

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
ANDA 214068

Name: Risperidone; 12.5 MG, 25 MG, 37.5 MG, and 50 MG Vials

Sponsor: Teva Pharmaceuticals USA Inc.

Approval Date: December 05, 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214068

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 214068

APPROVAL LETTER



ANDA 214068

ANDA APPROVAL

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054
Attention: Narendra Racharla
Director Regulatory Affairs, US Generics

Dear Narendra Racharla:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

Your product is a combination product as defined by 21 CFR 3.2(e) and is comprised of drug and device constituent parts.

Reference is also made to the complete response letter issued by this office on March 25, 2022, and to any amendments thereafter.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug meets the requirements for approval under the FD&C Act. Accordingly the ANDA is **approved**, effective on the date of this letter. We have determined your Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial to be bioequivalent and therapeutically equivalent to the reference listed drug (RLD), Risperdal Consta Long-Acting Injectable Suspension, of Janssen Pharmaceuticals Inc.

Please note that if FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for a listed drug, an ANDA referencing that listed drug also will be required to have a REMS. See section 505-1(i) of the FD&C Act.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standard for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly

stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website as <https://www.uspnf.com/>.

REQUIREMENTS AND RECOMMENDATIONS POST APPROVAL

Under applicable statutes, regulations, and guidances, your ANDA may be subject to certain requirements and recommendations post approval, including requirements regarding changes to approved ANDAs, postmarketing reporting, promotional materials, and annual facility fees, among others. For information on post-approval requirements and recommendations for ANDAs and a list of resources for ANDA holders, we refer you to <https://www.fda.gov/drugs/abbreviated-new-drug-application-anda/requirements-and-resources-approved-andas>.

Sincerely yours,

{See appended electronic signature page}

For Edward M. Sherwood
 Director
 Office of Regulatory Operations
 Office of Generic Drugs
 Center for Drug Evaluation and Research



Julie
Kuriakose

Digitally signed by Julie Kuriakose
Date: 12/05/2023 02:00:46PM
GUID: 556dc322004ee2eb183a54842fb7fae3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RISPERIDONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION safely and effectively. See full prescribing information for RISPERIDONE FOR EXTENDED-RELEASE INJECTABLE SUSPENSION.

RISPERIDONE for extended-release injectable suspension, for intramuscular use

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. Risperidone for Extended-Release Injectable Suspension is not approved for use in patients with dementia-related psychosis. (5.1)

INDICATIONS AND USAGE

Risperidone for Extended-Release Injectable Suspension 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 risperidone, tolerability should be established with oral risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension. (2)
- Administer by deep intramuscular 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 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 risperidone (or another antipsychotic medication) should be given with the first injection of Risperidone for Extended-Release Injectable Suspension, and continued for 3 weeks (and then discontinued) to ensure adequate therapeutic plasma concentrations from Risperidone for Extended-Release Injectable Suspension. (2)
- Upward dose adjustment of Risperidone for Extended-Release Injectable Suspension should not be made more frequently than every 4 weeks. Clinical effects of each upward dose adjustment should not be anticipated earlier than 3 weeks after injection. (2)
- Avoid inadvertent administration into a blood vessel. (5.16)
- See Full Prescribing Information Section 2.8 for instructions for use.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Known hypersensitivity to risperidone, paliperidone, or to any excipients in Risperidone for Extended-Release Injectable Suspension. (4)

WARNINGS AND PRECAUTIONS

- Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis. Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension. 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 Risperidone for Extended-Release Injectable Suspension should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- Potential for cognitive and motor impairment: has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery, including automobiles. (5.10)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- Dysphagia: Esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia. (5.12)
- Priapism: has been reported. Severe priapism may require surgical intervention. (5.13)
- Avoid inadvertent administration into a blood vessel. (5.15)

ADVERSE REACTIONS

The most common adverse reactions in clinical trials in patients with schizophrenia ($\geq 5\%$) 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 ($\geq 10\%$ 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 Teva at 1-888-838-2872 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Renal or Hepatic Impairment: dose appropriately with oral risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension. A lower starting dose of Risperidone for Extended-Release Injectable Suspension of 12.5 mg may be appropriate in some patients. (2.4)
- Pediatric Use: safety and effectiveness not established in patients less than 18 years of age. (8.4)

- Elderly: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly may be more predisposed to orthostatic effects than nonelderly. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 3/2022

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Risperidone for Extended-Release Injectable Suspension 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

Risperidone for Extended-Release Injectable Suspension is indicated for the treatment of schizophrenia [see Clinical Studies (14.1)].

1.2 Bipolar Disorder

Risperidone for Extended-Release Injectable Suspension 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 risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension.

Risperidone for Extended-Release Injectable Suspension should be administered every 2 weeks by deep intramuscular 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 intramuscular every 2 weeks. Although dose response for effectiveness has not been established for Risperidone for Extended-Release Injectable Suspension, 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 Risperidone for Extended-Release Injectable Suspension every 2 weeks. No additional benefit was observed with dosages greater than 50 mg Risperidone for Extended-Release Injectable Suspension; however, a higher incidence of adverse effects was observed.

The efficacy of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, 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 Risperidone for Extended-Release Injectable Suspension at the lowest dose needed. The physician who elects to use Risperidone for Extended-Release Injectable Suspension 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 intramuscular 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 Risperidone for Extended-Release Injectable Suspension 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 risperidone (or another antipsychotic medication) should be given with the first injection of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension in a single administration.

2.4 Dosage in Special Populations

Elderly

For elderly patients treated with Risperidone for Extended-Release Injectable Suspension, the recommended dosage is 25 mg intramuscular every 2 weeks. Oral risperidone (or another antipsychotic medication) should be given with the first injection of Risperidone for Extended-Release Injectable Suspension 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 risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension. The recommended starting dose is 0.5 mg oral risperidone 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 risperidone is well tolerated, an injection of 25 mg Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, supplementation with oral risperidone (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 Risperidone for Extended-Release Injectable Suspension, or concerning concomitant administration with other antipsychotics. Previous antipsychotics should be continued for 3 weeks after the first injection of Risperidone for Extended-Release Injectable Suspension 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 risperidone, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension. As recommended with other antipsychotic medications, the need for continuing existing EPS medication should be re-evaluated periodically.

2.7 Coadministration of Risperidone for Extended-Release Injectable Suspension with Certain Other Medications

Coadministration 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 Risperidone for Extended-Release Injectable Suspension 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 to 8 weeks, since the dose of Risperidone for Extended-Release Injectable Suspension may need to be adjusted. A dose increase, or additional oral risperidone, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of Risperidone for Extended-Release Injectable Suspension should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension dose to 12.5 mg or necessitates interruption of Risperidone for Extended-Release Injectable Suspension 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 to 2.8 fold and 3 to 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 coadministered. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dose of Risperidone for Extended-Release Injectable Suspension. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the Risperidone for Extended-Release Injectable Suspension dose to 12.5 mg or necessitates interruption of Risperidone for Extended-Release Injectable Suspension treatment. When Risperidone for Extended-Release Injectable Suspension is initiated in patients already receiving fluoxetine or paroxetine, a starting dose of 12.5 mg can be considered. The efficacy of the 12.5 mg dose has not been investigated in clinical trials. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9-hydroxyrisperidone have not been studied [see *Drug Interactions* (7.11)].

2.8 Instructions for Use

For deltoid or gluteal intramuscular injection only

Each injection should be administered by a healthcare professional.

IMPORTANT RESOURCES

For additional information call Teva at 1-888-838-2872.

Important Information

Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension. Risperidone for Extended-Release Injectable Suspension 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.

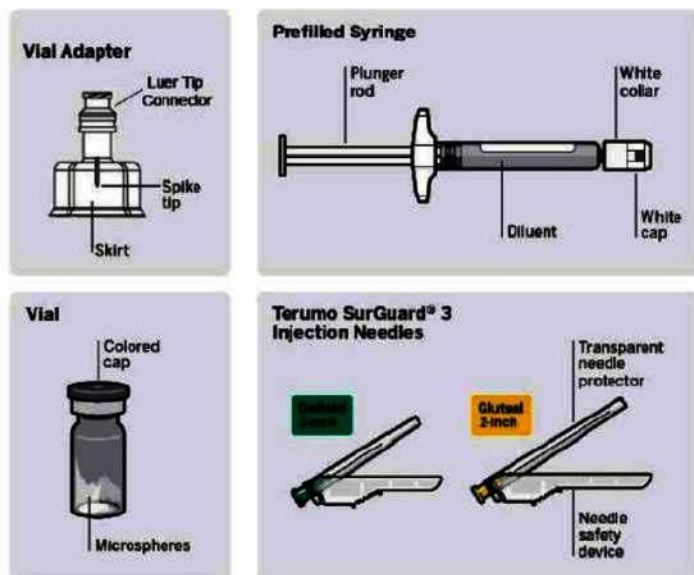
Proper dosing

The entire contents of the vial must be administered to ensure intended dose of Risperidone for Extended-Release Injectable Suspension is delivered.

SINGLE-DOSE DEVICE

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

Dose pack contents



Step 1 Assemble components

Take out dose pack



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.

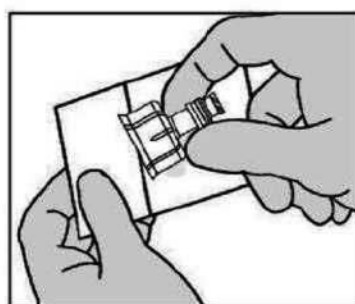
Connect vial adapter to vial



Remove cap from vial
Flip off colored cap from vial.

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

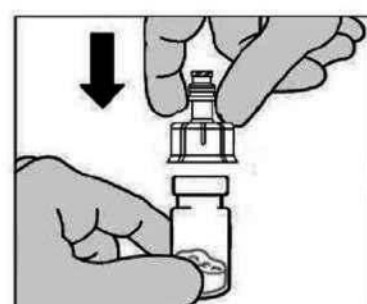
Do not remove grey rubber stopper.



Prepare vial adapter
Hold sterile blister as shown.

Peel the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt.

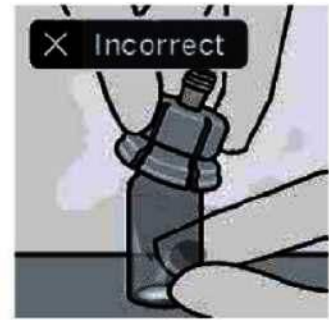
Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.



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.

CLEAN the luer tip of the vial adapter with an alcohol wipe

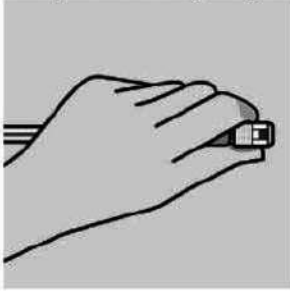
Do not place vial adapter on at an angle or diluent may leak upon transfer to the vial.



Do not shake.

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

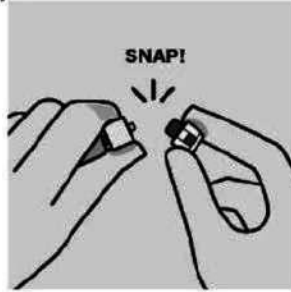
Connect prefilled syringe to vial adapter



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

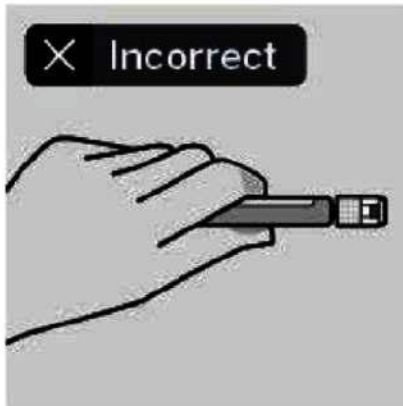
Hold vial adapter by skirt to keep stationary.

Hold syringe by white collar then insert tip into the luer tip connector 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

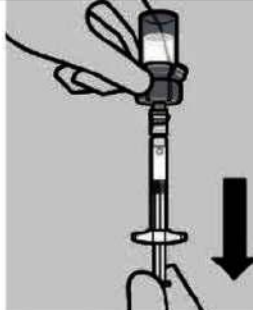
Continuing to hold down the plunger rod, **shake vigorously for at least 10 seconds**, as shown.

Check the suspension.

When properly mixed, the suspension appears uniform, thick and milky in color.

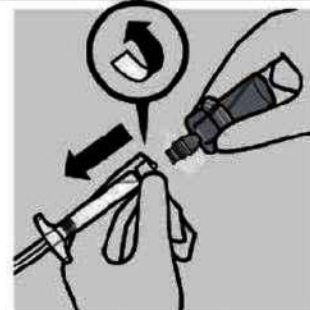
Microspheres will be visible in the liquid.

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

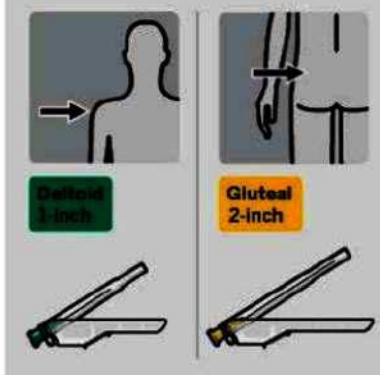
Hold white collar on the syringe and unscrew from vial adapter.

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.

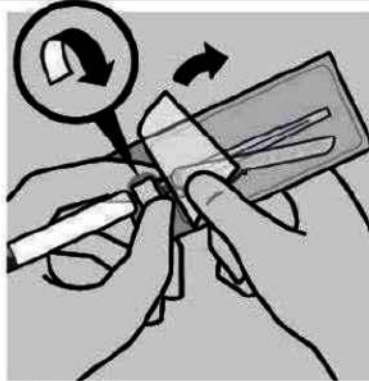
Step 3

Attach needle



Select appropriate needle

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

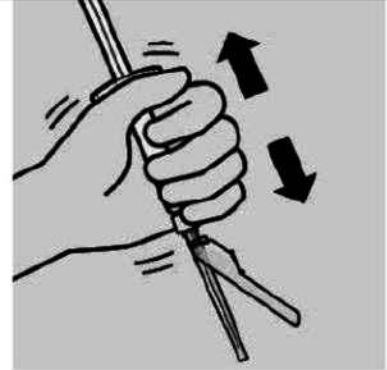


Attach needle

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.



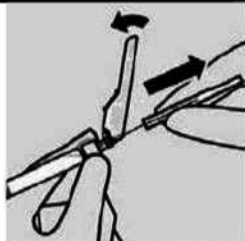
Resuspend microspheres

Fully remove the blister pouch.

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

Step 4

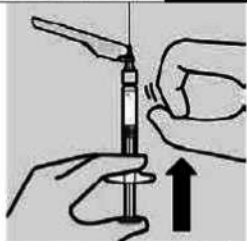
Inject dose



Remove transparent needle protector

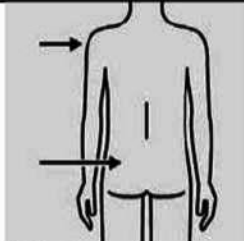
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

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.

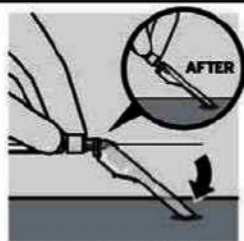


Inject

Immediately inject entire contents of syringe intramuscularly into the gluteal or deltoid muscle of the patient.

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

Do not administer intravenously.



Secure needle in safety device

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

Avoid needle stick injury:

Do not use two hands.

Do not intentionally disengage or mishandle the needle safety device.

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



Properly dispose of needles

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

Also discard the unused needle provided in the dose pack.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Risperidone for Extended-Release Injectable Suspension is contraindicated in patients with a known hypersensitivity to either risperidone or paliperidone, or to any of the excipients in the Risperidone for Extended-Release Injectable Suspension formulation. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported in patients treated with risperidone and in patients treated with paliperidone.

Paliperidone is a metabolite of risperidone.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Risperidone for Extended-Release Injectable Suspension 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 to 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. Risperidone for Extended-Release Injectable Suspension 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

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status including delirium, and 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.

If NMS is suspected, immediately discontinue Risperidone for Extended-Release Injectable Suspension and provide symptomatic treatment and monitoring.

5.4 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting 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 predict which patients will 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 increase with the duration of treatment and the cumulative dose. The syndrome can develop after relatively brief treatment periods, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

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

If signs and symptoms of tardive dyskinesia appear in a patient treated with Risperidone for Extended-Release Injectable Suspension, drug discontinuation should be considered. However, some patients may require treatment with Risperidone for Extended-Release Injectable Suspension 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 risperidone. 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 risperidone, 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 risperidone, should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics, including risperidone, 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 risperidone, should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic, including risperidone, was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of risperidone.

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

	Placebo	Risperidone	
		1 to 8 mg/day	>8 to 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	0.6%	0.4%	0%
(<140 mg/dL to ≥200 mg/dL)	(3/525)	(3/702)	(0/158)

In longer-term, controlled and uncontrolled studies in adult subjects, risperidone 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

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

In longer-term, controlled and uncontrolled studies, risperidone 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 $\geq 7\%$ Gain in Body Weight From a Placebo-Controlled, 12-Week, Fixed-Dose Study in Adult Subjects With Schizophrenia

	Placebo (N=83)	Risperidone for Extended-Release Injectable Suspension	
		25 mg (N=90)	50 mg (N=87)
Weight (kg)			
Change from baseline	-1.4	0.5	1.2
Weight Gain			
$\geq 7\%$ increase from baseline	6%	10%	8%

In an uncontrolled, longer-term, open-label study, Risperidone for Extended-Release Injectable Suspension 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

Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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).

Risperidone for Extended-Release Injectable Suspension 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 risperidone and antihypertensive medication.

5.8 Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including Risperidone for Extended-Release Injectable Suspension, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect: In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including Risperidone for Extended-Release Injectable Suspension. 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 Risperidone for Extended-Release Injectable Suspension 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 $<1000/\text{mm}^3$) should discontinue Risperidone for Extended-Release Injectable Suspension and have their WBC followed until recovery.

5.10 Potential for Cognitive and Motor Impairment

Somnolence was reported by 5% of patients treated with Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension does not affect them adversely.

5.11 Seizures

During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with Risperidone for Extended-Release Injectable Suspension. Therefore, Risperidone for Extended-Release Injectable Suspension should be used cautiously in patients with a history of seizures.

5.12 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. Risperidone for Extended-Release Injectable Suspension and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [*see also Boxed Warning and Warnings and Precautions (5.1)*].

5.13 Priapism

Priapism has been reported during postmarketing surveillance [*see Adverse Reactions (6.2)*]. Severe priapism may require surgical intervention.

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 risperidone or Risperidone for Extended-Release Injectable Suspension use. Caution is advised when prescribing Risperidone for Extended-Release Injectable Suspension for patients who will be exposed to temperature extremes.

5.15 Administration

Risperidone for Extended-Release Injectable Suspension 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 Osteodystrophy and Tumors in Animals

Risperidone for Extended-Release Injectable Suspension 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 intramuscular every 2 weeks.

Risperidone for Extended-Release Injectable Suspension produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered intramuscular every 2 weeks. In addition, Risperidone for Extended-Release Injectable Suspension 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 intramuscular 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 intramuscular maximum recommended human dose (MRHD) (50 mg) on a mg/m² basis and is associated with a plasma exposure (AUC) 2 times the expected plasma exposure (AUC) at the intramuscular MRHD. The no-effect dose for these findings was 5 mg/kg (equal to the intramuscular MRHD on a mg/m² basis). Plasma exposure (AUC) at the no-effect dose was one third the expected plasma exposure (AUC) at the intramuscular 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 intramuscular MRHD in a 1-year toxicity study.

