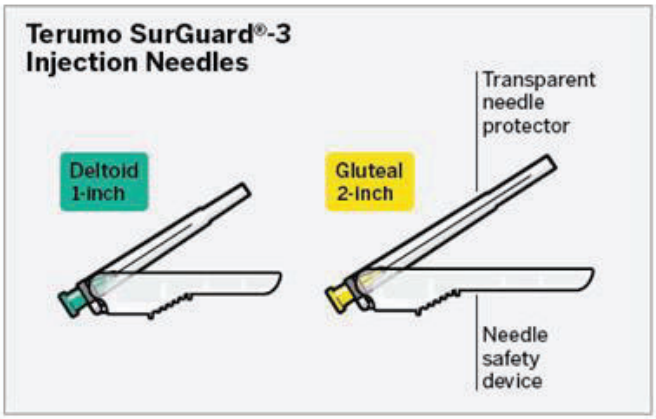
Diluent Primary Container Glass Syringe Barrel	[redacted] (b) (4) glass syringe barrel, supplied by Becton-Dickinson with luer tip conus having smooth exterior surface.	[redacted] (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group, with luer tip conus having roughened exterior surface









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Force to remove (b) (4) cap from syringe barrel conus		Pass
Insertion force of vial adapter spike into vial stopper		Pass
Vial adapter attachment force		Pass
Force to disconnect vial adapter from vial		Pass

3. Documents Reviewed:

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- Meeting Request Information packet
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- 510(k) submission K072511, Medimop Vial Adapter
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- (b) (4)

4. CDRH Review and Comments:

This review was limited to the new device kit components which include a (b) (4) glass barrel syringe, safety needle and vial adapter.

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2. Please provide complete test reports that show the 2-inch gluteal injection needle 1-inch deltoid injection needle ,both supplied by Terumo (K113422 & K122249), is compatible with the (b) (4) glass syringe (no leakage, doesn't fall off, doesn't damage syringe tip, etc).
3. Please provide the break loose, glide force and dose accuracy for the syringe when used with the drug.

5. Recommendation:

The Sponsor has provided a summary of the performance test completed and device information regarding the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group, with added roughened-surface conus. The Sponsor provided an authorization letter from Stevanato Group for review of DMF (b) (4) glass syringe (b) (4) No data on the performance testing c ed in DMF (b) (4) for th (b) (4) glass syringe to be used in the new device kit. The Sponsor needs to de complete information and test reports to assess the safety and effectiveness of the (b) (4) glass syringe barrel, supplied by Nuovo OMPI, Stevanato Group.

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3. Please provide complete test reports for break loose, glide force and dose accuracy for the syringe when used with the drug.

Please contact Kathleen FitzGerald at (301) 796 – 6292, if you have any questions.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Kathleen E. Fitzgerald -S Digitally signed by Kathleen E. Fitzgerald -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -S Date: 2014.05.21 12:49:58 -04'00'
Branch Chief Sign-Off	
Division Sign-Off	

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/s/

TESHARA G BOUIE
05/21/2014
for Kathleen FitzGerald (CDRH ODE).

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

Office of Compliance, Division of Manufacturing & Quality

Respiratory, ENT, General Hospital, and Ophthalmic Device Branch

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DATE: May 16, 2014

TO: Robert Levin, Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, Center for Drug Evaluation and Research

Robert.Levin@fda.hhs.gov

Mitchell Mathis, Division of Psychiatry Products, Division of Psychiatry Products, Office of Drug Evaluation I, Office of New Drugs, Center for Drug Evaluation and Research

Mitchell.Mathis@fda.hhs.gov

Office of combination products at combination@fda.gov

Through: Francisco Vicenty, Chief, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 2642

Francisco Vicenty -S
2014.05.19 14:24:40 -04'00'

From: Jennifer Kelly, REGO, DMQ, OC, CDRH, OMPT. WO-66, Room 3429

Applicant: Janssen

1125 Trenton-Habourton Road, PO Box 200

Titusville, New Jersey 08560

FEI# 3002807336

Application # NDA021346/S-052

Product Name:	Risperdal Consta
Consult Instructions:	We would appreciate any comments and advice regarding the sponsor's proposed new device kit for Resperdal Consta. Do you think the sponsor has provided adequate data to review the application, and does compliance data support approval of the application?