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

The relevance of these findings to human risk is unknown.

6 ADVERSE REACTIONS

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

- Increased mortality in elderly patients with dementia-related psychosis [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis [*see Warnings and Precautions (5.2)*]
- Neuroleptic malignant syndrome [*see Warnings and Precautions (5.3)*]
- Tardive dyskinesia [*see Warnings and Precautions (5.4)*]
- Metabolic changes [*see Warnings and Precautions (5.5)*]

- Hyperprolactinemia [see Warnings and Precautions (5.6)]
- Orthostatic hypotension [see Warnings and Precautions (5.7)]
- Falls [see Warnings and Precautions (5.8)]
- Leukopenia/Neutropenia and Agranulocytosis [see Warnings and Precautions (5.9)]
- Potential for cognitive and motor impairment [see Warnings and Precautions (5.10)]
- Seizures [see Warnings and Precautions (5.11)]
- Dysphagia [see Warnings and Precautions (5.12)]
- Priapism [see Warnings and Precautions (5.13)]
- 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)]
- Osteodystrophy and tumors in animals [see Warnings and Precautions (5.16)]

The most common adverse reactions in clinical trials in patients with schizophrenia ($\geq 5\%$) 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 ($\geq 10\%$ 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 $\geq 1\%$ 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 Risperidone for Extended-Release Injectable Suspension for the treatment of schizophrenia. Of these 2392 patients, 332 were patients who received Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension. The conditions and duration of treatment with Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension extension period (N=160).

Safety data are also presented from a trial assessing the efficacy and safety of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for Risperidone for Extended-Release Injectable Suspension 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 Clinical Trials Experience

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

Table 4 lists the adverse reactions reported in 2% or more of Risperidone for Extended-Release Injectable Suspension-treated patients with schizophrenia in one 12-week double-blind, placebo-controlled trial.

Table 4. Adverse Reactions in $\geq 2\%$ of Risperidone for Extended-Release Injectable Suspension-Treated Patients with Schizophrenia in a 12-Week Double-Blind, Placebo-Controlled Trial

System/Organ Class Adverse Reaction	Percentage of Patients Reporting Event		
	Risperidone for Extended-Release Injectable Suspension		Placebo
	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.

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 Risperidone for Extended-Release Injectable Suspension-treated patients in the 24-month double-blind, placebo-controlled treatment

period of the trial assessing the efficacy and safety of Risperidone for Extended-Release Injectable Suspension when administered as monotherapy for maintenance treatment in patients with Bipolar I Disorder.

Table 5. Adverse Reactions in $\geq 2\%$ of Patients with Bipolar I Disorder Treated with Risperidone for Extended-Release Injectable Suspension as Monotherapy in a 24-Month Double-Blind, Placebo-Controlled Trial

System/Organ Class	Percentage of Patients Reporting Event	
	Risperidone for Extended-Release Injectable Suspension (N=154)	Placebo (N=149)
Adverse Reaction		
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 Risperidone for Extended-Release Injectable Suspension when administered as adjunctive maintenance treatment in patients with bipolar disorder.

Table 6. Adverse Reactions in $\geq 4\%$ of Patients with Bipolar Disorder Treated with Risperidone for Extended-Release Injectable Suspension as Adjunctive Therapy in a 52-Week Double-Blind, Placebo-Controlled Trial

System/Organ Class	Percentage of Patients Reporting Event	
	Risperidone for Extended-Release Injectable Suspension + Treatment as Usual ^a (N=72)	Placebo + Treatment as Usual ^a (N=67)
Adverse Reaction		
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		

^a Patients received double-blind Risperidone for Extended-Release Injectable Suspension 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.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone

The following additional adverse reactions occurred in < 2% of the Risperidone for Extended-Release Injectable Suspension-treated patients in the above schizophrenia double-blind, placebo-controlled trial dataset, in < 2% of the Risperidone for Extended-Release Injectable Suspension-treated patients in the above double-blind, placebo-controlled period of the monotherapy bipolar disorder trial dataset, or in < 4% of the Risperidone for Extended-Release Injectable Suspension-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 Risperidone for Extended-Release Injectable Suspension-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 Risperidone

The following is a list of additional adverse reactions that have been reported during the clinical trial evaluation of oral risperidone, 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

Discontinuations Due to Adverse Reactions

Schizophrenia

Approximately 11% (22/202) of Risperidone for Extended-Release Injectable Suspension-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 Risperidone for Extended-Release Injectable Suspension-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 Risperidone for Extended-Release Injectable Suspension when administered as monotherapy for maintenance treatment in patients with bipolar I disorder, 1 (0.6%) of 154 Risperidone for Extended-Release Injectable Suspension-treated patients discontinued due to an adverse reaction (hyperglycemia).

In the 52-week double-blind phase of the placebo-controlled trial in which Risperidone for Extended-Release Injectable Suspension was administered as adjunctive therapy to patients with bipolar disorder in addition to continuing with their treatment as usual, approximately 4% (3/72) of Risperidone for Extended-Release Injectable Suspension-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 Risperidone for Extended-Release Injectable Suspension-treated patients were: hypokinesia (one patient) and tardive dyskinesia (one patient).

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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension was comparable to that of patients treated with placebo; the incidence of EPS-related adverse reactions was higher in patients treated with 50 mg Risperidone for Extended-Release Injectable Suspension.

The median change from baseline to endpoint in total ESRS score showed no worsening in patients treated with Risperidone for Extended-Release Injectable Suspension 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.

Changes in ECG

The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension.

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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 25 mg, 37.5 mg, or 50 mg when administered as adjunctive treatment in addition to continuing treatment as usual compared to placebo.

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 Risperidone for Extended-Release Injectable Suspension experienced redness, swelling, or induration at the injection site.

In a separate study to observe local-site tolerability in which Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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.

6.2 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, catatonia, 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, somnambulism, Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), thrombocytopenia, thrombotic thrombocytopenic purpura, urinary retention, and water intoxication. In addition, the following adverse reactions have been observed during postapproval use of Risperidone for Extended-Release Injectable Suspension: cerebrovascular disorders, including cerebrovascular accidents, and diabetes mellitus aggravated.

Retinal artery occlusion after injection of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension during postmarketing surveillance. Isolated cases required surgical intervention.

Very rarely, cases of anaphylactic reaction after injection with Risperidone for Extended-Release Injectable Suspension have been reported during postmarketing experience in patients who have previously tolerated oral risperidone.

Postmarketing cases of extrapyramidal symptoms (dystonia and dyskinesia) have been reported in patients concomitantly taking methylphenidate and risperidone when there was an increase or decrease in dosage, initiation, or discontinuation of either or both medications.

7 DRUG INTERACTIONS

The interactions of Risperidone for Extended-Release Injectable Suspension with coadministration of other drugs have not been systematically evaluated. The drug interaction data provided in this section is based on studies with oral risperidone.

7.1 Centrally-Acting Drugs and Alcohol

Given the primary CNS effects of risperidone, caution should be used when Risperidone for Extended-Release Injectable Suspension is administered in combination with other centrally-acting drugs or alcohol.

7.2 Drugs with Hypotensive Effects

Because of its potential for inducing hypotension, Risperidone for Extended-Release Injectable Suspension may enhance the hypotensive effects of other therapeutic agents with this potential.

7.3 Levodopa and Dopamine Agonists

Risperidone for Extended-Release Injectable Suspension 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 risperidone.

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 Methylphenidate

Concomitant use with methylphenidate, when there is change in dosage of either medication, may increase the risk of extrapyramidal symptoms (EPS). Monitor for symptoms of EPS with concomitant use of Risperidone for Extended-Release Injectable Suspension and methylphenidate [see *Adverse Reactions* (6.2)].

7.7 Clozapine

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

7.8 Lithium

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

7.9 Valproate

Repeated doses of oral risperidone (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 risperidone.

7.10 Digoxin

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

7.11 Topiramate

Oral risperidone administered at doses from 1 to 6 mg/day concomitantly with topiramate 400 mg/day resulted in a 23% decrease in risperidone C_{max} and a 33% decrease in risperidone AUC_{0-12 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 risperidone on the pharmacokinetics of topiramate.

7.12 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 to 2.8 fold and 3 to 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 Risperidone for Extended-Release Injectable Suspension. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, it is recommended to continue treatment with the 25 mg dose unless clinical judgment necessitates lowering the Risperidone for Extended-Release Injectable Suspension dose to 12.5 mg or necessitates interruption of Risperidone for Extended-Release Injectable Suspension treatment. When Risperidone for Extended-Release Injectable Suspension 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 risperidone and erythromycin.

7.13 Carbamazepine and Other CYP 3A4 Enzyme Inducers

Carbamazepine coadministration with oral risperidone decreased the steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. Coadministration 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 Risperidone for Extended-Release Injectable Suspension treatment. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4 to 8 weeks, since the dose of Risperidone for Extended-Release Injectable Suspension may need to be adjusted. A dose increase, or additional oral risperidone, may need to be considered. On discontinuation of carbamazepine or other CYP 3A4 hepatic enzyme inducers, the dosage of Risperidone for Extended-Release Injectable Suspension should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension dose to 12.5 mg or necessitates interruption of Risperidone for Extended-Release Injectable Suspension treatment. The efficacy of the 12.5 mg dose has not been investigated in clinical trials [see also *Dosage and Administration* (2.5)]

7.14 Drugs Metabolized by CYP 2D6

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

Risk Summary

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

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3 to 4 times the maximum recommended human dose (MRHD) with maternal toxicity observed at 4-times the MRHD based on mg/m² body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the MRHD based on mg/m² body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the MRHD based on mg/m² body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the MRHD and offspring mortality increased at doses 0.1 to 3 times the MRHD based on mg/m² body surface area.

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including Risperidone for Extended-Release Injectable Suspension, during the third trimester of

pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk major of birth defects (RR=1.26, 95% CI 1.02 to 1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88 to 1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3 times the MRHD of 16 mg/day based on mg/m² body surface area; maternal toxicity occurred at 4 times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6 times the MRHD of 16 mg/day risperidone based on mg/m² body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6 times the MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6 and 1.2 times the MRHD based on mg/m² body surface area; postnatal development and growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1 to 3 times the MRHD of 16 mg/day based on mg/m² body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams; a no-effect dose could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5 times the MRHD based on mg/m² body surface area.

In a rat cross-fostering study the number of live offspring was decreased, the number of stillbirths increased, and the birth weight was decreased in offspring of drug-treated pregnant rats. In addition, the number of deaths increased by Day 1 among offspring of drug-treated pregnant rats, regardless of whether or not the offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that offspring body weight gain and survival (from Day 1 to 4 of lactation) were reduced in offspring born to control but reared by drug-treated dams. All of these effects occurred at 5 mg/kg which is 3 times the MRHD based on mg/m² and the only dose tested in the study.

8.2 Lactation

Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone (*see Clinical Considerations*). Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of Risperidone for Extended-Release Injectable Suspension [*see Clinical Pharmacology (12.3)*], and the clinical significance on the breastfed infant is not known. There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Risperidone for Extended-Release Injectable Suspension and any

potential adverse effects on the breastfed child from Risperidone for Extended-Release Injectable Suspension or from the mother's underlying condition.

Clinical Considerations

Infants exposed to Risperidone for Extended-Release Injectable Suspension through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

8.3 Females and Males of Reproductive Potential

Infertility

Females

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

8.4 Pediatric Use

Safety and effectiveness of Risperidone for Extended-Release Injectable Suspension in pediatric patients have not been established. However, juvenile animal toxicology studies have been conducted with oral risperidone.

Juvenile Animal Studies

Juvenile dogs were treated with oral risperidone from weeks 10 to 50 of age (equivalent to the period of childhood through adolescence in humans), at doses of 0.31, 1.25, or 5 mg/kg/day, which are 1.2, 3.4 and 13.5 times the MRHD of 6 mg/day for children, based on mg/m² body surface area. Bone length and density were decreased with a no-effect dose of 0.31 mg/kg/day; this dose produced plasma AUC of risperidone plus its active metabolite paliperidone (9-hydroxy-risperidone) that were similar to those in children and adolescents receiving the MRHD of 6 mg/day. In addition, sexual maturation was delayed at all doses in both males and females. The above effects showed little or no reversibility in females after a 12 week drug-free recovery period. Juvenile rats, treated with oral risperidone from days 12 to 50 of age (equivalent to the period of infancy through adolescence in humans) showed impaired learning and memory performance (reversible only in females), with a no-effect dose of 0.63 mg/kg/day which is 0.5 times the MRHD of 6 mg/day for children, based on mg/m² body surface area. This dose produced plasma AUC of risperidone plus paliperidone about half the exposure observed in humans at the MRHD. No other consistent effects on neurobehavioral or reproductive development were seen up to the highest tested dose of 1.25 mg/kg/day which is 1 time the MRHD and produced plasma AUC of risperidone plus paliperidone that were about two thirds of those observed in humans at the MRHD of 6 mg/day for children.

8.5 Geriatric Use

In an open-label study, 57 clinically stable, elderly patients (≥ 65 years old) with schizophrenia or schizoaffective disorder received Risperidone for Extended-Release Injectable Suspension every 2 weeks for up to 12 months. In general, no differences in the tolerability of Risperidone for Extended-Release Injectable Suspension 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. Risperidone for Extended-Release Injectable Suspension is not approved for the treatment of patients with dementia-related psychosis [see *Boxed Warning* and *Warnings and Precautions* (5.1)].

8.6 Renal or Hepatic Impairment

In patients with renal or hepatic impairment, carefully titrate with oral risperidone prior to initiating treatment with Risperidone for Extended-Release Injectable Suspension [see *Dosage and Administration* (2.4)].

Patients with renal impairment may have less ability to eliminate risperidone than patients with normal renal function. Patients with impaired hepatic function may have an increase in the free fraction of risperidone, possibly resulting in an enhanced effect [see *Clinical Pharmacology* (12.3)].

8.7 Patients with Parkinson's Disease or Lewy Body Dementia

Patients with Parkinson's Disease or Dementia with Lewy Bodies can experience increased sensitivity to Risperidone for Extended-Release Injectable Suspension. Manifestations can include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with neuroleptic malignant syndrome.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Risperidone for Extended-Release Injectable Suspension is not a controlled substance.

9.2 Abuse

Risperidone for Extended-Release Injectable Suspension has not been systematically studied in animals or humans for its potential for abuse. Because Risperidone for Extended-Release Injectable Suspension is to be administered by health care professionals, the potential for misuse or abuse by patients is low.

9.3 Dependence

Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension. Because Risperidone for Extended-Release Injectable Suspension is to be administered by health care professionals, the potential for overdosage by patients is low.

In premarketing experience with oral risperidone, there were eight reports of acute risperidone 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 risperidone 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 risperidone overdose include prolonged QT interval and convulsions. Torsade de pointes has been reported in association with combined overdose of oral risperidone and paroxetine.

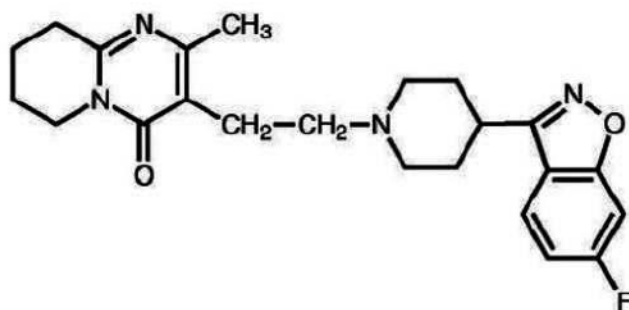
10.2 Management of Overdosage

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 for Extended-Release Injectable Suspension contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The chemical designation is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidiny]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.

Risperidone for Extended-Release Injectable Suspension 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, sterile, 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 microencapsulated in 75:25 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 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection.

Risperidone for Extended-Release Injectable Suspension is provided as a single-dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of risperidone in schizophrenia is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT₂) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major active metabolite, 9-hydroxyrisperidone (paliperidone) [see *Clinical Pharmacology* (12.3)]. Antagonism at receptors other than D₂ and 5HT₂ may explain some of the other effects of risperidone [see *Clinical Pharmacology* (12.1)].

12.2 Pharmacodynamics

Risperidone is a monoaminergic antagonist with high affinity (K_i of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT₂), dopamine Type 2 (D₂), α₁ and α₂ adrenergic, and H₁ histaminergic receptors. Risperidone showed low to moderate affinity (K_i of 47 to 253 nM) for the serotonin 5HT_{1C}, 5HT_{1D}, and 5HT_{1A} receptors, weak affinity (K_i of 620 to 800 nM) for the dopamine D₁ and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10⁻⁵ M) for cholinergic muscarinic or β₁ and β₂ adrenergic receptors.

12.3 Pharmacokinetics

Absorption

After a single intramuscular (gluteal) injection of Risperidone for Extended-Release Injectable Suspension, 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 injection. Therefore, oral antipsychotic supplementation should be given during the first 3 weeks of treatment with Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, 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 (intramuscular injections every 2 weeks) of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension, 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 to 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% to 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 Risperidone for Extended-Release Injectable Suspension with coadministration of other drugs have not been systematically evaluated in human subjects. Drug interactions are based primarily on experience with oral risperidone. 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 risperidone in patients receiving quinidine have not been evaluated, but observations in a modest number ($n \cong 70$) of poor metabolizers given oral risperidone do not suggest important differences between poor and extensive metabolizers. Second, coadministration of carbamazepine and other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with oral risperidone 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 Risperidone for Extended-Release Injectable Suspension administration is 3 to 6 days, and is associated with a monoexponential decline in plasma concentrations. This half-life of 3 to 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 Risperidone for Extended-Release Injectable Suspension. 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 risperidone, 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 Risperidone for Extended-Release Injectable Suspension, it is recommended that patients with renal impairment be carefully titrated on oral risperidone before treatment with Risperidone for Extended-Release Injectable Suspension 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 risperidone 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 α 1-acid glycoprotein. Although patients with hepatic impairment were not studied with Risperidone for Extended-Release Injectable Suspension, it is recommended that patients with hepatic impairment be carefully titrated on oral risperidone before treatment with Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension for up to 12 months fell within the range of values observed in otherwise healthy nonelderly patients. Dosing recommendations are the same for otherwise healthy elderly patients and nonelderly patients [see *Dosage and Administration* (2)].

Race and Gender Effects

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis - Oral

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

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

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

An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear [see *Warnings and Precautions* (5.6)].

Carcinogenesis - Intramuscular

Risperidone was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with intramuscular 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/m² 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 intramuscular MRHD on a mg/m² basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the intramuscular MRHD on a mg/m² basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the intramuscular MRHD on a mg/m² 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 intramuscular MRHD.

Dopamine D₂ receptor antagonists have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the carcinogenicity studies of oral risperidone; however, measurements taken during subchronic toxicity studies showed that oral risperidone elevated serum prolactin levels 5- to 6-fold in mice and rats at the same doses used in the oral carcinogenicity studies. Serum prolactin levels increased in a dose-dependent manner up to 6- and 1.5-fold in male and female rats, respectively, at the end of the 24-month treatment with risperidone every 2 weeks intramuscular. Increases in the incidence of pituitary gland, endocrine pancreas, and mammary gland neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and may be prolactin-mediated.

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

Mutagenesis

No evidence of mutagenic or clastogenic potential for risperidone was found in the *in vitro* tests of Ames gene mutation, the mouse lymphoma assay, rat hepatocyte DNA-repair assay, the chromosomal aberration test in

human lymphocytes, Chinese hamster ovary cells, or in the *in vivo* micronucleus test in mice, and the sex-linked recessive lethal test in *Drosophila*.