The Office of Compliance at CDRH received a consult request from CDER to evaluate NMD021346/S-052, to review the compliance data for supporting approval of this submission.

Resperdal Consta is indicated for use to treat schizophrenia. Risperdal Consta is a long acting atypical antipsychotic for the treatment of schizophrenia, and in some markets, for the maintenance treatment of Bipolar I Disorder. The drug uses Alkermes' Medisorb technology to deliver and maintain therapeutic medication levels in the body with one intramuscular injection every two weeks. The extended release technology involves encapsulation of the small molecule drug into microspheres made from biodegradable polymer. The dried microspheres are contained in a vial and must be suspended in a diluent prior to intramuscular injection.

Risperdal Consta is administered every two weeks by deep intramuscular deltoid or gluteal injection. Each injection is administered by a healthcare professional using the appropriate safety needle included in the kit. For deltoid administration, a 1-inch needle is used, alternating injections between the two arms. Sufficient muscle mass is required for deltoid muscle injections. For gluteal administration, a 2-inch needle is used, alternating injections between the two gluteal muscles.

Application documents evaluation

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product. The following documents were evaluated:

Documents describing sterilization validation and documentation, the qualification of sterilization cycles (acceptance criteria), release of incoming lots (release controls) and process controls and validation all appear to be adequate.

Detailed information on facilities, operations, validation methods, and microbiological monitoring practices in compliance with current Good Manufacturing Practices are presented, as recommended by FDA, CDER, and CVM in "Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products", dated November 1994 (b) (4)

(b) (4)

(b) (4).

Documentation describing design controls (i.e., the plastic flip-off cap on the aluminum seal does not come in contact with the drug product and is intended to be a unique identifier of the dose strength) appear to be adequate.

Documentation describing injection efficiency and overfill requirements, and functionality testing applying to the scientific evaluation of the factors influencing the use of risperidone extended release microspheres for injection and its diluent for reconstitution appear to be adequate.

The functionality test results supporting the 12.5-mg dose strength of risperidone extended release microspheres for injection in combination with diluent for reconstitution provide assurance that the product can be administered in a consistent, reliable, and predictable manner.

Janssen Research & Development has developed a mid-term solution to address complaints associated with the Risperdal Consta preparation and administration kit. This solution consists of component swap-outs for the vial adapter and safety needle to: (1) further reduce complaint rates, (2) better address unmet user needs, and (3) reduce the potential for future issues that might result in complaints. Changes have also been made to the instructions for use (IFU). The changes appear to be adequate and in compliance.

The firm identified the intended device users by conducting a survey with over 6,500 participants, which indicated that 88% of the users are nurses, the Sponsor recognizes that preparation is sometimes performed by pharmacists and that physicians sometimes prepare and/or administer the product. Physicians and pharmacists are also professionally educated.
The firm identified environmental variables that may affect device use safety and effectiveness:

- Distractions
- Gloved/ungloved hands
- Lighting
- Noise
- Wet/dry finger

Instructions for use and operating sequence appear to be adequate. The Sponsor has implemented the following design modifications and design controls in response to the known use problems listed in their supplement:

- Replaced the original, soft plastic vial adapter packaging with a hard plastic packaging (in response to sterility issues).
- Replaced the original safety needles with Terumo safety needles with improved/enhanced safety shielding mechanisms (in response to accidental needle sticks).
- Made changes to the instructions for use

The firm's risk analysis appears to be adequate. The firm's testing study with representative users appears to be adequate as was their data collection and follow-up risk analysis.

Corrective and preventative actions and Device Design Verification Test Report and Protocol appear to be adequate.

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application

NDA021346/S-052 and has the following recommendations:

Application NDA021346/S-052 is approvable from the perspective of the Medical Device Regulations. The desk review of the application for compliance with the Medical Device Regulations showed no deficiencies, and no facilities need to be inspected with regards to the Medical Devices Regulations prior to approval.