In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for Risperidone for Extended-Release Injectable Suspension.

Impairment of Fertility

Oral risperidone (0.16 to 5 mg/kg) impaired mating, but not fertility, in rat reproductive studies at doses 0.1 to 3 times the oral maximum recommended human dose (MRHD of 16 mg/day) based on mg/m² body surface area. The effect appeared to be in females, since impaired mating behavior was not noted in the male fertility study. In a subchronic study in Beagle dogs in which oral risperidone was administered at doses of 0.31 to 5 mg/kg, sperm motility and concentration were decreased at doses 0.6 to 10 times the oral MRHD on mg/m² basis. Dose-related decreases were also noted in serum testosterone at the same doses. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued. A no-effect dose could not be determined in either rat or dog.

14 CLINICAL STUDIES

14.1 Schizophrenia

The effectiveness of Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 risperidone. Patients who received Risperidone for Extended-Release Injectable Suspension were given doses of oral risperidone (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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension (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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension as compared to placebo. The relapse types were about half depressive and half manic or mixed episodes.

16 HOW SUPPLIED/STORAGE AND HANDLING

Risperidone for Extended-Release Injectable Suspension is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone. It is provided as a single-dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperidone for Extended-Release Injectable Suspension, a 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 0480-1554-08): 43 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 0480-1554-01).

25 mg vial/kit (NDC 0480-1232-08): 81 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 0480-1232-01).

37.5 mg vial/kit (NDC 0480-1342-08): 120 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 0480-1342-01).

50 mg vial/kit (NDC 0480-1453-08): 156 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 0480-1453-01).

Storage and Handling

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

If refrigeration is unavailable, Risperidone for Extended-Release Injectable Suspension 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 Risperidone for Extended-Release Injectable Suspension.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported in association with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or report to the emergency room if they experience signs and symptoms of NMS, including hyperpyrexia, muscle rigidity, altered mental status including delirium, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) [*see Warnings and Precautions (5.3)*].

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur [*see Warnings and Precautions (5.4)*].

Metabolic Changes

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus and the need for specific monitoring, including blood glucose, lipids, and weight [*see Warnings and Precautions (5.5)*].

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension and syncope, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose. [*see Warnings and Precautions (5.7)*].

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia that they should have their CBC monitored while being treated with Risperidone for Extended-Release Injectable Suspension [*see Warnings and Precautions (5.9)*].

Hyperprolactinemia

Counsel patients on signs and symptoms of hyperprolactinemia that may be associated with chronic use of Risperidone for Extended-Release Injectable Suspension. Advise them to seek medical attention if they experience any of the following: amenorrhea or galactorrhea in females, erectile dysfunction or gynecomastia in males. [See *Warnings and Precautions* (5.6)].

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery, or operating a motor vehicle, until they are reasonably certain that Risperidone for Extended-Release Injectable Suspension therapy does not affect them adversely [see *Warnings and Precautions* (5.10)].

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct the patient to seek immediate medical attention in the event of priapism [see *Warnings and Precautions* (5.13)].

Heat Exposure and Dehydration

Counsel patients regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions* (5.14)].

Concomitant Medication

Advise patients to inform their healthcare providers if they are taking, or plan to take any prescription or over-the-counter drugs, as there is a potential for interactions [see *Drug Interactions* (7)].

Alcohol

Advise patients to avoid alcohol during treatment with Risperidone for Extended-Release Injectable Suspension [see *Drug Interactions* (7.1)].

Pregnancy

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

Lactation

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

Infertility

Advise females of reproductive potential that Risperidone for Extended-Release Injectable Suspension may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible [see *Use in Specific Populations* (8.3)].

Brands listed are the trademarks of their respective owners.

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Pharmathen International S.A.
Rodopi, 69300, Greece

Manufactured For:
Teva Pharmaceuticals
Parsippany, NJ 07054

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INSTRUCTIONS FOR USE
Risperidone (ris per' i done)
for Extended-Release Injectable Suspension

For deltoid or gluteal intramuscular injection only

Each injection should be administered by a healthcare professional.

IMPORTANT RESOURCES

For additional information call Teva at 1-888-838-2872.

Risperidone for Extended-Release Injectable Suspension requires close attention to these step-by-step Instructions for Use to help ensure successful administration.

SINGLE-DOSE DEVICE

Do not reuse. Medical devices require specific material characteristics to perform as intended. These characteristics have been verified for single-dose 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.

Important Information

Use components provided

The components in this dose pack are specifically designed for use with Risperidone for Extended-Release Injectable Suspension. Risperidone for Extended-Release Injectable Suspension 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

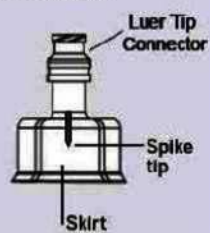
Administer dose as soon as possible after reconstitution to avoid settling.

Proper dosing

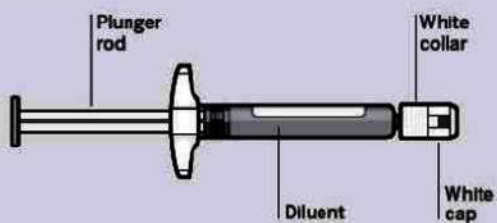
The entire contents of the vial must be administered to ensure intended dose of Risperidone for Extended-Release Injectable Suspension is delivered.

Dose pack contents

Vial Adapter



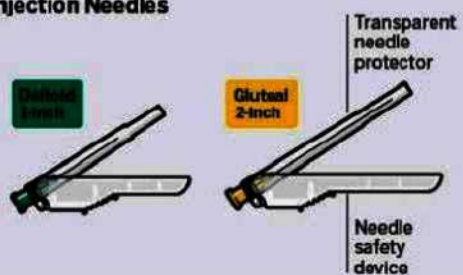
Prefilled Syringe



Vial



Terumo SurGuard® 3 Injection Needles



Step 1

Assemble components

Take out dose pack



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.

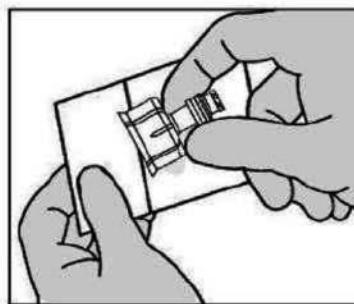
Connect vial adapter to vial



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 the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt.

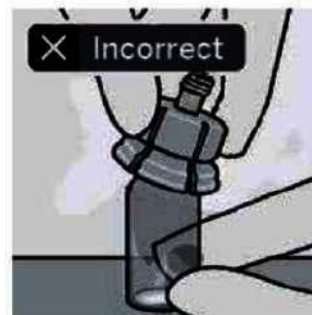
Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.



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.

CLEAN the luer tip of the vial adapter with an alcohol wipe

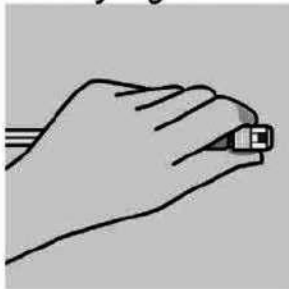
Do not place vial adapter on at an angle or diluent may leak upon transfer to the vial.



Do not shake.

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

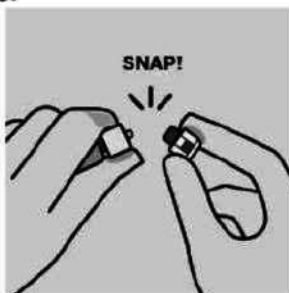
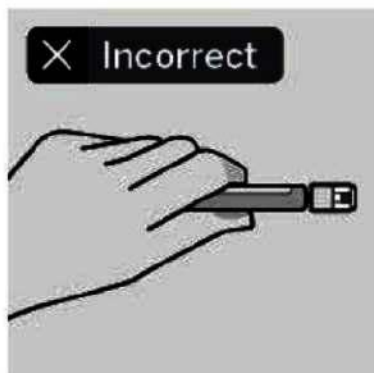
Connect prefilled syringe to vial adapter



Use proper grip

Hold by white collar at the tip of the syringe.

Do not hold syringe by the glass barrel during assembly.

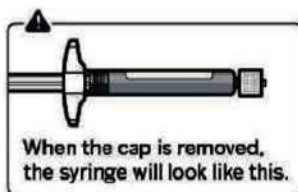


Remove cap

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 tip connector of the vial adapter.

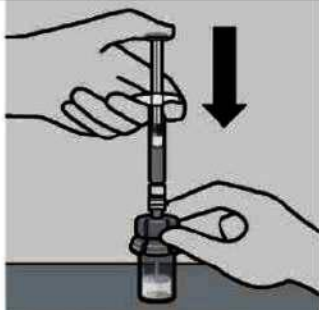
Do not hold the glass syringe barrel. This may cause the white collar to loosen or detach.

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

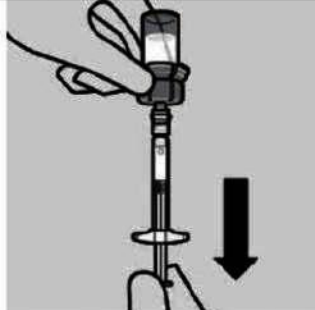
Continuing to hold down the plunger rod, **shake vigorously for at least 10 seconds**, as shown.

Check the suspension.

When properly mixed, the suspension appears uniform, thick and milky in color.

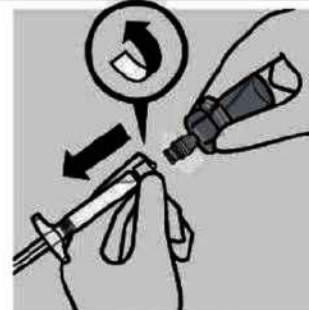
Microspheres will be visible in the liquid.

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

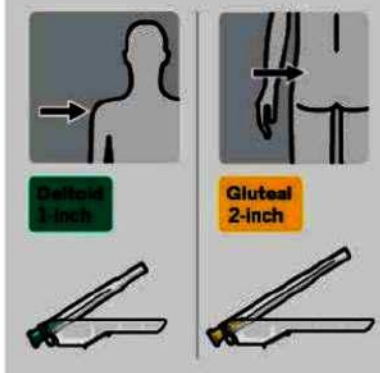
Hold white collar on the syringe and unscrew from vial adapter.

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.

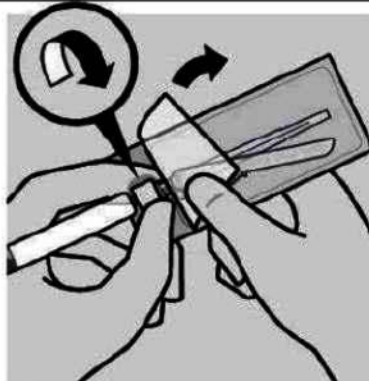
Step 3

Attach needle



Select appropriate needle

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

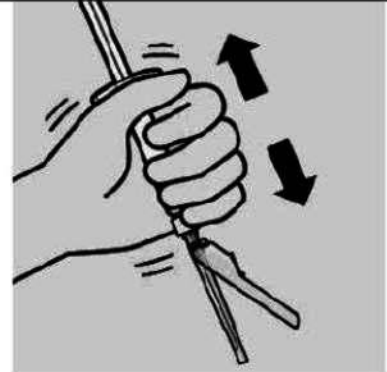


Attach needle

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.



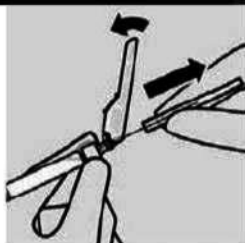
Resuspend microspheres

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

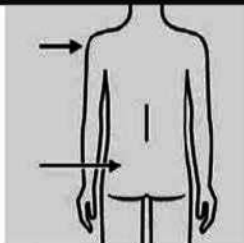
Move the needle safety device back towards the syringe, as shown. Then hold white collar on syringe and carefully pull the transparent needle protector straight off.

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.

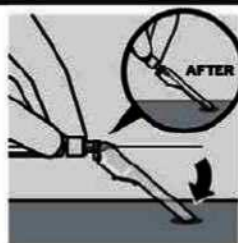


Inject

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

Avoid needle stick injury:

Do not use two hands.

Do not intentionally disengage or mishandle the needle safety device.

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



Properly dispose of needles

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

Also discard the unused needle provided in the dose pack.

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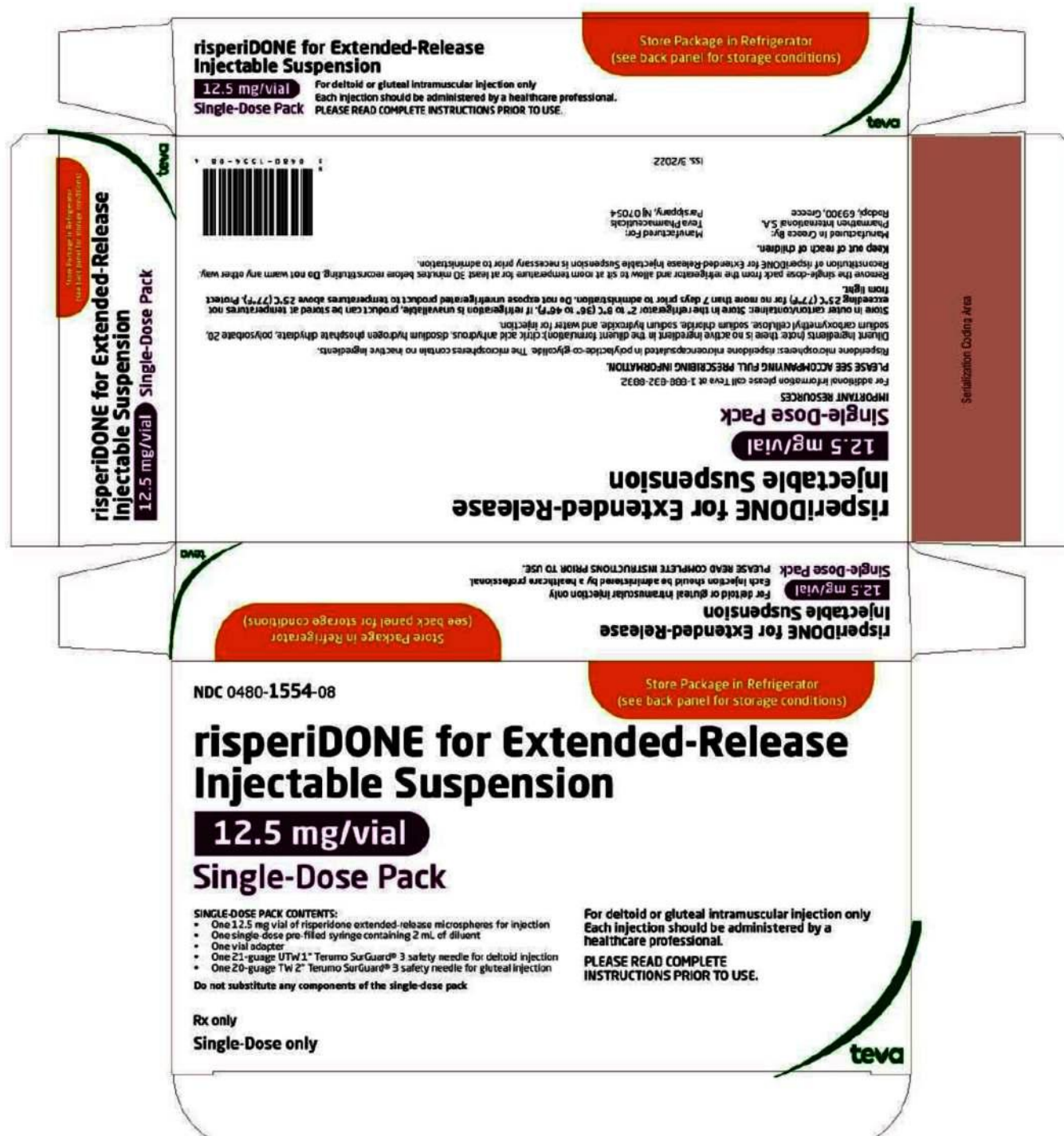
Iss. 3/2022











For deltoid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Store Package in Refrigerator
(see back panel for storage conditions)

90-ZCZ1-DR40

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Remove the single-dose pack from the refrigerator and allow to acclimatise at room temperature for at least 30 minutes before reconstituting. Do not warm any other vial, or concentration of reconstituted Bactera Suspension is necessary prior to administration.

For additional information please call 1-800-832-8832.
PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

IMPORTANT RESOURCES

25 mg/vial

**risperidone for Extended-Release
Injectable Suspension**

25 mg/vial
Single-Dose Pack

For deltoid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

trisperidone for extended-release
Injectable Suspension
(see back panel for storage conditions)

Store Package in Refrigerator
(see back panel for storage conditions)

NDC 0480-1232-08

25 mg/vial
Single-Dose Pack

SINGLE-DOSE PACK CONTENTS:

- One 25 mg vial of risperidone extended-release microspheres for injection
- One single-dose pre-filled syringe containing 2 mL of diluent
- One vial adapter
- One 21-gauge UTW1[®] Terumo SurGuard[®] 3 safety needle for deltoid injection
- One 20-gauge TW2[®] Terumo SurGuard[®] 3 safety needle for gluteal injection

Do not substitute any components of the single-dose pack

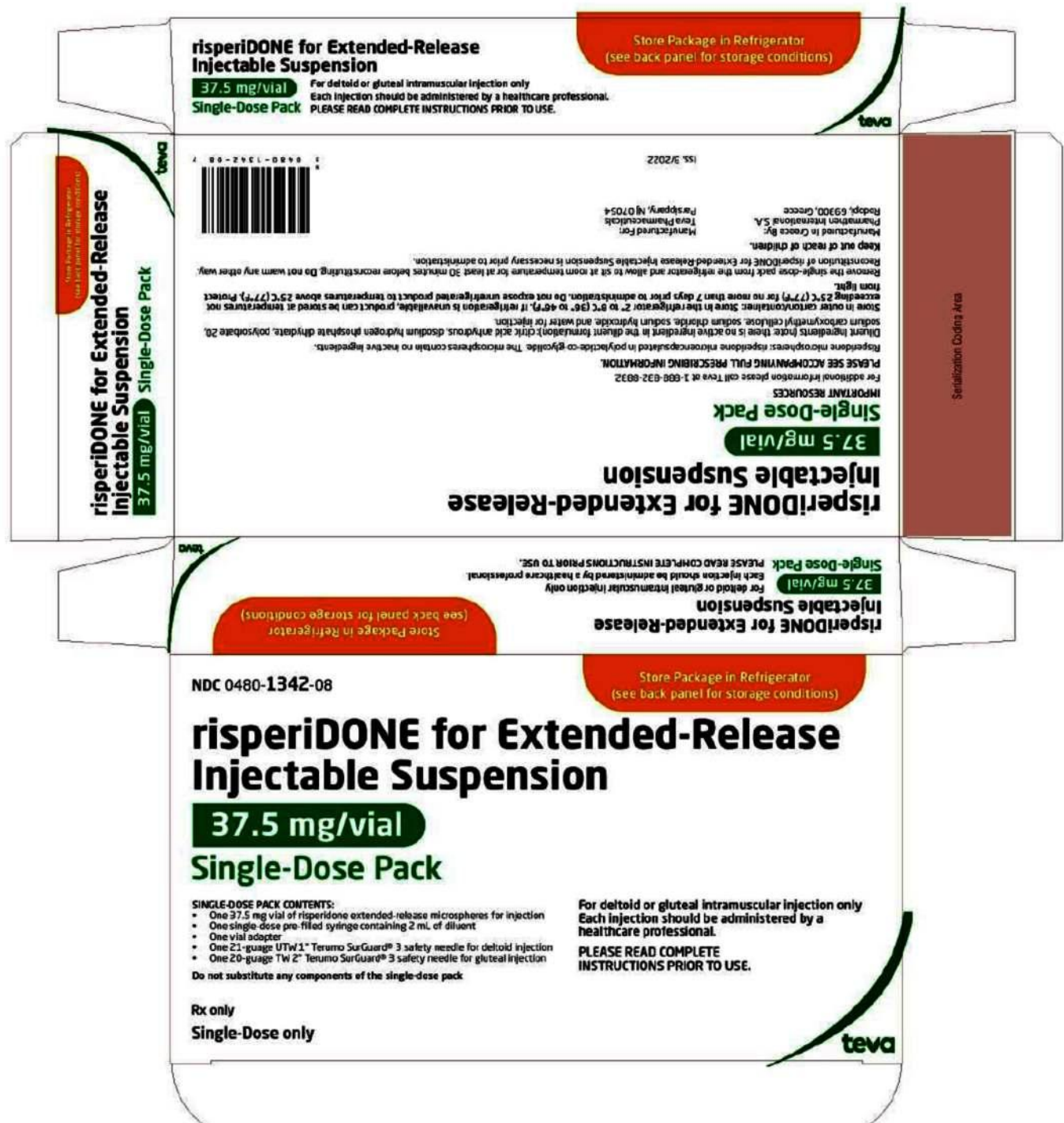
For deltoid or gluteal intramuscular injection only
Each injection should be administered by a
healthcare professional.

PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Rx only
Single-Dose only

tevc

crystallization condition Area



Page 66 of 641



(b)(4)

NDC 0480-1200-21 Single-Dose only

Diluent (2 mL) for suspension of

**risperiDONE for Extended-Release
Injectable Suspension**

For Deltoid or Gluteal Intramuscular Injection Only

Rx only

Mfg. In Greece For:
Teva Pharmaceuticals
Parsippany, NJ 07054
Iss. 3/2022

Lot: 

Exp: 


N 3 0 4 8 0 - 1 2 0 0 - 2 1 9

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 214068

LABELING REVIEW(s)

Labeling Review
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	September 5, 2023
ANDA Number(s)	214068
Review Number	4
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial
Proposed Proprietary Name	NA
Submission Received Date	February 27, 2023
Primary Labeling Reviewer	Pariban Dhanormchitphong
Secondary Labeling Reviewer	Eunjung Chuh
Review Conclusion ☒ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☐ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant	
On Policy Alert List	☐ Yes ☒ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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1 **LABELING COMMENTS (C4)**

1.1 **LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C4)**

1.2 **COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C4)**

The Division of Labeling has no further questions/comments at this time based on your labeling submission received February 27, 2023.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST-APPROVAL REVISIONS (C4)**

These comments will be addressed post approval (in the first labeling supplement review).

2 **INSTRUCTIONS FOR ASSESSMENT (C4)**

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.

Yes	No	
		This April 2023 update supersedes previous information: ▪ Pregnancy Registry (PR) is a third party's PR ▪ Add comment for Cycle 1 or if the PR is new in the NDA labeling ▪ If ANDA included the PR in labeling, we should comment for the ANDA applicant to ensure the accuracy of the PR in their labeling. The applicant should reach out to third party and verify that the data for the generic product will be accepted and if the applicant joins/intends to join the PR, the ANDA applicant can continue to include the PR in labeling. If the applicant does not intend to join the PR, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: <i>The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party and you intend to join the pregnancy registry, you can continue including the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party or if you do not intend to join the pregnancy registry, please remove the pregnancy registry information in your labeling.</i> ◦ If ANDA did not include PR in labeling, we should encourage the applicant to reach out to third party and verify that the data for the generic product will be accepted and if the applicant joins/intends to join the PR, the ANDA applicant can continue to include the PR in labeling. If the applicant does not intend to join the PR, the ANDA applicant should remove the PR in labeling. ▪ Example comment to include in SCD: <i>The reference listed drug (RLD) for your drug product contains third party pregnancy registry information in its labeling. Please reach out to the third party to verify if the data for your generic drug product will be accepted as part of their pregnancy registry. If it is verified that the data for your generic drug product will be accepted by the third party and you intend to join the pregnancy registry, please include the pregnancy registry information in your labeling. If it is determined that the data for your generic drug product will not be accepted by the third party or if you do not intend to join the pregnancy registry, you can continue excluding the pregnancy registry information in your labeling.</i>

Yes	No			
		From CAPT Golson's email dated 3/12/2015. See attachment above for link. Below, in addition to a link to the published list, are four more name pairs approved for tall man lettering. Although they do not appear on the list on the FDA website, DMEPA, who approves proposed pairs, has been made aware of these names and will be updating the list. CISplatin and CARBOplatin (b)(4) risperiDONE and rOPINIRole traZADONE and traMADOL It is noted that risperidone is listed on the FDA website. <table border="1"> <tr> <td>Risperidone</td> <td>risperiDONE</td> </tr> </table>	Risperidone	risperiDONE
Risperidone	risperiDONE			
☐	☒	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint ?		

4.2 MODEL PRESCRIBING INFORMATION (C4)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)

☒ MOST RECENTLY APPROVED NDA MODEL LABELING

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021346 / S-061

Supplement Approval Date: 02/12/2021

Proprietary Name: RISPERDAL

Established Name: risperiDONE long-acting injection

Description of Supplement:

These Prior Approval supplemental new drug applications provide for the following revisions to the Prescribing Information:

Risperdal Consta (risperidone) long-acting injection: The term "catatonia" and language about cases of extrapyramidal symptoms reported with concomitant use of risperidone and methylphenidate were added to Adverse Reactions-Postmarketing Experience (Section 6.2). A drug interaction for concomitant use of risperidone and methylphenidate was added to Drug Interactions (Section 7) and revisions were made to Warnings and Precautions (Section 5) and Patient Counseling (Section 17) to align with class labeling language. In addition, "single-use" was added to Dosage Forms and Strength (Section 3) and Description (Section 11), terms were added to Adverse Reactions-Postmarketing Experience (Section 6.2) and Use in Specific Populations (Sections 8.6 and 8.8) were added to align with the revisions to Warnings and Precautions.

Link: https://analytics.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4729427_4318700_090140af805d213c_NDA021346_2792324

☐ MOST RECENTLY APPROVED ANDA MODEL LABELING

**Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)**

☐ OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C4)

The [Orange Book](#) was searched on 09/05/2023

Table 4 provides Orange Book patents for the Model Labeling (NDA021346) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

C4 Labeling Review comments

- There are no currently listed patents or exclusivities for the RLD.

C3 Labeling Review comments

Patent 6667061 has expired since the last labeling review. As the applicant certified PIII to patent 6667061, the expiration does require any revision to the labeling.

Deficiency Comments:

4.4 UNITED STATES PHARMACOPEIA (USP) (C4)

The USP was searched on 09/06/2023

Table 6: USP

	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.

Reviewer Comments:

From labeling review #1:

The RLD states the established name as "risperiDONE long acting injection"; however, "long acting injection" is not defined as a type of injection by the USP. Subject ANDA (b)(4)

(b)(4)

name to read "risperiDONE for extended-release injectable suspension" to be in line with USP nomenclature guidelines as the drug product comes as a lyophilized powder with diluent.

Per USP, General Chapter, General Information <1121> Nomenclature:

Solutions administered by injection are officially titled Injections (see Injections and Implanted Drug Products (1)). The route of administration is omitted for drugs that are injected, because the route (e.g. intravenous, intramuscular, subcutaneous, etc.) must appear on the labels and in the labeling. USP defines seven types of injections:

[DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.

[DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.

[DRUG] Injectable Emulsion—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

[DRUG] Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium.

[DRUG] for Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

[DRUG] Extended-Release Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium and formulated in a manner that allows the contained API to be available over an extended period of time.

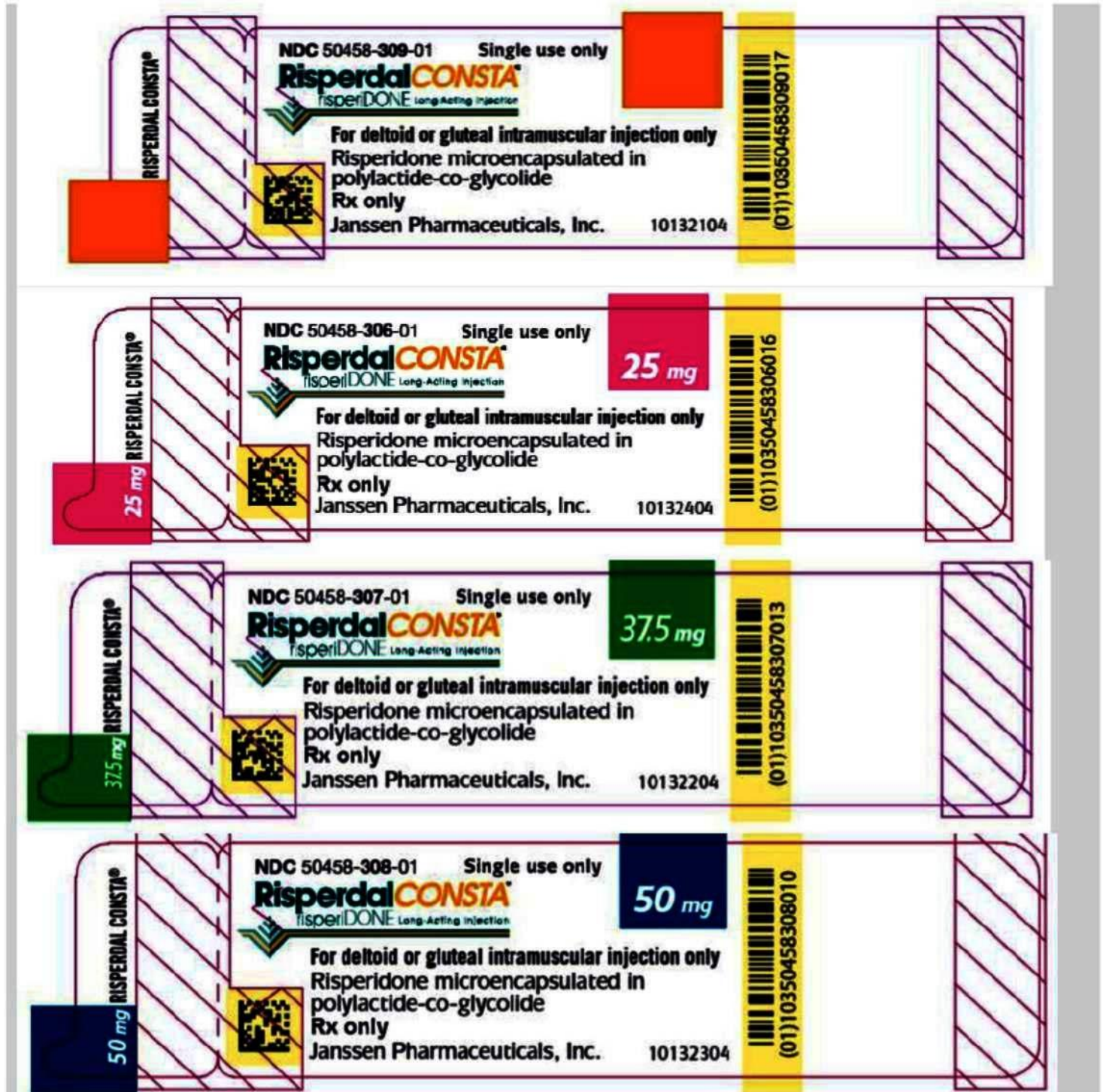
[DRUG] for Extended-Release Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Extended-Release Injectable

Suspensions

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C4)

Model container/carton/blister labels (Source: NDA 021346/ANRPT-S-020 submitted 12/22/2022)



Page 12

37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.



3 50458 30711 5



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

IMPORANT RESOURCES
www.risperdalconsta.com
For additional information, ask your pharmacist, or call Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736).

PLEASE SEE ADDITIONAL FULL PRESCRIPTION INFORMATION.

Risperdal Microspheres: Risperdalone microencapsulated in poly(lactide-co-glycolide). The microspheres contain no inactive ingredients.

Other ingredients (filler): there is no active ingredient in the filler (formulation): Polypropylene 20, Sodium Carboxymethylcellulose, Croscarmellose, Hydroxyethyl Cellulose, Croscarmellose, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in cool or cold storage: Store in the refrigerator, 2°C – 8°C (36°F – 46°F). If refrigeration is unavailable, protect from light and store at controlled room temperature, 20°C – 25°C (68°F – 77°F) for no more than 7 days prior to use. Do not expose unopened product to temperatures above 25°C (77°F). Protect from light.

Remove the single-use dose pack from refrigerator and allow to sit at room temperature for at least 30 minutes before reconstructing. Do not warm any other components of RISPERDAL CONSTA® in any way prior to administration.

37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

SINGLE-USE DOSE PACK CONTENTS:

- One 37.5 mg vial of risperdalone extended-release microspheres for injection
- One single-use pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge 1 1/2" Terumo SureGuard® 3 safety needle for deltid injection
- One 20-gauge 1 1/2" Terumo SureGuard® 3 safety needle for gluteal injection

Do not substitute any components of the single-use dose pack.

For deltid or gluteal intramuscular injection only
Each injection should be administered by a health care professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Single-Use
Dose Pack

**Store Package
in Refrigerator**
(see bottom panel for
storage conditions)



Don't place anything on the layer "Diecut"

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5 ASSESSMENT OF ANDA LABELING AND LABELS (C4)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C4)

5.1.1 DRUG PRODUCT REVIEW (C4)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

A2140686 Drug Product R03a_AQ-8-21-2023.docx dated 8/21/2023 (pending secondary as of 9/6/2023)

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in
DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for
Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC
products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

5.1.2 DESCRIPTION (C4)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	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 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. RISPERDAL CONSTA® is provided as a single-use dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).
Previous ANDA Labeling	Risperidone for Extended-Release Injectable Suspension 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, sterile, 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 microencapsulated in 75:25 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

	of microspheres. The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. Risperidone for Extended-Release Injectable Suspension is provided as a single-dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).
Current ANDA Labeling	Risperidone for Extended-Release Injectable Suspension 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, sterile, 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 microencapsulated in 75:25 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 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. Risperidone for Extended-Release Injectable Suspension is provided as a single-dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration). Assessment: No change. Adequate.

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C4)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	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 single-use dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL CONSTA®, a 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-
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Table 8: Comparison of Model Labeling to ANDA Labeling

	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.
Previous ANDA Labeling	(b)(4)
Current ANDA Labeling	16 HOW SUPPLIED/STORAGE AND HANDLING Risperidone for Extended-Release Injectable Suspension is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone. It is provided as a single-dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperidone for Extended-Release Injectable Suspension, a 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 0480-1554-08): 43 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 0480-1554-01).

Table 8: Comparison of Model Labeling to ANDA Labeling

	25 mg vial/kit (NDC 0480-1232-08); 81 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 0480-1232-01). 37.5 mg vial/kit (NDC 0480-1342-08); 120 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 0480-1342-01). 50 mg vial/kit (NDC 0480-1453-08); 156 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 0480-1453-01). Storage and Handling The entire dose pack should be stored in the refrigerator (36° to 46°F; 2° to 8°C) and protected from light. If refrigeration is unavailable, Risperidone for Extended-Release Injectable Suspension 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. Assessment: Adequate. Change in NDC number.
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5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER (C4)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Previous ANDA Labeling		
Name and Address on ANDA Prescribing Information	(b)(4)	
Current ANDA Labeling		
Name and Address on ANDA Prescribing Information	Manufactured In Greece By: Pharmathen International S.A. Rodopi, 69300, Greece Manufactured For: Teva Pharmaceuticals. Parsippany, NJ 07054 Assessment: Minor change. Adequate.	

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Deficiency	No Deficiency	
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text(written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number: prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol.
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.].
☐	☒	Gluten statement is appropriately stated.
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products.
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure, cite source, and any issues in Reviewer Comments below.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

C4 Labeling Review comments

- CONTAINER LABELS were found adequate in a previous Labeling review.
- The applicant submitted revised CONTAINER LABELS due to change in (b)(4) and manufacturing statement.
- CONTAINER LABELS are adequate.

From labeling review #2:

The following comment was sent to the applicant:

CONTAINER LABEL (Drug Product and Diluent)

We acknowledge the request to revise the established name to read "Risperidone for Extended-Release Injectable Suspension"; however, revise the established name to include "Tall Man" lettering (i.e., risperidONE for Extended-Release Injectable Suspension).

Assessment:

The applicant satisfactorily revised the container label to be in line with the Agency's "Tall Man" lettering.

(b)(4)

It is noted the approval letter for the last approved model labeling for the RLD, NDA 021346/S-061, included container and carton labeling. Editorial revision was made as well revision to the Manufacturer statement and removal of the "Product of" statement. No revision to subject ANDA's container label is needed.



(b)(4)

The applicant submits a diluent label with the established name revised to be in line with the Agency's "Tall Man" lettering. Subject ANDA's diluent label is found acceptable.

Previous submission:

(b)(4)

Currently proposed:

(b)(4)

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule over seal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is violet, pink, green, blue. NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments:

Subject ANDA states "single dose only" where the RLD states "single use only". This is acceptable.

Deficiency Comments:

5.2.1.1 CONTAINER LABEL FOR SOLID INJECTABLE (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength is expressed in terms of the total amount of drug per vial.
☐	☒	Container label includes instructions for reconstitution and resultant concentration provided, if space permits.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii) .
☐	☒	Aluminum content is present on immediate container label (SVP, LVP, or PBP) and warning is present in the prescribing information for single-dose products.

Reviewer Comments:

Container does not include instructions for reconstitution or inactive ingredients in line with the RLD.

Deficiency Comments:

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Unit-Dose Carton expression of strength appropriately stated.
☐	☒	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:**C4 Labeling Review comments**

- The applicant submitted revised CARTON LABELS in accordance with C3 Labeling Review comments.
- CARTON LABELS are adequate.

C3 Labeling Review comments

Deficiency comment from labeling review #2:

We acknowledge the request to revise the established name to read "Risperidone for Extended-Release Injectable Suspension"; however, revise the established name to include "Tall Man" lettering (i.e., risperiDONE for Extended-Release Injectable Suspension).

Assessment:

The applicant satisfactorily updated the established name to be in line with the Agency's "Tall Man" lettering.

(b)(4)

It is noted the approval letter for the last approved model labeling for the RLD, NDA 021346/S-061, includes container and carton labeling. Due to revision to the carton, revision to the carton will be requested. Please see comments below.

Deficiency Comments:

Deficiency # 1

On the PDP, revise (b)(4) to read "SINGLE-DOSE PACK CONTENTS:".

Created in C3

Carton Labeling

Response / Assessment:	Applicant revised as requested.
Deficiency # 2	Under SINGLE-DOSE PACK CONTENTS:, second bullet: Revise to read "One single-dose pre-filled syringe container 2 mL of diluent".
Created in C3	
Carton Labeling Response / Assessment:	Applicant revised as requested.
Deficiency # 3	Revise (b)(4) to read "Do not substitute components of the single-dose pack".
Created in C3	
Carton Labeling Response / Assessment:	Applicant revised as requested.
Deficiency # 4	On the back panel, below IMPORTANT RESOURCES, revise (b)(4) to read "PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION."
Created in C3	
Carton Labeling Response / Assessment:	Applicant revised as requested.
Deficiency # 5	Revise (b)(4) associated with the strength statement on all panels to read "Single-Dose Pack".
Created in C3	
Carton Labeling Response / Assessment:	Applicant revised as requested.
Deficiency # 6	On the back panel, last paragraph, first sentence: Revise (b)(4) to read "Remove the single-dose pack from refrigerator...."
Created in C3	
Carton Labeling Response / Assessment:	Applicant revised as requested.