Jennifer Y. Kelly -S

Digitally signed by Jennifer Y. Kelly -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000822908, cn=Jennifer Y. Kelly -S
Date: 2014.05.19 08:02:53 -04'00'

Jennifer Y. Kelly

Prepared: JYKelly: 05/07/14

Reviewed: FVicenty: 5/16/14

CTS No.: ICC1400159

NDA021346/S-052

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Inspectional guidance

Firm to be inspected:

Firm Name

Address

FEI:

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CDRH recommends the inspection under the applicable Medical Device Regulations of Firm Name, located in City, Country (FEI # 12345). OPTIONS:

(1) A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

(2) A limited inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), Final Acceptance Activities (21 CFR 820.80), and Design Controls (21 CFR 820.30)

for the Combination product name (Application number).

Additionally, evaluate the manufacturing activities associated with the manufacturing/assembly of the finished combination product, including in process and final acceptance activities. Detailed inspection guidance will be provided upon request.

Yellow highlights: Delete

Gray fields: Fill-in

ALWAYS: DELETE WHAT DOES NOT APPLY

REGULATORY STRATEGY

The establishment inspection report (EIR) for the firm should be shared with CDRH (The EIR should be assigned to CDER and then sent to CDRH as a consult for review). If the inspection is being classified Official Action Indicated (OAI), the District should consider recommending appropriate regulatory action with consultation from CDER and CDRH and whether the violation is drug or device related.

Questions regarding this consult should be referred to one of the following individuals:

Primary Contact

Reviewer Name
Title,
Branch
Division
Office of Compliance, WO66 RM XXXX
Phone: 301-796-XXXX

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Secondary Contacts (if Primary is unavailable and a timely answer is required)

Branch Chief Name
Chief
Branch Name
Division
Office of Compliance, WO66 RM XXXX
Phone: 301-796- 5770

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THIS ATTACHMENT IS NOT TO BE PROVIDED TO THE FIRM OR SHOWN TO THEM DURING THE INSPECTION. THIS ATTACHMENT CONTAINS PREDECISIONAL INFORMATION

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

/s/

TESHARA G BOUIE
05/21/2014
T.Bouie checking in review on behalf of Francisco Vicenty (CDRH OC).

HUMAN FACTORS STUDY AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 19, 2014
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 021346/S-052
Product Name and Strength:	Risperdal Consta (Risperidone) Long-Acting Injection 12.5 mg, 25 mg, 37.5 mg, and 50 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Pharmaceuticals, Inc.
Submission Date:	February 7, 2014
OSE RCM #:	2014-521
DMEPA Primary Reviewer:	Loretta Holmes, BSN, PharmD
Associate Director Leader:	Irene Z. Chan, PharmD, BCPS

1 REASON FOR REVIEW

This prior approval chemistry supplement (NDA 021346/S-052), submitted on February 7, 2014, proposes changes to the device components supplied in Risperdal Consta kits along with labeling changes in the instructions for use (IFU) leaflet and full prescribing information. See Appendix F for a brief regulatory history and a summary of the proposed changes.

The Division of Psychiatry Products (DPP) asked DMEPA to review the Risperdal Consta Usability Study results (version date October 22, 2013). This is the third of three Risperdal Consta validation usability studies conducted. The previous two studies resulted in additional changes to the kit and/or labeling that required revalidation. DPP also requested a review of the revised kit and labeling to determine if the revised product is at risk for medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B (N/A)
Previous DMEPA Reviews	C
Human Factors Study (HFS)	D
ISMP Newsletters	E (N/A)
Other • Regulatory History and Summary of Proposed Changes • Risperdal Consta Demo Kit • Summary of Risperdal Consta Usability Studies #1 and #2	F
Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Janssen has proposed several changes to the Risperdal Consta kit components (see Appendix F.1) in order to address concerns with the currently marketed kits. These concerns relate to detachments or loosening of kit components occurring before, during, or after drug administration and leakage or clogging of the vial adaptors. Some of these detachments and loosening have resulted in needle stick injuries to healthcare providers, the needle being retained in the patient after injection, and leakage during drug preparation and administration. Thus, Janssen has proposed the following changes to the kit components:

- Replacing the current Beckton Dickinson glass syringe barrel with Nuovo OMPI glass syringe barrels with roughened conus surface
- Replacing the current Smiths Medical needles with Terumo needles
- Replacing the current Alaris vial adapters with West vial adapters
- Updates to the IFU and Full Prescribing Information

To validate the proposed changes, Janssen conducted three usability studies. After each of the first two studies, additional changes to the kit and/or labeling were introduced, requiring revalidation.