5.4 PRESCRIBING INFORMATION (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at the end of HIGHLIGHTS section (PLR) or end of prescribing information (non-PLR).
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21)

Deficiency	No Deficiency	
		☐ latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(i)(D)].
☐	☒	Dosage form, pharmacologic/therapeutic class, and route of administration properly listed [21 CFR 201.57(c)(12)(i)(B)] and [21 CFR 201.57(c)(12)(i)(E)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
REGULATORY/OVERALL ASSESSMENT:		
☐	☒	STC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing information meets formatting requirements [21 CFR 201.57 (PLR) or 21 CFR 201.80 (non-PLR)].
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

C4 Labeling Review comments

- (b)(4)
- **PRESCRIBING INFORMATION** is adequate.

C3 Labeling Review comments

From labeling review #2:

The following comment was conveyed to the applicant:

(b)(4)

Assessment:

The applicant states that they "respectfully decline to adhere to this comment". As this request was a recommendation, we find the applicant's position acceptable.

It is noted that section 2.8 Instructions for Use is in line with the separate Instructions for Use labeling. The Instructions for Use has been found acceptable in the DCR review. (The last approved model labeling, NDA

021346/S-061 did not update the IFU.)

Deficiency Comments:

Deficiency # 1

Created in C3

Prescribing Information
Response / Assessment:

(b)(4)

5.5 OTHER PATIENT LABELING (C4)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

C4 Labeling Review comments

- The applicant submitted revised IFU in accordance with the change of their manufacturing statement.
- IFU is adequate.

C3 Labeling Review comments

Deficiency comments from labeling review #2:

INSTRUCTIONS FOR USE

a.

(b)(4)

b. Add "Each injection should be administered by a healthcare professional." directly below

(b)(4)

The 6/12/20 DCR review does not have comments.

<https://panorama.fda.gov/task/view?ID=5e42da760031da9d1d1aedcb961fc5d0>

We note the differences in IFU align with difference in vial adapter and are found acceptable by DCR.

Table 3: Comparison of IFU Labels – RLD Risperdal Consta® (NDA 021346) and Proposed Product Risperidone IM Injection (ANDA 214068)

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
 Prepare vial adapter Hold sterile blister as shown. Peel the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.	 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.
(b)(4)	 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.
	Remove sterile blister  Remove vial adapter 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.

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
(b)(4)	Hold syringe by white collar then insert tip into the luer opening of the vial adapter.
Reviewer Comments: Although the proposed product contains similar components, the vial adapter has design differences when compared to the RLD and the Applicant has modified the Instructions for Use (IFU) to align with these design differences. These differences are: • • • • • (b)(4) As discussed in Section 2.2, these modifications to the IFU regarding the vial adapter are consistent with those recommended by DCR for another Teva product⁷, Ocreotide Acetate for Injectable Suspension. Therefore, these differences in the IFU are acceptable. There was one additional difference between the IFUs of the proposed product and RLD. (b)(4) (b)(4)	
3 CONCLUSION From a clinical safety perspective, the differences in luer tip of the vial adapter, syringe, blister pack removal, as well as additions to the IFU to account for these physical differences between the RLD and proposed product are minor and unlikely to impact the safe and effective use of the proposed product as a substitute for the RLD. DCR finds the proposed risperidone IM injection acceptable. 4 RECOMMENDATION The Clinical Discipline has completed its review of the comparative (threshold) analyses and has no comments at this time. ☐ Major ☐ Minor ☒ N/A (Review is Adequate) Assessment: The applicant satisfactorily addressed both comments. IFU is found acceptable. It is noted that the last approved model labeling, NDA 021346/S-061 did not update the IFU. Deficiency Comments:	

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C4)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)

☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reviewer Comments:

A214068N000DCR-Review01-Risperidone Injection.pdf dated 6/16/2020:

3 CONCLUSION

From a clinical safety perspective, the differences in luer tip of the vial adapter, syringe, blister pack removal, as well as additions to the IFU to account for these physical differences between the RLD and proposed product are minor and unlikely to impact the safe and effective use of the proposed product as a substitute for the RLD. DCR finds the proposed risperidone IM injection acceptable.

4 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has no comments at this time.

Deficiency Comments:



Pariban
Dhanormchitphon
g

Digitally signed by Pariban Dhanormchitphong
Date: 9/07/2023 11:22:48AM
GUID: 54077981000a14b52c4b9fb39e992361



Esther
Chuh

Digitally signed by Esther Chuh
Date: 9/07/2023 08:41:20PM
GUID: 508da70700028b78f2f9ebd95bfb4a18

Labeling Review
 Division of Labeling Review
 Office of Regulatory Operations
 Office of Generic Drugs (OGD)
 Center for Drug Evaluation and Research (CDER)

Date of This Review	10/01/2021
ANDA Number(s)	214068
Review Number	3
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial
Proposed Proprietary Name	NA
Submission Received Date	05/27/2021
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Ellen Koo
Review Conclusion ☐ Acceptable - No Comments ☐ Acceptable - Include Post Approval Comments ☒ Minor Deficiency* - Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency** - Refer to Labeling Deficiencies and Comments for Letter to Applicant *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Acceptable For Filing	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No

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1 LABELING COMMENTS (C3)

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT (C3)

Labeling deficiencies based on your submission received May 27, 2021:

1. CARTON LABELING

- a. On the PDP, revise (b)(4) to read "SINGLE-DOSE PACK CONTENTS:".
- b. Under SINGLE-DOSE PACK CONTENTS:, second bullet: Revise to read "One single-dose pre-filled syringe container 2 mL of diluent".
- c. Revise (b)(4) to read "Do not substitute components of the single-dose pack".
- d. On the back panel, below IMPORTANT RESOURCES, revise (b)(4) to read "PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION."
- e. Revise (b)(4) associated with the strength statement on all panels to read "Single-Dose Pack".
- f. On the back panel, last paragraph, first sentence: Revise (b)(4) to read "Remove the single-dose pack from refrigerator...."

2. PRESCRIBING INFORMATION

- a. HIGHLIGHTS/RECENT MAJOR CHANGES: Revise this section to be in line with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE (C3)

1.3 POST-APPROVAL REVISIONS (C3)

These comments will be addressed post approval (in the first labeling supplement review).

2 INSTRUCTIONS FOR ASSESSMENT (C3)

General Comments:

Select the "no deficiency" or "deficiency" radio button as appropriate for each row. If a "Deficiency Comments" appears, ensure it is appropriate for your situation, edit, or enter "Reviewer Comments" if necessary.

If there is no issue/concern, or if the question is not applicable. No "Deficiency Comments" will appear but reviewers can still enter "Reviewer Comments" if desired.

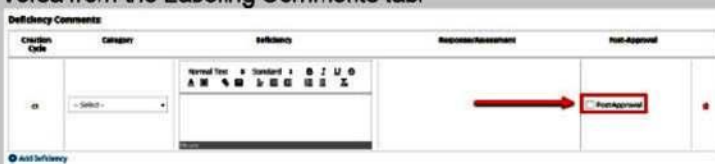
☐	☒	There is information in the Orange Book that the applicant needs to address.
☒	☐	Information in the Orange Book has expired and the applicant needs to revise labeling.

Reviewer Comments:

Enter free text in this section as necessary.

Deficiency Comments:

- Standardized comments/deficiencies are available for certain questions. For a complete list of standardized comments, reference the [DLR Standardized Comments](#) SharePoint.
- Reviewers can modify standardized comments/deficiencies for their situation.
- Deficiencies will have a review number, deficiency number, and roman numeral in the user interface. For first original reviews the review number and iteration numeral will align; however, older reviews may have review numbers and iteration numerals that differ due to some reviews being completed under past practices.
- Deficiency comments will populate by default to the Labeling Comments deficiency section unless you select the Post-Approval checkbox. Assessors also have the option to move all comments to the Post-Approval Revisions section or vice versa from the Labeling Comments tab.



3 OVERALL ASSESSMENT OF MATERIALS REVIEWED (C3)

Table 1: Review Summary of Container Label and Carton Labeling

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Final	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	5/27/2021	Satisfactory
Blister	N/A	N/A		
Carton	Final	One vial and one pre-filled syringe with diluent	5/27/2021	Revise
Diluent (in pre-filled syringe)	Final	2 mL	5/27/2021	Satisfactory

Table 2: Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 4/2021	5/27/2021	Revise
Medication Guide	N/A	N/A		
Patient Information	N/A	N/A		
Instructions for Use	Draft	Iss. 4/2021	5/27/2021	Satisfactory
SPL Data Elements				

4 LABELING REVIEW INFORMATION(C3)

4.1 REGULATORY INFORMATION (C3)

Yes	No							
☒	☐	Are there any applicable issues in DLR's SharePoint Drug Facts ? There is a pregnancy registry established by the Massachusetts General Hospital and Harvard Medical school for the class of psychiatric medications. There are three different groups under the pregnancy registry but the phone number for the PR is the same for all three. 1. The National Pregnancy Registry for Atypical Antipsychotics 2. The National Pregnancy Registry for Antidepressants 3. The National Pregnancy Registry for ADHD Medications. Per DPMH, this NDA holders are required to list this PR in their insert labeling. We will request all ANDAs for psychiatric medications to list this PR in their labeling to be the same as the RLD. We do NOT need to ask the firm to confirm that they are registered with this organization to participate in the PR. **Updated 4/14/2021: Added active ingredients for Atypical Antipsychotics, Antidepressants, and ADHD Medication. Please update as needed.** From CAPT Golson's email dated 3/12/2015. See attachment above for link. Below, in addition to a link to the published list, are four more name pairs approved for tall man lettering. Although they do not appear on the list on the FDA website, DMEPA, who approves proposed pairs, has been made aware of these names and will be updating the list. CISplatin and CARBOplatin (b)(4) risperiDONE and rOPINIRole traZADONE and traMADOL It is noted that risperidone is listed on the FDA website. <table border="1"> <tr> <td>Risperidone</td> <td>risperiDONE</td> </tr> </table>	Risperidone	risperiDONE				
Risperidone	risperiDONE							
☒	☐	Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? <table border="1"> <tr> <td>CP</td> <td>FDA-2011-P-0086</td> <td>Risperdal Consta</td> </tr> <tr> <td colspan="2"> Risperidone long-acting injection No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead </td> <td> Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and, the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug are highlighted by the real-world situation of LY03084, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence prior to contacting Policy Lead </td> </tr> </table> There are applications affected by this petition, as of 12/16/19.	CP	FDA-2011-P-0086	Risperdal Consta	Risperidone long-acting injection No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead		Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and, the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug are highlighted by the real-world situation of LY03084, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence prior to contacting Policy Lead
CP	FDA-2011-P-0086	Risperdal Consta						
Risperidone long-acting injection No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead		Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and, the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug are highlighted by the real-world situation of LY03084, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd. No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence prior to contacting Policy Lead						

4.2 MODEL PRESCRIBING INFORMATION (C3)

Table 3: Review Model Labeling for Prescribing Information/Patient Labeling (Check the box used as the Model Labeling) ☒ MOST RECENTLY APPROVED <u>NDA</u> MODEL LABELING

**Table 3: Review Model Labeling for Prescribing Information/Patient Labeling
(Check the box used as the Model Labeling)**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): NDA021346 / S-061

Supplement Approval Date: 02/12/2021

Proprietary Name: RISPERDAL

Established Name: risperidONE long-acting injection

Description of Supplement:

These Prior Approval supplemental new drug applications provide for the following revisions to the Prescribing Information:

Risperdal Consta (risperidone) long-acting injection: The term "catatonia" and language about cases of extrapyramidal symptoms reported with concomitant use of risperidone and methylphenidate were added to Adverse Reactions-Postmarketing Experience (Section 6.2). A drug interaction for concomitant use of risperidone and methylphenidate was added to Drug Interactions (Section 7) and revisions were made to Warnings and Precautions (Section 5) and Patient Counseling (Section 17) to align with class labeling language. In addition, "single-use" was added to Dosage Forms and Strength (Section 3) and Description (Section 11), terms were added to Adverse Reactions-Postmarketing Experience (Section 6.2) and Use in Specific Populations (Sections 8.6 and 8.8) were added to align with the revisions to Warnings and Precautions.

Link: https://palantir.fda.gov/workspace/hubble/external/object/v0/fda-communication?pk_communication=4729427_4318700_090140af805d213c_NDA021346_2792324

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

☒ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

S-062 and S-064 are approved CMC supplements that do not affecting labeling.

S-063 is an approved labeling supplement that provides for new safety information pertaining to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	ANDA is up-to-date with the RLD/Model labeling.
Reviewer Comments:		
Deficiency Comments:		

4.3 PATENTS AND EXCLUSIVITIES (C3)

The [Orange Book](#) was searched on 10/01/2021

Table 4 provides Orange Book patents for the Model Labeling (NDA021346) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 4: Impact of Model Labeling Patents on ANDA Labeling

Strengths	Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
	N/A						

Table 5 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 5: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling						
Strengths	Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
	N/A					

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	There is information in the Orange Book that the applicant needs to address.
☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
Reviewer Comments: Patent 6667061 has expired since the last labeling review. As the applicant certified PIII to patent 6667061, the expiration does require any revision to the labeling.		
Deficiency Comments:		

4.4 UNITED STATES PHARMACOPEIA (USP) (C3)

The USP was searched on 10/01/2021

Table 6: USP				
	YES or NO	Date	Monograph Title (N/A if no monograph)	Packaging and Storage/Labeling Statements (N/A if no monograph)
Currently Official	No		N/A	N/A
Not Yet Official	No		N/A	N/A

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name.
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information.
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate.
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities.
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay.
Reviewer Comments: From labeling review #1: The RLD states the established name as "risperiDONE long acting injection"; however, "long acting injection" is not defined as a type of injection by the USP. (b)(4) (b)(4)		

name to read “risperiDONE for extended-release injectable suspension” to be in line with USP nomenclature guidelines as the drug product comes as a lyophilized powder with diluent.

Per USP, General Chapter, General Information <1121> Nomenclature:

Solutions administered by injection are officially titled Injections (see Injections and Implanted Drug Products <1>). The route of administration is omitted for drugs that are injected, because the route (e.g. intravenous, intramuscular, subcutaneous, etc.) must appear on the labels and in the labeling. USP defines seven types of injections:

[DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.

[DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.

[DRUG] Injectable Emulsion—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

[DRUG] Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium.

[DRUG] for Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

[DRUG] Extended-Release Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium and formulated in a manner that allows the contained API to be available over an extended period of time.

[DRUG] for Extended-Release Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Extended-Release Injectable Suspensions

Deficiency Comments:

4.5 MODEL CONTAINER LABELS (C3)

Model container/carton/blister labels (Source: NDA 021346/S-061 approval letter in DARRTS dated 2/12/2021)



GTN 00350453081116
SN
LOT
EXP

For delirium or glaucoma intramuscular injection only
Each injection should be administered by a health care professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

For only
Single use only

- SINGLE-USE DOSE PACK CONTENTS:**
- One 25 mg of risperidone extended-release microspheres for injection
 - One single-use pre-filled syringe containing 2 mL of diluent
 - One 1 mL Adapter
 - One 21-gauge 1.5" Terumo SurGuard® 3 safety needle for deltoid injection
 - One 20-gauge 1.5" Terumo SurGuard® 3 safety needle for gluteal injection
- Do not substitute any components of the single-use dose pack.

Risperdal CONSTA
risperidone Long-Acting Injection

NDC 3055-365-11

25 mg
Single-Use
Dose Pack

Store Package
in Refrigerator
for Injection and for
Storage and Use

Risperdal CONSTA
risperidone Long-Acting Injection

For delirium or glaucoma intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

25 mg
Single-Use
Dose Pack

Risperdal CONSTA
risperidone Long-Acting Injection

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

PLEASE SEE ACCOMPANYING FULL PRESCRIPTION INFORMATION.

Risperidone Microspheres: Risperidone microsphere is a polylactide-co-polyglycolide. The microspheres contain no inactive ingredients.

Diluent Ingredients: There is no active ingredient in the diluent (formulation). Ingredients: 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in water cartons/containers. Store in the refrigerator, 2°C - 8°C (36°F - 46°F). If refrigeration is unavoidable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose Risperdal CONSTA to temperatures above 25°C (77°F). Protect from light.

Remove the single-use dose pack from refrigerator and allow to reach room temperature for at least 30 minutes before administering. Do not warm any other vial. Reconstitution of RISPERDAL CONSTA is necessary prior to administration.

Product of Janssen
Pharmaceuticals, Inc.
Manufactured by
Janssen Pharmaceutics
N.V., Turnhout, Belgium
Water Pumping Group & Co. NV
Lange Wijk 1, 3584 MS
Utrecht, The Netherlands
Risperdal CONSTA is
a registered trademark of
Janssen Pharmaceutics, Inc.
© 2011 Janssen Pharmaceutics, Inc.



JANSSEN
© 2011 Janssen Pharmaceutics, Inc.

Risperdal CONSTA
risperidone Long-Acting Injection

For delirium or glaucoma intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

25 mg
Single-Use
Dose Pack

For delirium or glaucoma intramuscular injection only
Each injection should be administered by a health care professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

For only
Single use only

- SINGLE-USE DOSE PACK CONTENTS:**
- One 37.5 mg of risperidone extended-release microspheres for injection
 - One single-use pre-filled syringe containing 2 mL of diluent
 - One 1 mL Adapter
 - One 21-gauge 1.5" Terumo SurGuard® 3 safety needle for deltoid injection
 - One 20-gauge 1.5" Terumo SurGuard® 3 safety needle for gluteal injection
- Do not substitute any components of the single-use dose pack.

Risperdal CONSTA
risperidone Long-Acting Injection

NDC 3055-365-11

37.5 mg
Single-Use
Dose Pack

Store Package
in Refrigerator
for Injection and for
Storage and Use

Risperdal CONSTA
risperidone Long-Acting Injection

For delirium or glaucoma intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Single-Use
Dose Pack

Risperdal CONSTA
risperidone Long-Acting Injection

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

PLEASE SEE ACCOMPANYING FULL PRESCRIPTION INFORMATION.

Risperidone Microspheres: Risperidone microsphere is a polylactide-co-polyglycolide. The microspheres contain no inactive ingredients.

Diluent Ingredients: There is no active ingredient in the diluent (formulation). Ingredients: 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in water cartons/containers. Store in the refrigerator, 2°C - 8°C (36°F - 46°F). If refrigeration is unavoidable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose Risperdal CONSTA to temperatures above 25°C (77°F). Protect from light.

Remove the single-use dose pack from refrigerator and allow to reach room temperature for at least 30 minutes before administering. Do not warm any other vial. Reconstitution of RISPERDAL CONSTA is necessary prior to administration.

Product of Janssen
Pharmaceuticals, Inc.
Manufactured by
Janssen Pharmaceutics
N.V., Turnhout, Belgium
Water Pumping Group & Co. NV
Lange Wijk 1, 3584 MS
Utrecht, The Netherlands
Risperdal CONSTA is
a registered trademark of
Janssen Pharmaceutics, Inc.
© 2011 Janssen Pharmaceutics, Inc.



JANSSEN
© 2011 Janssen Pharmaceutics, Inc.

Risperdal CONSTA
risperidone Long-Acting Injection

For delirium or glaucoma intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Single-Use
Dose Pack

50 mg
Single-Use
Dose Pack

Risperdal CONSTA
risperidone Long-Acting Injection

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

IMPORTANT RESOURCES
For additional information, visit www.risperdalconsta.com or call Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-525-7739).
PLEASE SEE ACCOMPANYING FULL PRESCRIPTION INFORMATION.

Warnings: Risperidone microencapsulated in polylactide-co-glycolide. The microencapsules contain no toxic ingredients. Observe hypotension (low blood pressure) in the absence of orthostatic hypotension. Do not administer to patients with known hypersensitivity to risperidone, risperidone hydrochloride, or any of the other ingredients. Do not administer to patients with known hypersensitivity to any of the other ingredients. Do not administer to patients with known hypersensitivity to any of the other ingredients. Do not administer to patients with known hypersensitivity to any of the other ingredients.

How to use: Risperdal CONSTA is a long-acting injection. It is administered by intramuscular injection into the deltoid or gluteal muscle. It is not intended for intravenous use. It is not intended for use in patients with known hypersensitivity to any of the other ingredients. It is not intended for use in patients with known hypersensitivity to any of the other ingredients. It is not intended for use in patients with known hypersensitivity to any of the other ingredients.

Storage: Store in the refrigerator, 2°C to 8°C (36°F to 46°F). Do not freeze. If the product has been frozen, it should be discarded. Do not use if the product has been exposed to temperatures above 25°C (77°F). Protect from light.

Remove the Risperdal CONSTA microencapsulated product from the refrigerator and allow to reach room temperature for at least 30 minutes before administering. Do not warm any other way. Reconstitution of RISPERDAL CONSTA is necessary prior to administration.

30458-108-1

JANSSEN
© 2011 Janssen Pharmaceuticals, Inc.

Product of Janssen Pharmaceuticals, Inc.
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

50 mg
Single-Use
Dose Pack

Risperdal CONSTA
risperidone Long-Acting Injection

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

SINGLE-USE DOSE PACK CONTENTS:

- One 50 mg vial of risperidone extended-release microencapsules for injection
- One single-use pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge UTW 1" Insurmo SurGuard® 3 safety needle for deltoid injection
- One 20-gauge TW 2" Insurmo SurGuard® 3 safety needle for gluteal injection

Do not substitute any components of this single-use dose pack.

For deltoid or gluteal intramuscular injection only
Each injection should be administered by a health care professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

50 mg
Single-Use
Dose Pack

Store Package in Refrigerator
Do not remove from refrigerator until ready to use.

Rx only
Single use only

NDA 021346/S-044

Rx only **Single use only**
Diluent (2mL) for suspension of
RISPERDAL® CONSTA® (risperidone)
Long-Acting Injection
For deltoid or gluteal intramuscular injection only

Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
© Janssen 2005

Lot: **Exp:**

10131703

(01)10350458311010

5 ASSESSMENT OF ANDA LABELING AND LABELS (C3)

5.1 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS) (C3)

5.1.1 DRUG PRODUCT REVIEW (C3)

Insert screenshot of Labeling portion from drug product review if completed:
Drug Product Review complete

A2140686 Drug Product R01b-IQ

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

5.1.2 DESCRIPTION (C3)

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	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
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Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

	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 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. RISPERDAL CONSTA® is provided as a single-use dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).
ANDA Labeling	Previous labeling review: (b) (4) administration). Currently proposed: Risperidone for Extended-Release Injectable Suspension 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, sterile, 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 microencapsulated in 75:25 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 1 mg/mL citric acid anhydrous, 1.27 mg/mL disodium hydrogen phosphate dihydrate, 1 mg/mL polysorbate 20, 22.5 mg/mL sodium carboxymethyl cellulose, 6 mg/mL sodium chloride, 0.54 mg/mL sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. Risperidone for Extended-Release Injectable Suspension is provided as a single-dose pack, consisting of a vial containing the microspheres, a pre-filled syringe

Table 7: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

	containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration). Assessment: (b)(4) added in line with the updated RLD labeling. Acceptable
--	---

5.1.3 HOW SUPPLIED/STORAGE AND HANDLING (C3)

Table 8: Comparison of Model Labeling to ANDA Labeling

Model Labeling	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 single-use dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for RISPERDAL CONSTA®, a 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.
ANDA Labeling	Previous labeling review: (b)(4)

Table 8: Comparison of Model Labeling to ANDA Labeling

(b) (4)

Currently proposed:

Risperidone for Extended-Release Injectable Suspension is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone. It is provided as a single-dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperidone for Extended-Release Injectable Suspension, a 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 0703-7234-08): 43 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 0703-7234-01).

25 mg vial/kit (NDC 0703-7244-08): 81 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 0703-7244-01).

37.5 mg vial/kit (NDC 0703-7254-08): 120 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 0703-7254-01).

50 mg vial/kit (NDC 0703-7264-08): 156 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 0703-7264-01).

Storage and Handling

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

If refrigeration is unavailable, Risperidone for Extended-Release Injectable Suspension 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.

Table 8: Comparison of Model Labeling to ANDA Labeling

	Assessment: (b)(4) in line with RLD.
--	--------------------------------------

5.1.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER(C3)

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	(b)(4)	
Name and Address on ANDA Container/Carton	(b)(4)	
Name and Address on ANDA Prescribing Information	Previous labeling review: Manufactured In Greece By: Pharmathen International S.A. Rodopi, 69300, Greece Manufactured For: Teva Pharmaceuticals USA, Inc. Parsippany, NJ 07054 Currently proposed: Manufactured In Greece By: Pharmathen International S.A. Rodopi, 69300, Greece Manufactured For: Teva Pharmaceuticals USA, Inc. Parsippany, NJ 07054 Assessment: No change noted	

Table 9: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Manufactured by	Manufactured for	Distributed by	Distributed for
-----------------	------------------	----------------	-----------------

5.2 CONTAINER LABEL (FOR BLISTERS GO TO UNIT-DOSE BLISTERS) (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Container meets the too small exemption [21 CFR 201.10(i)]. Please enter Reviewer/Deficiency Comments if you select Deficiency.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage .
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel.
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength.
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Dosage statement.
☐	☒	NDC number : prominence, linear bar code, and its orientation.
☐	☒	Expiration date and lot number (or placeholder).
☐	☒	Equivalency statement (product strength).
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)].
☐	☒	Controlled Substance Symbol .
☐	☒	Image of drug product represents the true size, color, and imprint.
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Latex warning statement is properly displayed [21 CFR 801.437.].
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means.
☐	☒	Labels of proposed product is differentiated from related products .
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6) or 21 CFR 201.1(i)].
☐	☒	Tamper evident (controlled substances) requirements are met.
☐	☒	Use of child-resistant closure (CRC) or non-CRC is appropriate. Describe container closure , cite source, and any issues in Reviewer Comments below. Please enter Reviewer/Deficiency Comments if you select Deficiency.
OVERALL ASSESSMENT:		
☐	☒	Requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100). Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: From labeling review #2: The following comment was sent to the applicant: CONTAINER LABEL (Drug Product and Diluent) We acknowledge the request to revise the established name to read "Risperidone for Extended-Release Injectable Suspension"; however, revise the established name to include "Tall Man" lettering (i.e., risperiDONE for Extended-Release Injectable Suspension). Assessment: The applicant satisfactorily revised the container label to be in line with the Agency's "Tall Man" lettering.		

(b)(4)

It is noted the approval letter for the last approved model labeling for the RLD, NDA 021346/S-061, included container and carton labeling. Editorial revision was made as well revision to the (b)(4)

(b)(4)

No revision to subject ANDA's container label is needed.



A diluent label was not included in the approval letter for last approved model labeling for the RLD. The applicant submits a diluent label with the established name revised to be in line with the Agency's "Tall Man" lettering. Subject ANDA's diluent label is found acceptable.

Previous submission:

(b)(4)

Currently proposed:

(b)(4)

Deficiency Comments:

5.2.1 INJECTABLE PRODUCTS (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use).
☐	☒	IV, IM, or SC was spelled out.
☐	☒	There is text on the cap/ferrule over seal of this injectable product. If "Yes", does the text comply with the recommendations in USP General Chapter <7> Labeling.
☐	☒	The cap color is violet, pink, green, blue. NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.
Reviewer Comments: Subject ANDA states "single dose only" where the RLD states "single use only". This is acceptable.		
Deficiency Comments:		

5.2.1.1 CONTAINER LABEL FOR SOLID INJECTABLE (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Strength is expressed in terms of the total amount of drug per vial.
☐	☒	Container label includes instructions for reconstitution and resultant concentration provided, if space permits.
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 314.94(a)(8) .
Reviewer Comments: Container does not include instructions for reconstitution or inactive ingredients in line with the RLD.		
Deficiency Comments:		

5.3 CARTON (OUTER OR SECONDARY PACKAGING) LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☒	☐	The answers to the Container Label questions are the same for the Carton Labeling. Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments: Deficiency comment from labeling review #2: We acknowledge the request to revise the established name to read "Risperidone for Extended-Release Injectable Suspension"; however, revise the established name to include "Tall Man" lettering (i.e., risperi DONE for Extended-Release Injectable Suspension).		
Assessment: The applicant satisfactorily updated the established name to be in line with the Agency's "Tall Man" lettering.		

(b)(4)

It is noted the approval letter for the last approved model labeling for the RLD, NDA 021346/S-061, includes container and carton labeling. Due to revision to the carton, revision to the carton will be requested. Please see comments below.

Deficiency Comments:

Deficiency # 1

On the PDP, revise (b)(4) to read "SINGLE-DOSE PACK CONTENTS:".

Created in C3

Carton Labeling

Response / Assessment:

Deficiency # 2

Under SINGLE-DOSE PACK CONTENTS:, second bullet: Revise to read "One single-dose pre-filled syringe container 2 mL of diluent".

Created in C3

Carton Labeling

Response / Assessment:

Deficiency # 3

Revise (b)(4) to read "Do not substitute components of the single-dose pack".

Created in C3

Carton Labeling

Response / Assessment:

Deficiency # 4

On the back panel, below IMPORTANT RESOURCES, revise (b)(4) to read "PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION."

Created in C3

Carton Labeling

Response / Assessment:

Deficiency # 5

Revise (b)(4) associated with the strength statement on all panels to read "Single-Dose Pack".

Created in C3

Carton Labeling

Response / Assessment:

Deficiency # 6 Created in C3 Carton Labeling Response / Assessment:	On the back panel, last paragraph, first sentence: Revise (b)(4) to read "Remove the single-dose pack from refrigerator...." (b)(4)
--	--

5.4 PRESCRIBING INFORMATION (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly.
☐	☒	Revision date appears at end of HIGHLIGHTS section.
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201) Check only if applicable: ☒ Sulfite (21 CFR 201.22) ☐ Yellow #5 (Tartrazine) (21 CFR 201.20) ☐ Phenylalanine/aspartame (21 CFR 201.21) ☐ Latex (21 CFR 801.437). Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)].
☐	☒	Gluten statement is appropriately stated. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Sterile product statement [21 CFR 201.57(c)(12)(D)].
☐	☒	Dosage form and route of administration properly listed [21 CFR 201.57(c)(12)(B)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section.
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed.
☐	☒	NDC numbers are present.
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	"Discard unused portion" for single-dose products.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable [21 CFR 201.1(h)(5) or (6)] or 21 CFR 201.1(i)].
HOW SUPPLIED/STORAGE and HANDLING/MANUFACTURER:		
☐	☒	STIC requirements addressed appropriately.
☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval.
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Patent/exclusivity carve out is acceptable. Please enter Reviewer/Deficiency Comments if you select Deficiency.
☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) . Please enter Reviewer/Deficiency Comments if you select Deficiency.
Reviewer Comments:		
From labeling review #2:		

The following comment was conveyed to the applicant:

(b)(4)

Assessment:

(b)(4)

Deficiency Comments:

Deficiency # 1

(b)(4)

Created in C3

Prescribing Information
Response / Assessment:

5.5 OTHER PATIENT LABELING (C3)

Reviewer Assessment:

Deficiency	No Deficiency	
☐	☒	Other patient labeling is the same as the model labeling except for allowable differences. Please enter Reviewer/Deficiency Comments if you select Deficiency.

Reviewer Comments:

Deficiency comments from labeling review #2:

INSTRUCTIONS FOR USE

a.

(b)(4)

b. Add "Each injection should be administered by a healthcare professional." directly below

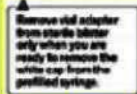
(b)(4)

The 6/12/20 DCR review does not have comments.

<https://panorama.fda.gov/task/view?ID=5e42da760031da9d1d1aedcb961fc5d0>

We note the differences in IFU align with difference in vial adapter and are found acceptable by DCR.

Table 3: Comparison of IFU Labels – RLD Risperdal Consta® (NDA 021346) and Proposed Product Risperidone IM Injection (ANDA 214068)

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
 Prepare vial adapter Hold sterile blister as shown. Peel the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.	 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.
Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
(b)(4)	 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.
	Remove sterile blister  Remove vial adapter 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.

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
(b)(4)	Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

Reviewer Comments: Although the proposed product contains similar components, the vial adapter has design differences when compared to the RLD and the Applicant has modified the Instructions for Use (IFU) to align with these design differences. These differences are:

- -
 -
 -
 -
- (b)(4)

As discussed in Section 2.2, these modifications to the IFU regarding the vial adapter are consistent with those recommended by DCR for another Teva product⁷, Octreotide Acetate for Injectable Suspension. Therefore, these differences in the IFU are acceptable.

There was one additional difference between the IFUs of the proposed product and RLD. 0010

(b)(4)

3 CONCLUSION

From a clinical safety perspective, the differences in luer tip of the vial adapter, syringe, blister pack removal, as well as additions to the IFU to account for these physical differences between the RLD and proposed product are minor and unlikely to impact the safe and effective use of the proposed product as a substitute for the RLD. DCR finds the proposed risperidone IM injection acceptable.

4 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has no comments at this time.

- ☐ Major
☐ Minor
☒ N/A (Review is Adequate)

Assessment:

The applicant satisfactorily addressed both comments. IFU is found acceptable. It is noted that the last approved model labeling, NDA 021346/S-061 did not update the IFU.

Deficiency Comments:

6 COMMENTS/CONSULTS FOR OTHER DISCIPLINES (C3)

A labeling statement required verification from another division discipline. Check only if applicable.

Reviewer Assessment:

☐	Rubber
☐	Latex
☐	Gluten
☐	Alcohol (ethanol)
☐	Aluminum (small/large volume parenteral and pharmacy bulk package)
☐	Sulfite
☐	Phenylalanine (aspartame) - content calculation
☐	Yellow #5 (tartrazine)
☐	Ghost tablet/capsule (i.e. solid or semi-solid mass in stool)
☐	Other
Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB): (For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)	
Reviewer Comments:	
Deficiency Comments:	



Esther
Kim

Digitally signed by Esther Kim

Date: 10/13/2021 08:07:57AM

GUID: 5423006c00721ec9406da22c031498a2



Ellen
Koo

Digitally signed by Ellen Koo

Date: 10/13/2021 10:29:08AM

GUID: 508da73d0002b687dfbf9b3859d80789

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

Date of This Review	July 9, 2020
ANDA Number(s)	214068
Review Number	2
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial
Proposed Proprietary Name	NA
Submission Received Date	May 11, 2020 (DRL response), June 9, 2020 (amendment)
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page
Review Conclusion ☐ ACCEPTABLE – No Comments ☐ ACCEPTABLE – Include Post Approval Comments ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant ☐ Major Deficiency [†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant [†] Theme - Choose an item. Justification for Major Deficiency - Choose an item. *Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.	
On Policy Alert List	☒ Yes ☐ No
Combined Insert/Outsert	☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on July 9, 2020 based on your submission(s) received May 11, and June 9, 2020:

1. CONTAINER LABEL (Drug Product and Diluent)

We acknowledge the request to revise the established name to read "Risperidone for Extended-Release Injectable Suspension"; however, revise the established name to include "Tall Man" lettering (i.e., risperidONE for Extended-Release Injectable Suspension).

2. CARTON LABELING

Refer to comment 1 above.

3. PRESCRIBING INFORMATION

(b)(4)

4. INSTRUCTIONS FOR USE

a

(b)(4)

b. Add "Each injection should be administered by a healthcare professional." directly below

(b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

NA

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
None

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments:

Labeling review #1 based on the submission dated December 16, 2019 determined deficiencies and recommendations for Container (drug product and diluent), Carton, Prescribing Information, Instructions for Use, and SPL as well as comments regarding the established name and text on the (b)(4)

The May 11, 2020 submission satisfactorily addresses the deficiencies and recommendations; (b)(4)
(b)(4) We will request the applicant revise to use Tall Man lettering. Please refer to section 1.1 above.

The applicant confirms that there is no text on the (b)(4) in compliance with USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.

The June 9, 2020 submission is in response to a DCR IR and updates the IFU labeling and 2.8 Instructions for Use in the Prescribing Information. This submission supersedes the insert labeling from the May 11, 2020 submission.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were NOT requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments:

Previously submitted drug product Container:	Currently proposed drug product Container:
(b)(4)	

The applicant made the following revisions:

(b)(4)

Previously submitted diluent Container:	Currently proposed diluent Container:
(b)(4)	

The applicant revised the established name of the drug product as requested.

Previously submitted Carton:

(b)(4)

DELETED PAGES INFORMATION SHEET

IT IS NOT REASONABLE TO SEGREGATE MEANINGFUL PORTIONS OF THE RECORD FOR RELEASE.

INFORMATION HAS BEEN WITHHELD IN ITS ENTIRETY IN ACCORDANCE WITH THE FOLLOWING EXEMPTIONS(S):

(b) (4)

5 U.S.C. 552 (b) (4) - trade secrets and commercial or financial information obtained from a person and privileged or confidential.

(b)(4)

The applicant made the following revisions:

(b)(4)

The applicant made the requested revisions: (b)(4)

(b)(4) As such, we will request the applicant revise the established name on Container and Carton to read "risperiDONE for Extended-Release Injectable Suspension".

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments:

Drug Facts lists “risperidone” as approved for tall man lettering

Below, in addition to a link to the published list, are four more name pairs approved for tall man lettering. Although they do not appear on the list on the FDA website, DMEPA, who approves proposed pairs, has been made aware of these names and will be updating the list.

CISplatin and CARBOplatin

(b)(4)

risperiDONE and rOPINIRole

traZADONE and traMADOL

We note “risperiDONE” is now listed on the tall man lettering FDA website.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT**3.1 REGULATORY INFORMATION**

Are there any pending issues in [DLR's SharePoint Drug Facts](#)? YES

If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on [OGD's SharePoint](#)? YES

If Yes, please explain.

CP	FDA-2011-P-0086	Risperdal Consta	Risperidone long-acting injection
Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and, the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug are highlighted by the real-world situation of LY03004, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd.			
No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead		No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence	

Is the drug product listed on the [Susceptibility Test Interpretive Criteria web page](#)? NO

3.2 MODEL LABELING

Table 1: Review Model Labeling
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021346/S-063

Supplement Approval Date: 2/5/2020

Proprietary Name: Risperdal Consta

Established Name: risperDONE long-acting injection

Description of Supplement:

We also refer to our letter dated December 5, 2019, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for risperidone. This information pertains to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN).

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement:

☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.

☐ **OTHER (Describe):**

S-061 is a pending labeling supplement that proposes to update the Warnings and Precautions and Interactions sections to add concomitant administration of psychostimulants such as methylphenidate, and to include "catatonia" as an adverse drug reaction (ADR).