3.1 CHANGE IN GLASS SYRINGE

In a 2011 response to an Agency Information Request (IR), Janssen stated the needle disconnects were caused by the needles and not by the syringe. However, they subsequently sought an alternate supplier of syringes for the kit. According to Janssen, the proposed Nuovo OMPI syringe barrel provides better design and manufacturing controls of conus size and shape/taper. In the first usability study, Janssen used an OMPI syringe without a roughened conus. After identifying device attributable detachment issues, they changed to the OMPI syringe with roughened conus surface. The OMPI syringe with roughened conus surface was used in the second and third usability studies, and there were no device component attributable disconnects that occurred in either study.

Additionally, there were no instances where the injection needle remained in the study mannequin in the second and third studies. However, we do not know whether the physical characteristics of the mannequin adequately mimic injection into a human. This information was not found in the submission. Therefore, it is difficult to assess whether this finding can be generalized to humans. We also don't know whether this finding is attributable to the changed syringe, the change in needles (see section 3.2 below), or a combination of both.

The OMPI syringe with roughened conus surface appears to be an improvement as compared the smooth conus surface syringes.

3.2 CHANGE IN NEEDLES

The currently marketed Smiths Medical needles have a two piece luer design that can disconnect at two points. Per Janssen, the Terumo needle safety shield is attached to the injection needle hub as a permanent fastening rather than as an additional luer connection to the needle hub that could loosen during use. This design difference reduces the number of connection points that have historically been involved with disconnections.

Two (2/136, 1.5%) needle detachments occurred in the third usability study. However, these were attributed to user error and not attributed to the needle itself. The use of syringes with roughened conus may have also had an impact on the number of needle detachments so we are not able to attribute this result to the use of Terumo needles alone. Furthermore, there were only 136 trials in this study and we have no data regarding the true rate of disconnections attributed to the Smiths Medical needles. Therefore, the small number of trials and the fact that we have no data to compare it to make it difficult to use this study result to project what may occur when these needles are used on a much larger scale. However, based on the needle descriptions, it appears the Terumo needles are an improvement as compared to those provided by Smiths Medical given there is one less connection point were needle detachment can occur.

3.3 CHANGE IN VIAL ADAPTER

Some of the problems that Janssen identified with the Alaris vial adapter included leakage during reconstitution and also device clogging. Leakage can occur if a blocked pathway for diluent is created by not fully piercing the vial stopper. Per Janssen, the proposed West adapter has an improved spike design and has the interior of the collar designed to help properly center spike insertion and seat the adapter on the vial. Furthermore, the West adapter blister packaging also provides for improved aseptic handling.

There were no reports of leakage or clogging occurring with the West vial adapter during the third usability validation study. There was one vial adapter detachment that occurred; however, the study report did not state whether leakage occurred as a result. Furthermore, the detachment was attributed to user error. The description provided for the West adapter seems to indicate it has characteristics that will help to address the issue of leakage and clogging and are an improvement as compared to the Alaris adapter.

3.4 INSTRUCTIONS FOR USE

The IFU used in the first two validation studies (see Appendix G.2) was revised prior to use in the final usability validation study in an attempt to help further reduce the number of user errors. The overall success rate was similar in the final usability study when compared to the previously conducted usability study, thus it does not appear that the changes in the IFU led to significant improvements in usability of the kit. However, we did not identify any evidence that user failures increased with the introduction of the revised IFU either.

When asked to compare both the revised IFU and the IFU used in the previous usability studies, 44%, (15/34) of participants preferred the revised IFU, 29% (10/34) preferred the previous IFU, and the remainder had no preference. Comments provided by participants when questioned about needed improvements to the revised IFU included: specifying an amount of time after which the medicine could not be used after initial reconstitution; using more color to highlight more important steps and notes in the instructions; and emphasizing that connecting the vial adapter or needle to the syringe required twisting the pieces together. DMEPA has considered these comments and identified some areas where improvements can be made in order to emphasize important information and minimize the risk for user errors.