(b)(4)

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**

Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old), or 201.66 (OTC)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

(b)(4)

Instructions for Use:

(b)(4)

Add "Each injection should be administered by a healthcare professional." directly below (b)(4)

(b)(4)

From labeling review #1:

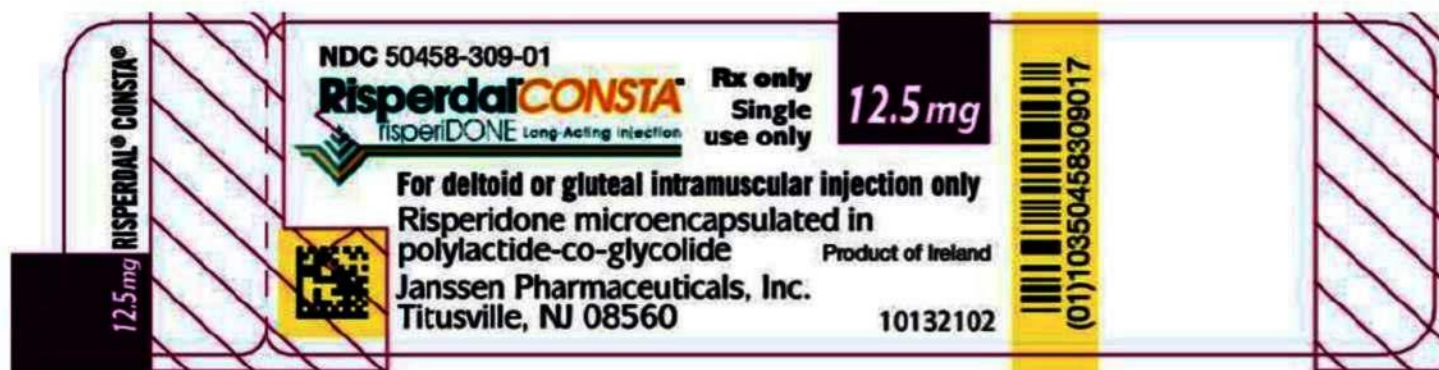
We note a stand-alone IFU is listed as a separate labeling piece in all AR but not provided on drugs@FDA. The content of the stand-alone IFU (from AR-15, 12/22/17) is the same as what is provided in section 2.8 of the Prescribing Information. An email was sent to OND to provide this labeling piece to drugs@FDA.

3.3 MODEL CONTAINER LABELS

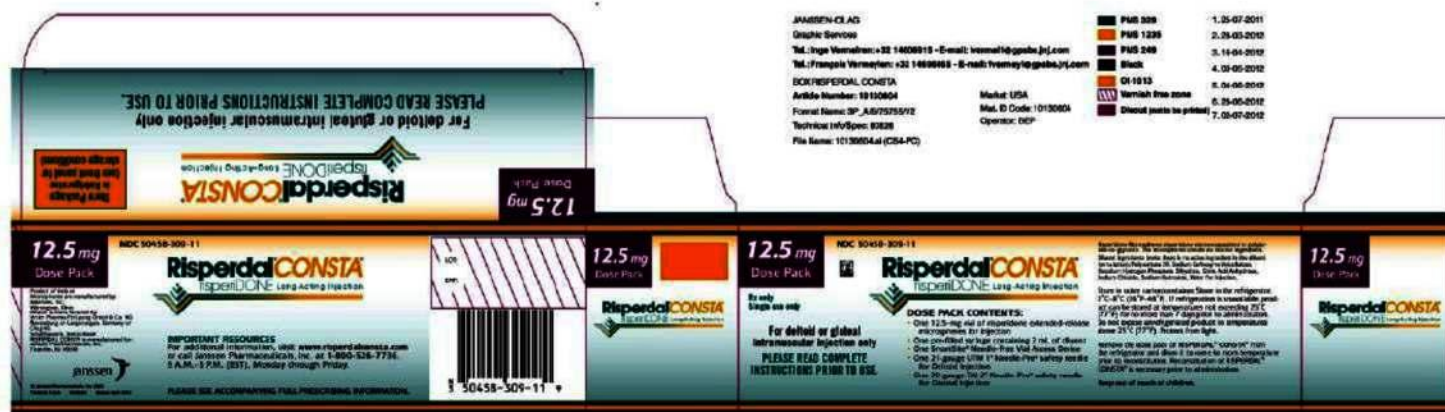
Model container/carton/blister labels [Source: see below]

NDA 021346/S-044 is the last approved Container, Carton, and diluent that provided for tall man lettering for the “risperiDONE”.

Vial:



Carton:



Enlarged Carton:

12.5 mg
Dose Pack

Product of Ireland
Microspheres are manufactured by:
Allergan, Inc.
Vilnius, Lithuania
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Rummingen or Langensiefen, Germany or
Cilag AG
Schaffhausen, Switzerland
RISPERDAL CONSTA is manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

janssen

© JanssenPharmaceutica, Inc. 2005
Printed in U.S.A. 10131703 Printed April 2003

Risperdal CONSTA
risperiDONE Long-Acting Injection

IMPORTANT RESOURCES
For additional information, visit www.risperdalconsta.com
or call Janssen Pharmaceuticals, Inc. at 1-800-526-7736,
9 A.M.-5 P.M. (EST), Monday through Friday.

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

12.5 mg
Dose Pack

LOT: _____
EXP: _____



N 3 50458-309-11 9

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

12.5 mg
Dose Pack

Rx only
Single use only

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Risperdal CONSTA
risperiDONE Long-Acting Injection

DOSE PACK CONTENTS:

- One 12.5-mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One SmartSite® Needle-Free Vial Access Device
- One 21-gauge UTW 1" Needle-Pro® safety needle for Deltoid Injection
- One 20-gauge TW 2" Needle-Pro® safety needle for Gluteal Injection

Risperidone Microspheres: risperidone microencapsulated in poly(lactide-co-glycolide). The microspheres contain no inactive ingredients. Diluent ingredients (note: there is no active ingredient in the diluent formulation): Polysorbate 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in outer carton/container. Store in the refrigerator, 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). Protect from light.

Remove the dose pack of RISPERDAL® CONSTA® from the refrigerator and allow it to come to room temperature prior to reconstitution. Reconstitution of RISPERDAL® CONSTA® is necessary prior to administration.

Keep out of reach of children.

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

Diluent:

Rx only **Single use only**

Diluent (2mL) for suspension of
RISPERDAL® CONSTA® (risperiDONE)
Long-Acting Injection
For deltoid or gluteal intramuscular injection only

Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
© Janssen 2005





Lot: _____
Exp: _____

(01)10350458311010 10131703

S-044 provides labels and labeling for the 12.5 mg only

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25 mg
Dose Pack

Store Packages
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperidONE Long-Acting Injection

NDC 50458-306-11

DOSE PACK CONTENTS:

- One 25 mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge UTW 1" Terumo SureGuard® 3 safety needle for deltoid injection
- One 20-gauge TW 2" Terumo SureGuard® 3 safety needle for gluteal injection

Do not substitute any components of the dose pack.

For deltoid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.

PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Rx only
Single use only

25 mg
Dose Pack

Store Packages
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperidONE Long-Acting Injection

**For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.**

USA
10849024
184627 688184

25 mg
Dose Pack

Store Packages
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperidONE Long-Acting Injection

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

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

Risperidone Microspheres: risperidone microencapsulated in polylactide-co-glycolide. The microspheres contain no inactive ingredients.

Diluent Ingredients (note: there is no active ingredient in the diluent formulation): Polysorbate 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in outer carton/container. Store in the refrigerator, 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). Protect from light.

Remove the dose pack from refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting. Do not warm any other way. Reconstitution of RISPERDAL CONSTA® is necessary prior to administration.

Keep out of reach of children.

Product of Ireland
Microspheres are manufactured by:
Alkermes, Inc.
Wilmington, Ohio
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Langensargen, Germany
or Cilag AG
Schaffhausen, Switzerland
RISPERDAL CONSTA® is
manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08856


50458-306-11 8


© 2011 Janssen Pharmaceutical Companies
10849024

25 mg
Dose Pack

Store Packages
in Refrigerator
(see bottom panel for
storage conditions)

25 mg
Dose Pack

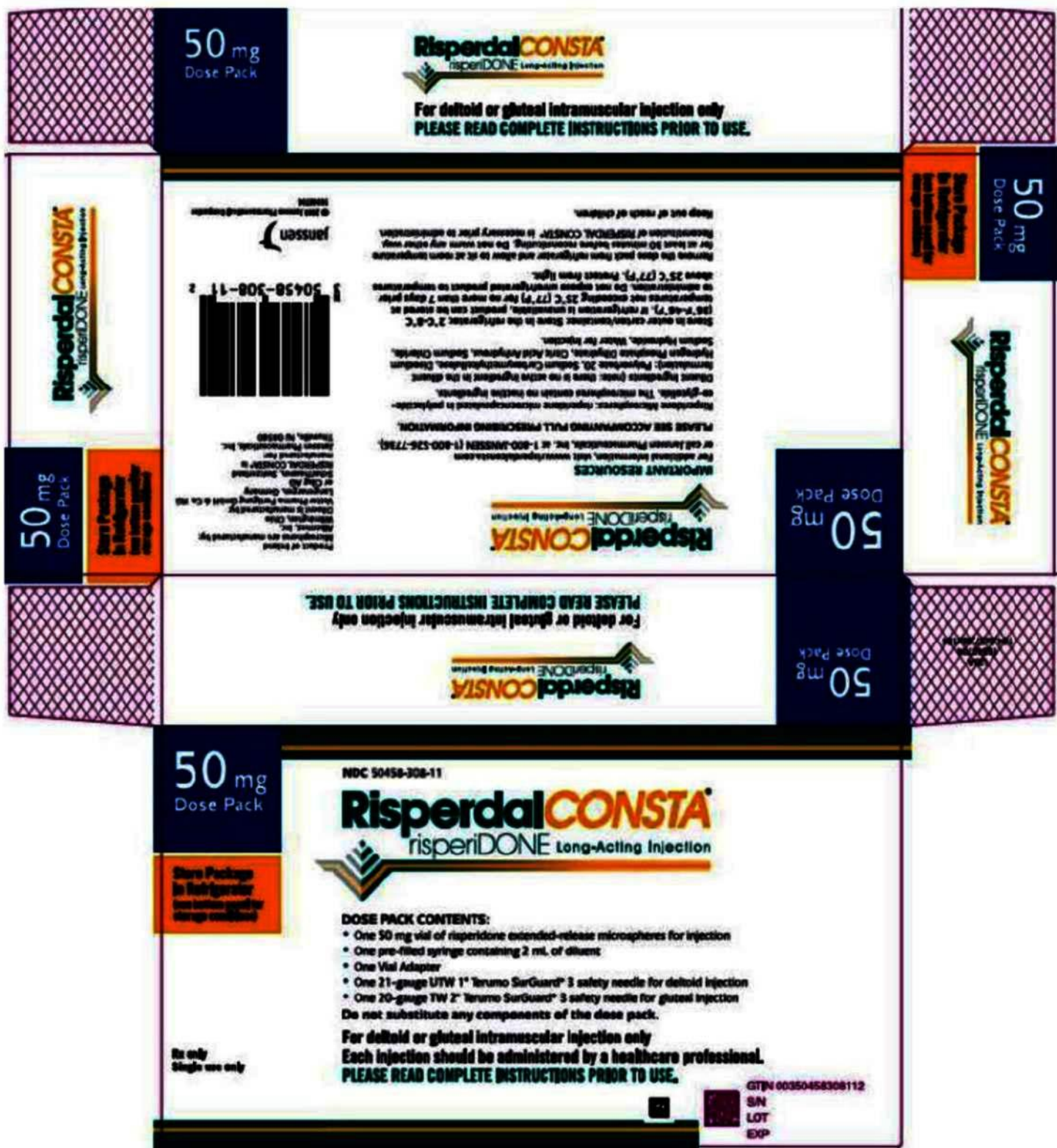
Store Packages
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperidONE Long-Acting Injection

**For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.**

USA
10849024
184627 688184

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3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 7/9/2020.

Table 2: United States Pharmacopeia (USP)

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

None

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 7/9/2020.

Table 3 provides Orange Book patents for the Model Labeling NDA 021346 and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
6667061	5/25/2020			III	12/16/19	None
6667061*PED	11/25/2020					

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments:

Patent 667061 is associated with the 25 mg/vial, 37.5 mg/ vial, and 50 mg/vial strengths only.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments:

There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **NO**

Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**

Are there changes to the manufacturer/distributor/packer statements? **YES**

If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
(b) (4)		

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment
--------------------------	--------------------	------------

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

(b) (4)

Table 7: Manufacturer/Distributor/Packer Statements

Previous Labeling Review	Currently Proposed	Assessment
(b) (4)		

5. COMMENTS/CONSULTS FOR OTHER DISCIPLINES

Describe questions, issues and consults sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

Refer to the [Consult Screening flow chart](#) to determine any necessary consults.

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:

The 6/9/20 Drug Product review does not have labeling issues.

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

The 6/12/20 DCR review does not have comments.

<https://panorama.fda.gov/task/view?ID=5e42da760031da9d1d1aedcb961fc5d0>

We note the differences in IFU align with difference in vial adapter and are found acceptable by DCR.

Table 3: Comparison of IFU Labels – RLD Risperdal Consta® (NDA 021346) and Proposed Product Risperidone IM Injection (ANDA 214068)

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
 Prepare vial adapter Hold sterile blister as shown. Peel the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.	 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.
Proposed Risperidone IM Injection (ANDA 214068) (b)(4)	RLD Risperdal Consta® (NDA 021346)  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 shake. Do not touch exposed luer tip connector on vial adapter. This will result in contamination.	Remove sterile blister  Keep vial vertical to prevent leakage. Hold base of vial and pull up on the sterile blister to remove. Do not shake. Do not touch exposed luer opening on vial adapter. This will result in contamination.

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
(b)(4)	Hold syringe by white collar then insert tip into the luer opening of the vial adapter.

Reviewer Comments: Although the proposed product contains similar components, the vial adapter has design differences when compared to the RLD and the Applicant has modified the Instructions for Use (IFU) to align with these design differences. These differences are:

-
-
-
-
-

(b)(4)

As discussed in Section 2.2, these modifications to the IFU regarding the vial adapter are consistent with those recommended by DCR for another Teva product⁷, Octreotide Acetate for Injectable Suspension. Therefore, these differences in the IFU are acceptable.

There was one additional difference between the IFUs of the proposed product and RLD. (b)(4)

(b)(4)

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item “Final, Draft, or “NA”. If you enter “NA” under the second column, you do NOT need to enter “NA” for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	5/11/20	Revise
Blister	NA			
Carton	Draft	One vial and one pre-filled syringe with diluent	5/11/20	Revise
Diluent (in pre-filled syringe)	Draft	2 mL	5/11/20	Revise
Table 9 Review Summary of Prescribing Information and Patient Labeling				

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 6/2020	6/11/20	Revise
Medication Guide	NA			
Instructions for Use	Draft	Iss. 6/2020	6/11/20	Revise
SPL Data Elements		Revised: 4/2020	5/11/20	Satisfactory



Esther
Kim

Digitally signed by Esther Kim

Date: 7/22/2020 11:49:35AM

GUID: 5423006c00721ec9406da22c031498a2



Lisa
Kwok

Digitally signed by Lisa Kwok

Date: 7/22/2020 12:59:35PM

GUID: 508da70800028c5cddf24c815a550d26

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

Date of This Review	4/7/2020
ANDA Number(s)	214068
Review Number	1
Applicant Name	Teva Pharmaceuticals USA, Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial
Proposed Proprietary Name	NA
Submission Received Date	12/16/2019
Primary Labeling Reviewer	Esther Kim
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

- ☐ ACCEPTABLE – No Comments
- ☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant
- ☐ Major Deficiency[†] – Refer to Labeling Deficiencies and Comments for Letter to Applicant

[†]Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☒ Yes	☐ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

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1 LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on April 7, 2020 based on your submission(s) received December 16, 2019:

1. GENERAL COMMENT

- a. Revise the name of your drug product to read "Risperidone for Extended-Release Injectable Suspension" to comply with USP nomenclature guidelines from USP General Chapter, General Information <1121> Nomenclature, on your labels and labeling.
- b. Comment as to whether text appears on your cap/ferrule over seal. Ensure your proposed cap/ferrule over seals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Over seals.

2. CONTAINER LABEL (Drug Product)

- a. Refer to comment 1a above.
- b. Revise the strength statement to express the strength in terms of the total amount of drug per vial. For example: XX mg/vial or XX mg per vial.

3. CONTAINER LABEL (Diluent)

Refer to comment 1a above.

4. CARTON LABELING

- a. Refer to comments 1a and 2b above.
- b. Revise (b)(4) on the side labels to read "PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE."

5. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Risperdal Consta, NDA 021346/S-063 approved on February 5, 2020 found on the Drugs@FDA website.
- b. Refer to comment 1a above.
- c. DESCRIPTION: Include "Sterile", as required for the proposed drug product. Refer to 201.57(c)(12)(D).

6. INSTRUCTIONS FOR USE

Refer to comment 1a above.

7. STRUCTURED PRODUCT LABELING (SPL)

- a. DATA ELEMENTS: Provide the data elements for the 25 mg, 37.5 mg, and 50 mg strengths.

- b. (b)(4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) received December 16, 2019.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

2 INSTRUCTIONS FOR ASSESSMENT

☒	☐	Check the left checkbox if there is an issue/concern. If a “standard” comment appears, ensure it is appropriate for your situation or enter “freeform” comments if necessary.
☐	☒	Check the right checkbox if there is no issue/concern, or if the question is not applicable. No “standard” comments will appear but reviewers can still enter “freeform” comments if desired.

Freeform Comments:

Enter free text in this section as necessary.

Standard Comments:

- Standardized comments appear in this section for certain questions when left checkboxes are checked.
- Reviewers can modify standardized comments for their situation but should avoid using this section to enter free text comments (i.e. avoid adding additional lines).
- Bullets are preferable to numbers for formatting.

3 LABELING REVIEW INFORMATION

3.1 REGULATORY INFORMATION

☒	☐	Are there any applicable issues in <u>DLR's SharePoint Drug Facts?</u> Drug Facts lists “risperidone” as approved for tall man lettering Below, in addition to a link to the published list, are four more name pairs approved for tall man lettering. Although they do not appear on the list on the FDA website, DMEPA, who approves proposed pairs, has been made aware of these names and will be updating the list. CISplatin and CARBOplatin SeroQUEL risperiDONE and rOPINIRole traZADONE and traMADOL We note “risperiDONE” is now listed on the tall man lettering FDA website.
☒	☐	Is the drug product listed in the Policy Alert Tracker on <u>OGD's SharePoint?</u> CP: Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and, the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug are highlighted by the real-world situation of LY03004, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd No Approval Actions (TA/AP) can be taken prior to contacting Policy Lead No CRL can be issued prior to contacting Policy Lead; No CC/IR/DRL for Bioequivalence

3.2 **MODEL PRESCRIBING INFORMATION**

Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)

NDA#/Supplement# (S-000 if original): 021346/S-063

Supplement Approval Date: 2/5/2020

Proprietary Name: Risperdal Consta

Established Name: risperiDONE long-acting injection

Description of Supplement:

We also refer to our letter dated December 5, 2019, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for risperidone. This information pertains to the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN).

**Table 1: Review Model Labeling for Prescribing Information, Patient Labeling, or Drug Facts Labeling (OTC)
(Check the box used as the Model Labeling)**

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.

Supplement Approval Date: Click here to enter text.

Proprietary Name: Click here to enter text.