3.5 FULL PRESCRIBING INFORMATION

Section 2.8 of the Full Prescribing Information (FPI) includes the steps reflected in the IFU, and was updated based on the revisions to the IFU. Any changes made to the IFU (see section 3.4 above) should be updated in the FPI as well. Section 16, How Supplied/Storage and Handling, contains information about the kit components, some of which are identified by their trademarked names; however, we note that this section was not updated to reflect the changes in kit components proposed in this supplement. Section 16 should be updated with the correct information.

3.6 USABILITY STUDY RESULTS

In the third usability validation study, each participant was asked to conduct four trials, with the first trial being conducted without training. The trials' success rates increased after participants received training on the use of the kit and with each successive trial as compared to using the IFU alone. However, the overall success rate was only 76% for both the naïve and experienced user groups on the final trial (see Appendix D.2 for the list of user tasks and use errors). This is less than expected given the fact that all participants were ultimately allowed to use the IFU and given training. Furthermore, a significant amount of failures and errors continued to occur despite the training received. Use errors that persisted included handling the kit components in a way that risked needle sticks or jeopardized sterility and included: use of two hands to engage the needle safety device, neglect to swab the vial with alcohol, not fully reconstituting the

medication (because of not shaking the vial for at least 10 seconds), and accidentally touching the luer connection of the vial adapter or needle. Additionally, participants persisted in neglecting to hold the syringe by the white collar while making or breaking luer connections and neglecting to mention to allow the kit to warm to room temperature before use. Directions for these user tasks are part of the currently approved IFU, and they are also addressed in the proposed IFU. However, it is not clear why these types of errors continued to occur despite participants' use of the IFU and training since the participants were not specifically probed on each error committed to determine the root cause.

We realize that some of the use errors committed, such as failure to swab the top of the vial with alcohol, recapping the needle, and closing the needle protection device with both hands instead of using one, may not be new for Risperdal Consta or unique to this kit and may occur with kits containing similar types of components. Therefore, it is unlikely that all of these use errors can be eliminated. While our analysis did not determine that the revised IFU and kit components are more vulnerable to medication errors compared to what is currently marketed, the fact that the number of user failures were high in the final trial by participants despite use of the revised IFU and training is concerning. Thus, we will closely monitor for any postmarketing reports of medication errors or confusion involving the use of Risperdal Consta. Additionally, we recommend DPP consider whether a post market commitment (PMC) to have the company submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, may be reasonable given the high failure rate observed in the usability study. If a PMC is imposed, the Applicant should determine an appropriate means to ensure that these reports are easily identifiable as relating to the new kits versus the currently marketed kits.

4 CONCLUSION & RECOMMENDATIONS

The proposed device components appear to be an improvement over those in the currently marketed kit, and we did not identify any evidence that the revised components or IFU are at greater risk for contributing to medication errors compared to the kit components that are currently marketed. However, we identified some areas in the IFU that can be improved to emphasize specific tasks and important information, and we provide recommendations in Section 4.1. We do not believe that these revisions require revalidation in another usability validation study. Additionally, the FPI needs to be updated to reflect accurate information.

If this supplement is approved, we will closely monitor for any postmarketing reports of medication errors or confusion involving the use of Risperdal Consta. Additionally, Janssen should submit details regarding their plans for introducing the new kits into the marketplace and tracking reported errors that involve the new Risperdal Consta kits.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. General Comments

1. We recommend DPP consider whether a post market commitment (PMC) to have the company submit all reports of complaints about the new Risperdal Consta kits, reports of detachments, or medication errors, regardless of whether a SAE occurs, may be reasonable given the high failure rate observed in the usability study.

2. We recommend Janssen submit their plans for introducing the new Risperdal Consta kits into the marketplace.

3. We recommend Janssen submit their plans for tracking medication errors and product complaints involving the new kits and clarify how they will address the challenges of differentiating reports for the new kits from reports involving the currently marketed kits.

4.2 RECOMMENDATIONS FOR THE APPLICANT

A. Instructions for Use

1. Risperdal Consta should be allowed to sit at room temperature for 30 minutes before reconstituting. To help mitigate the user errors identified with this task, we recommend moving the instruction for waiting so it immediately precedes instructions for assembling components. Additionally, the instruction for waiting could be marked as "Step 1", with step 1 consisting of tasks required to prepare for injection. Subsequent steps should then be renumbered accordingly.

2. Under Step 1 and Step 3, we recommend bolding the statement "clockwise twisting motion" for added prominence.

3. Under Step 1: "Connect syringe to vial adaptor", consider bolding, changing font color, or some other means to highlight the sentence portion "Hold syringe by white collar" to bring prominence to this instruction

4. Under Step 2, we recommend bringing more prominence to the 10 second timer graphic and/or the instruction about shaking for at least 10 seconds. Consider the use of color or some other means to bring attention to this since there were user errors with completing this task.

5. Under Step 3: "Attach needle", consider bolding, changing font color, or some other means to highlight the sentence portion "Holding the white collar on the syringe" to bring prominence to this instruction.

B. Dosage and Administration, Full Prescribing Information

Ensure that under Dosage and Administration section 2.8 of the Full Prescribing Information, the instructions are updated for consistency with changes made to the IFU.

C. How Supplied/Storage and Handling, Full Prescribing Information

Update this section with accurate information about the newly proposed kit components.

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APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Risperdal Consta that Janssen Pharmaceuticals, Inc. submitted on February 7, 20914 submitted on February 7, 2014.

Table 2. Relevant Product Information for Risperdal Consta	
Active Ingredient	Risperidone
Indication	Treatment of schizophrenia; as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
Route of Administration	Intramuscular
Dosage Form	Long-Acting Injection
Strengths	12.5 mg, 25 mg, 37.5 mg, and 50 mg
Dose and Frequency	• 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. • 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 or in patients who have a history of poor tolerability to psychotropic medications.
How Supplied	**Currently Marketed Kit:** Risperdal Consta 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 SmartSite® Needle-Free Vial Access Device, and two Needle-Pro® safety 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).
Storage	The entire dose pack should be stored in the refrigerator (36°- 46°F; 2°- 8°C) and protected from light.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive on April 17, 2014 using the terms, Risperdal Consta to identify reviews previously performed by DMEPA.

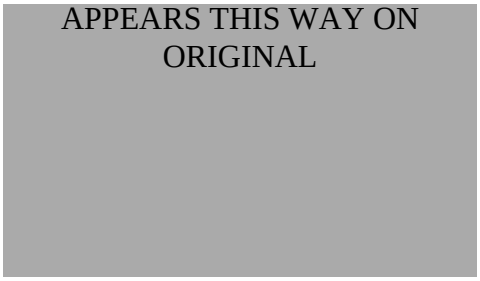
C.2 Results

Maslov, Yelena. Risperdal Consta (Risperidone) Long-Acting Injection Protocol and Instructions for Use Labeling Review, OSE Review 2012-174, dated March 21, 2012.

Maslov, Yelena. Risperdal Consta (Risperidone) Long-Acting Injection Medication Error Review, OSE Review 2010-1217, dated November 8, 2011.

Cantin, Lori. Risperdal Consta (Risperidone) Long-Acting Injection Postmarketing Review, OSE Review 2009-551, dated June 24, 2009.

We looked at these reviews in order to inform our current review.



APPENDIX D. HUMAN FACTORS STUDY

D.1 Study Design

Purpose

The purpose of this study was to conduct a follow-up round of usability testing (simulated-use design validation) of the Risperdal Consta Kit with representative users to assess if the proposed new commercial IFU would further improve users' performance with the kit. In addition, the study sought to demonstrate that the IFU supports the safe and effective use of the Risperdal Consta Kit by representative users under simulated use conditions without producing assembly or administration failures that would likely result in harm to users (i.e., HCPs) or patients. (b) (4) conducted this study.

Study Participants

The study's participants were representative of the Kit's intended users—i.e., doctors and nurses who work with psychiatric patients and who have a variety of experience working with Risperdal Consta. In total, 34 representative users participated in this study:

- 17 experienced users—doctors (M.D.s and D.O.s) and nurses (R.N.s) currently in clinical practice with experience preparing and/or administering Risperdal Consta. These participants are coded ED (experienced doctor) and EN (experienced nurse), respectively.
- 17 naïve users—doctors (M.D.s and D.O.s) and nurses (R.N.s) currently in practice with no experience preparing or administering Risperdal Consta, but with experience preparing and/or administering other injectable antipsychotic medications. These participants are coded ND (naïve doctor) and NN (naïve nurse), respectively.

Study Device

- One vial containing RISPERDAL® CONSTA® extended release microspheres
- One West Vial Adapter vial access device for reconstitution
- One prefilled syringe containing the diluent for RISPERDAL® CONSTA®
    - Based on the results from the first round of summative testing, the conus on the syringe was textured to reduce the likelihood that the syringe and vial would become disconnected.
- Two Terumo SurGuard3 needles for intramuscular injection (a 21G UTW 1-inch Terumo SurGuard3 safety needle for deltoid administration and a 20G TW 2-inch SurGuard3 safety needle for gluteal administration)
- IFU

Study Protocol

The study facilitator asked the experienced participants to first use the Kit without the associated instructions (to represent expected use) and then again with the instructions and training (to represent intended use). The study facilitator asked the naïve users to use the Kit initially with only the provided written instructions (to represent expected use) and then again with training (to represent the intended use).

Experienced Users

- *Trial 1*—For the participants with experience preparing and administering Risperdal Consta, the Study Facilitator withheld the associated written instructions (i.e. proposed new commercial IFU) during the first trial to represent an expected use in which the Risperdal Consta Kit is launched and a participant attempts to use it without first reading the instructions or receiving training on the change from the version currently on the market.

- *Trial 2*—After the first trial, the Study Facilitator asked all of the participants to repeat the use of the device while following the written instructions to evaluate the intuitiveness and efficacy of the instructions.

- *Trials 3-4*—Prior to the third trial, to simulate the training that participants often receive on how to inject new medications (i.e., the intended use), the Study Facilitator provided an in-person demonstration to the participants along with the associated instructions.

Naive Users

- *Trial 1*—For the participants naïve to preparing Risperdal Consta and LAI AP naïve, the Study Facilitator provided them the associated written instructions (i.e. proposed new commercial IFU), but without training, to evaluate the intuitiveness of the product (device and instructions). The purpose of this trial was to simulate an expected use scenario in which the Risperdal Consta Kit is launched and a user attempts to use it without first receiving any training.

- *Trials 2-4*—Prior to the second trial, to simulate the training that participants often receive on how to inject new medications (i.e., the intended use), the Study Facilitator provided an in-person demonstration to the participants along with the associated written instructions.

Evaluation of Success or Failure

- *Performance failure*—the participant does not complete the injection, requested assistance to complete the injection, or commits a potentially safety-related use error while completing the injection.

- *Performance success*—the participant completes the injection without committing potentially safety-related use errors (though they may commit other use errors).

D.2 Essential User Tasks and Use Errors

Essential Tasks

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During the simulated injections, the participants performed the following essential tasks (corresponding to each of the numbered steps in the IFU—[redacted]

1. Flipping off the plastic colored cap from the Vial.
2. Preparing the West Vial Adapter.
3. Connecting the West Vial Adapter to the vial.
4. Removing the West Vial Adapter's sterile blister.
5. Preparing the Prefilled Syringe by snapping off the smooth white cap.
6. Connecting the Prefilled Syringe, vial, and West Vial Adapter.
7. Injecting the entire contents of the syringe containing diluent into the Vial.
8. Suspending the Risperdal Consta® microspheres in the diluent.
9. Withdrawing the entire content of the suspension from the vial into the syringe.
10. Removing the West Vial Adapter and the vial from the syringe.
11. Selecting the appropriate needle provided with the dose pack based on the desired injection site location.
12. Correctly attaching the injection needle.
13. Removing any air from the suspension in the syringe.
14. Properly injecting the suspension in the syringe into the patient.
15. Properly disposing of the syringe and the injection needle.

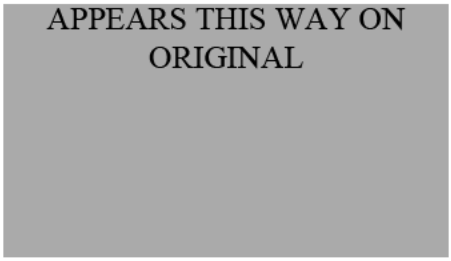
Use errors (potentially safety-related)	Other Use Errors (non-safety-related)
• Subject closed needle protection device with both hands instead of using 1-hand method	• Did not hold syringe by white collar while connecting to needle or vial adapter
• Potentially did not fully reconstitute; shook for less than 10 seconds and/or plunger not held at all while shaking may cause medication to not fully mix	• Did not indicate the need to warm product to room temperature prior to preparation and administration
• Subject touched a Luer connection on the vial adapter, syringe, or needle with hands or other surface	• Did not attach vial adapter to vial on a hard surface
• Did not swab the top of the vial with alcohol	• Did not remove air bubbles from the syringe prior to injection
• Administered a gluteal injection with a 1" needle	• Twisted off white cap instead of snapping off
• Did not use vial adapter	• Did not appear to inspect contents of the vial
• Recapped needle (before or after injection)	• Did not engage needle protection device before disposing
• Did not administer injection (due to the large presence of bubbles in the medicine or other reason).	• Used needle, rather than vial adapter, to reconstitute
• Refilled syringe using needle through vial adapter	
• Did not fully fill syringe	

D.3 Results

Success rates for all simulated injections (i.e., no safety-related use errors in any steps)

Trial	Naïve	Experienced
No IFU	NA	2/16 (13%)
IFU	4/17 (24%)	7/17 (41%)
Demo	12/17 (71%)	11/17 (65%)
After Demo Trial #1	11/17 (65%)	13/17 (76%)
After Demo Trial #2	13/17 (76%)	1/1 (100%)[6]

[6] This participant (b) (6) was originally recruited and tested as a naïve participant and therefore completed a Trial #2 attempt. However, based on her responses to the background questions, she was later categorized as an experienced participant. Therefore this participant was the only experienced participant that was tested under this trial (After Demo Trial #2).



APPENDIX F. Other

F.1 REGULATORY HISTORY AND SUMMARY OF PROPOSED CHANGES

Risperdal Consta was approved on October 29, 2003. At the time of approval, the product was marketed as a device kit consisting of the vial with risperidone lyophilized microspheres, prefilled BD Hypak syringe with the diluent, vial access device, and gluteal needle. In November 2008, the Applicant introduced a deltoid needle within the device kit. Since the introduction of the deltoid needle, the Applicant identified complaints such as needle stick and dosing errors related to separation or loosening of the needle from the syringe or needle safety device. Revisions to the instructions for use were implemented, however, this failed to resolve the issue and it was determined the device itself was at fault. Thus, the Applicant has proposed changes to the kit components in order to help address the problems associated with needle detachment and loosening.

The table below provides a high-level summary of the proposed changes. According to the Applicant, other than these modifications, there are no other changes being made to the currently-approved components, manufacturing procedures, specifications, or analytical test procedures for risperidone microspheres or diluent, or to their container-closure systems.

Component	Currently Approved	Proposed
(b) (4) glass syringe barrel container for diluent	Becton-Dickinson or Nuova OMPI supplied with luer tip conus having smooth exterior surface	Nuova OMPI supplied with luer tip conus having roughened exterior surface
2-inch gluteal injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo
1-inch deltoid injection needle with safety shield	Supplied by Smiths Medical	Supplied by Terumo
Vial adapter	Alaris type supplied by CareFusion	Supplied by West/Medimop
Instructions-for-Use (IFU) leaflet, and physician's prescribing information	Originally-approved format for the IFU	Improved format and layout for the IFU

The Applicant also previously conducted two formative studies and two summative human factors studies.

F.2 Risperdal Consta Demo Kit

No Images. The demo kit was used to inform our review.

APPENDIX G. LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Risperdal Consta labeling submitted by Janssen Pharmaceuticals, Inc. on February 7, 2014.

- Full Prescribing Information (no image)
- Instructions for Use Leaflet

We also compared the current instructions for use to the proposed instructions for use in order to inform our review.

G.2 Labeling Images, Instructions for Use

Proposed Instructions for Use Leaflet

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

LORETTA HOLMES
05/19/2014

IRENE Z CHAN
05/20/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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