Established Name: Click here to enter text.

Description of Supplement: Click here to enter text.

☐ **OTHER/TEMPLATE (e.g., Pending Supplements, BPCA, PREA, Carve-out):**

S-061 is a pending labeling supplement that proposes to update the Warnings and Precautions and Interactions sections to add concomitant administration of psychostimulants such as methylphenidate, and to include "catatonia" as an adverse drug reaction (ADR).

(b)(4)

Reviewer Assessment:

☒ ☐ **ANDA is up-to-date** with the RLD/Model labeling

Freeform Comments:

Click here to enter text.

Standard Comments:

GENERAL: Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Risperdal Consta, NDA 021346/S-063 approved on February 5, 2020 found on the Drugs@FDA website.

3.3 PATENTS AND EXCLUSIVITIES

The [Orange Book](#) was searched on 4/7/2020

Table 2 provides Orange Book patents for the Model Labeling (NDA 021346) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 2: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
6667061	5/25/2020			III	12/16/19	None
6667061*PED	11/25/2020					

Table 3 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 3: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
NA					

Reviewer Assessment:

☐ ☒ There is information in the Orange Book that the applicant needs to address.

☐	☒	Information in the Orange Book has expired and the applicant needs to revise labeling.
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Freeform Comments:

Patent 667061 is associated with the 25 mg/vial, 37.5 mg/ vial, and 50 mg/vial strengths only.

Standard Comments:

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 4/7/2020

Table 4: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	NA	NA	NA

Reviewer Assessment:

☒	☐	Established name is acceptable with regard to the USP monograph or the RLD's nonproprietary name
☐	☒	RLD's non-proprietary name is different from USP established name.
☐	☒	USP descriptor is correctly used in the appropriate sections of the prescribing information
USP RECOMMENDATIONS and/or DIFFERENCES IN TEST METHODS (QUALITY):		
☐	☒	DISSOLUTION: The applicant's dissolution statement is appropriate
☐	☒	ORGANIC IMPURITIES: Drug product meets USP acceptance criteria for organic impurities
☐	☒	ASSAY: Drug product meets USP acceptance criteria for assay

Freeform Comments:

The RLD states the established name as "risperiDONE long acting injection"; however, "long acting injection" is not defined as a type of injection by the USP. (b)(4)

(b)(4)

We will request revision of the established name to read "risperiDONE for extended-release injectable suspension" to be in line with USP nomenclature guidelines as the drug product comes as a lyophilized powder with diluent.

Per USP, General Chapter, General Information <1121> Nomenclature:

Solutions administered by injection are officially titled Injections (see Injections and Implanted Drug Products (1)). The route of administration is omitted for drugs that are injected, because the route (e.g. intravenous, intramuscular, subcutaneous, etc.) must appear on the labels and in the labeling. USP defines seven types of injections:

[DRUG] Injection—Liquid preparations that are drug substances or solutions thereof.

[DRUG] for Injection—Dry solids that, upon the addition of suitable vehicles, yield solutions conforming in all respects to the requirements for Injections.

[DRUG] Injectable Emulsion—Liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium.

[DRUG] Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium.

[DRUG] for Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Injectable Suspensions.

[DRUG] Extended-Release Injectable Suspension—Liquid preparations of solids suspended in a suitable liquid medium and formulated in a manner that allows the contained API to be available over an extended period of time.

[DRUG] for Extended-Release Injectable Suspension—Dry solids that, upon the addition of suitable vehicles, yield preparations conforming in all respects to the requirements for Extended-Release Injectable Suspensions

(b) (4)

Standard Comments:

3.5 QUALITY INFORMATION (DRUG PRODUCT MOU & BIOPHARMACEUTICS)

3.5.1 DRUG PRODUCT REVIEW

Insert screenshot of Labeling portion from drug product review if completed:
DP review is pending as of 4/7/2020.

3.5.2 DESCRIPTION

Table 5: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

Model Labeling	RISPERDAL CONSTA® (risperidone) Long-Acting Injection is a combination of extended-release microspheres for injection and diluent for parenteral use. The extended-release microspheres formulation is a white to off-white, free-flowing powder that is available in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial. Risperidone is micro-encapsulated in 7525 polylactide-co-glycolide (PLG) at a concentration of 381 mg risperidone per gram of microspheres. The diluent for parenteral use is a clear, colorless solution. Composition of the diluent includes citric acid anhydrous, disodium hydrogen phosphate dihydrate, polysorbate 20, sodium carboxymethyl cellulose, sodium chloride, sodium hydroxide, and water for injection. The microspheres are suspended in the diluent prior to injection. RISPERDAL CONSTA® is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration).
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Table 5: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section

ANDA Labeling	(b) (4)
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3.5.3 HOW SUPPLIED/STORAGE AND HANDLING

Table 6: Comparison of Model Labeling to ANDA Labeling

Model Labeling	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 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.
ANDA Labeling	(b) (4)

3.5.4 MANUFACTURER, DISTRIBUTOR, AND/OR PACKER

Table 7: Comparison of Manufacturer/Distributor/Packer Labeling Statements

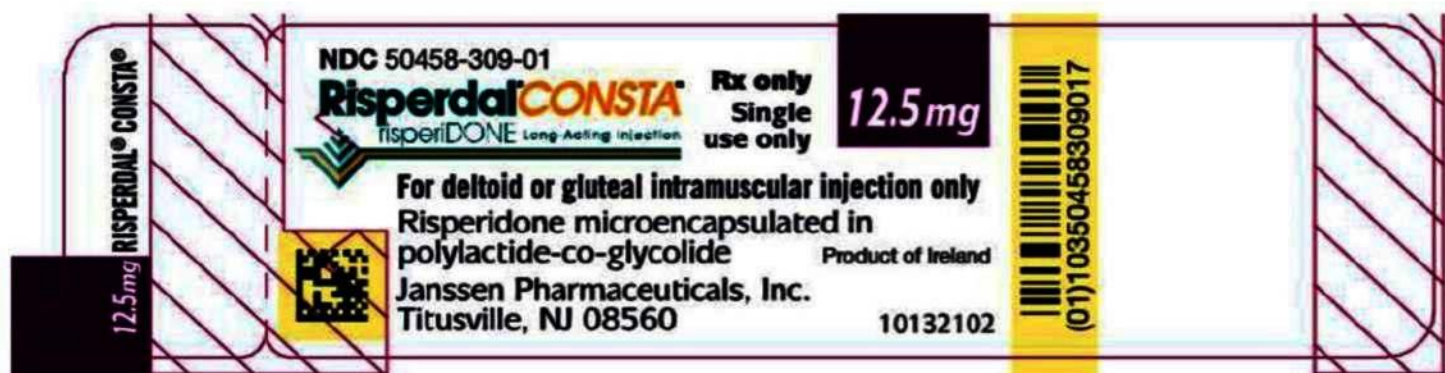
Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4)		

3.6 MODEL CONTAINER LABELS

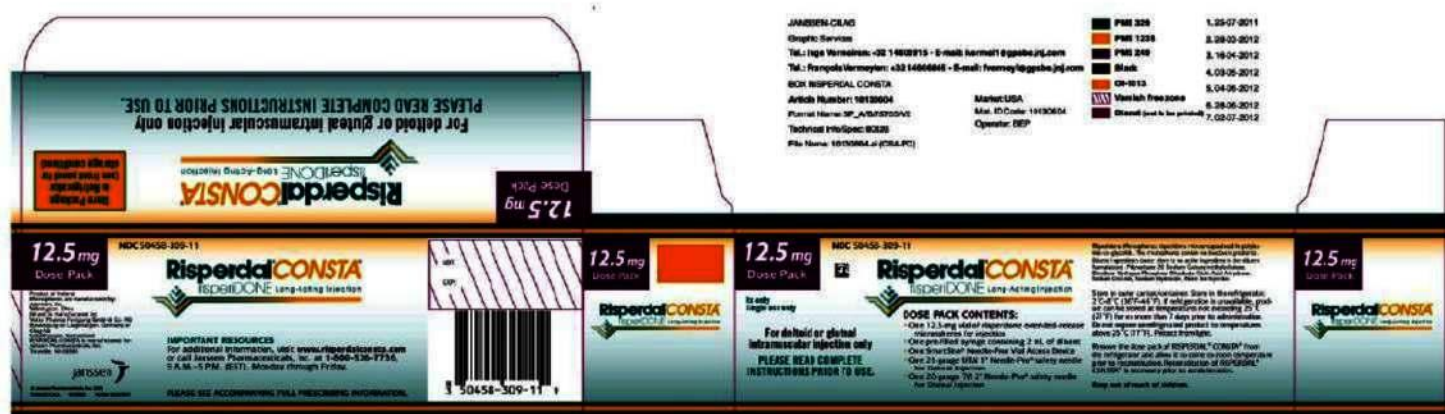
Model container/carton/blister labels (Source: see below)

NDA 021346/S-044 is the last approved Container, Carton, and diluent that provided for tall man lettering for the “risperiDONE”.

Vial:



Carton:



Enlarged Carton:

12.5 mg
Dose Pack

Product of Ireland
Microspheres are manufactured by:
Allergan, Inc.
Wilmington, Ohio
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Buenberg or Lengenroden, Germany or
Cilag AG
Schaffhausen, Switzerland
RISPERDAL CONSTA is manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

janssen

© Janssen Pharmaceuticals, Inc. 2012
Printed in U.S.A. 10130464 Revised April 2012

NDC 50458-309-11

Risperdal CONSTA
risperiDONE Long-Acting Injection

IMPORTANT RESOURCES
For additional information, visit www.risperdalconsta.com
or call Janssen Pharmaceuticals, Inc. at 1-800-526-7736,
9 A.M.-5 P.M. (EST), Monday through Friday.

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Store Package
in Refrigerator
(see front panel for
storage conditions)

LOT
EXP



N 3 50458-309-11 9

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

12.5 mg
Dose Pack

Rx only
Single use only

For deltoid or gluteal
intramuscular injection only
PLEASE READ COMPLETE
INSTRUCTIONS PRIOR TO USE.

NDC 50458-309-11

Risperdal CONSTA
risperiDONE Long-Acting Injection

DOSE PACK CONTENTS:

- One 12.5-mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One SmartSite® Needle-Free Vial Access Device
- One 21-gauge UTW 1" Needle-Pro® safety needle for Deltoid Injection
- One 20-gauge TW 2" Needle-Pro® safety needle for Gluteal Injection

Risperidone Microspheres: risperidone microencapsulated in poly(lactide-co-glycolide). The microspheres contain no inactive ingredients.
Diluent Ingredients (note: there is no active ingredient in the diluent formulation): Polysorbate 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in outer carton/container. Store in the refrigerator, 2°C–8°C (36°F–46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). Protect from light.

Remove the dose pack of RISPERDAL® CONSTA® from the refrigerator and allow it to come to room temperature prior to reconstitution. Reconstitution of RISPERDAL® CONSTA® is necessary prior to administration.

Keep out of reach of children.

12.5 mg
Dose Pack

Risperdal CONSTA
risperiDONE Long-Acting Injection

Diluent:

Rx only **Single use only**
Diluent (2mL) for suspension of
RISPERDAL® CONSTA® (risperiDONE)
Long-Acting Injection
For deltoid or gluteal intramuscular injection only

Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
© Janssen 2005





Lot: Exp:

10131703

(01)10350458311010

S-044 provides labels and labeling for the 12.5 mg only

12.5 mg
Dose Pack



Risperdal CONSTA
risperiDONE Long-Acting Injection

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Store Package in Refrigerator
(see bottom panel for storage conditions)

IMPORTANT INFORMATION: Visit www.risperdalconsta.com or call Janssen Pharmaceuticals, Inc. at 1-800-JANSSEN (1-800-526-7736).

PLEASE SEE ACCOMPANYING FULL PRESCRIPTION INFORMATION.

Risperdal CONSTA microspheres are manufactured by: Janssen Pharmaceutics, Inc., Kenilworth, NJ 07033

Risperdal CONSTA is manufactured by: Janssen Pharmaceutics, Inc., Kenilworth, NJ 07033

Risperdal CONSTA is manufactured by: Janssen Pharmaceutics, Inc., Kenilworth, NJ 07033

Store Package in Refrigerator
(see bottom panel for storage conditions)

12.5 mg
Dose Pack

12.5 mg
Dose Pack



Risperdal CONSTA
risperiDONE Long-Acting Injection

For deltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Store Package in Refrigerator
(see bottom panel for storage conditions)

DOSE PACK CONTENTS:

- One 12.5 mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge UTW 1" Terumo SurGuard® 3 safety needle for deltoid injection
- One 20-gauge TW 2" Terumo SurGuard® 3 safety needle for gluteal injection

Do not substitute any components of the dose pack.

For deltoid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Store Package in Refrigerator
(see bottom panel for storage conditions)

12.5 mg
Dose Pack

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperiDOne Long-Acting Injection

25 mg
Dose Pack

For diltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

DOSE PACK CONTENTS:

- One 25 mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge UTW 1" Terumo SureGuard® 3 safety needle for diltoid injection
- One 20-gauge TW 2" Terumo SureGuard® 3 safety needle for gluteal injection

Do not substitute any components of the dose pack.

For diltoid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

NDC 50458-306-11

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperiDOne Long-Acting Injection

25 mg
Dose Pack

For diltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

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

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

Risperidone Microspheres: risperidone microencapsulated in polylactide-co-glycolide. The microspheres contain no inactive ingredients.

Diluent Ingredients (note: there is no active ingredient in the diluent formulation): Polysorbate 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in outer carton/container. Store in the refrigerator 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). Protect from light.

Remove the dose pack from refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting. Do not warm any other way. Reconstitution of RISPERDAL CONSTA® is necessary prior to administration.

Keep out of reach of children.

Product of Ireland
Microspheres are manufactured by:
Alkermes, Inc.
Wilmington, Ohio
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Langensargen, Germany
or Clog AG
Schaffhausen, Switzerland
RISPERDAL CONSTA® is
manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560


50458-306-11


© 2011 Janssen Pharmaceutical Companies
10244004

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

Risperdal CONSTA
risperiDOne Long-Acting Injection

25 mg
Dose Pack

For diltoid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

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

PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION.

Risperidone Microspheres: risperidone microencapsulated in polylactide-co-glycolide. The microspheres contain no inactive ingredients.

Diluent Ingredients (note: there is no active ingredient in the diluent formulation): Polysorbate 20, Sodium Carboxymethylcellulose, Disodium Hydrogen Phosphate Dihydrate, Citric Acid Anhydrous, Sodium Chloride, Sodium Hydroxide, Water for Injection.

Store in outer carton/container. Store in the refrigerator 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration. Do not expose unrefrigerated product to temperatures above 25°C (77°F). Protect from light.

Remove the dose pack from refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting. Do not warm any other way. Reconstitution of RISPERDAL CONSTA® is necessary prior to administration.

Keep out of reach of children.

Product of Ireland
Microspheres are manufactured by:
Alkermes, Inc.
Wilmington, Ohio
Diluent is manufactured by:
Vetter Pharma Fertigung GmbH & Co. KG
Langensargen, Germany
or Clog AG
Schaffhausen, Switzerland
RISPERDAL CONSTA® is
manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560


50458-306-11


© 2011 Janssen Pharmaceutical Companies
10244004

25 mg
Dose Pack

Store Package
in Refrigerator
(see bottom panel for
storage conditions)

37.5 mg
Dose Pack



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Dose Pack

37.5 mg
Dose Pack



Keep out of reach of children.

Remove the dose pack from refrigerator and allow to sit at room temperature for at least 30 minutes before reconstituting. Do not warm any other way.

Reconstitute with 2 mL of Sterile Water for Injection. Mix gently. Do not shake. Do not expose reconstituted product to temperatures above 25°C (77°F). Protect from light.

Store in your refrigerator. Store in the refrigerator, 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration.

Store in your refrigerator. Store in the refrigerator, 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration.

Reconstitute with 2 mL of Sterile Water for Injection. Mix gently. Do not shake. Do not expose reconstituted product to temperatures above 25°C (77°F). Protect from light.

Store in your refrigerator. Store in the refrigerator, 2°C-8°C (36°F-46°F). If refrigeration is unavailable, product can be stored at temperatures not exceeding 25°C (77°F) for no more than 7 days prior to administration.



NDC 50458-507-11

37.5 mg
Dose Pack

37.5 mg
Dose Pack



For deltid or gluteal intramuscular injection only
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

37.5 mg
Dose Pack

37.5 mg
Dose Pack

NDC 50458-507-11



DOSE PACK CONTENTS:

- One 37.5 mg vial of risperidone extended-release microspheres for injection
- One pre-filled syringe containing 2 mL of diluent
- One Vial Adapter
- One 21-gauge UTW 1" Terumo SurGuard® 3 safety needle for deltoid injection
- One 20-gauge TW 2" Terumo SurGuard® 3 safety needle for gluteal injection

Do not substitute any components of the dose pack.

For deltid or gluteal intramuscular injection only
Each injection should be administered by a healthcare professional.
PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.

Rx only
Single use only

GTN 00360458307115
S/N
LOT
EXP

37.5 mg
Dose Pack

☒	☐	Container meets the too small exemption [21 CFR 201.10(i)]. Assessment applies to carton labeling.
ESTABLISHED/PROPRIETARY NAME and STRENGTH:		
☐	☒	Title case is used in expressing the established/proprietary name
☐	☒	Tall Man lettering complies with recommendations found on FDA webpage
☐	☒	Established/proprietary name and strength are the most prominent information on the Principal Display Panel
☐	☒	No intervening text (written, printed, or graphic matter) between established name and strength
THE FOLLOWING COMPONENTS ARE PROPERLY DISPLAYED:		
☐	☒	Net quantity statement.
☐	☒	Usual dosage statement
☐	☒	NDC number as linear bar code
☐	☒	Orientation of linear bar code [21 CFR 201.25(c)(2)]
☐	☒	Expiration date and lot number (or placeholder)
☐	☒	Equivalency statement (product strength)
☐	☒	Medication Guide Pharmacist instructions [21 CFR 208.24(d)]
☐	☒	Controlled substance symbol
☐	☒	Image of drug product represents the true size, color, and imprint
☐	☒	Yellow #5 (tartrazine) warning statement is properly displayed
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)]
☐	☒	Latex warning statement is properly displayed [21 CFR 201.10(d)(2)].
PRODUCT DIFFERENTIATION:		
☐	☒	ANDA is the same color as the RLD labels as required (e.g. warfarin, levothyroxine, enoxaparin).
☐	☒	Multiple strengths are differentiated by use of different color or other acceptable means
☐	☒	Labels of proposed product is differentiated from related products
STORAGE, DISPENSING, MANUFACTURER, and PACKAGING:		
☐	☒	Storage/dispensing statement is consistent with the How Supplied section of the insert/RLD/USP.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable and has address listed correctly
☐	☒	Tamper evident (controlled substances) requirements are met

Freeform Comments:

Title case is not used for “risperiDONE” as the applicant follow the Tall Man lettering recommendation and is in line with the RLD.

(b)(4)

Standard Comments:

4.1.1 ☐ UNIT-DOSE BLISTERS

4.1.1 ☐ OPHTHALMIC PRODUCTS

4.1.2 ☒ INJECTABLE PRODUCTS

Reviewer Assessment:

☐	☒	Appropriate package type term was used (e.g. multiple-dose, single-dose, single-patient-use)
☐	☒	IV, IM, or SC was spelled out
☒	☐	There is text on the cap/ferrule overseal of this injectable product. If “Yes”, does the text comply with the recommendations in USP General Chapter <7> Labeling
☐	☒	The cap color is (violet, pink, green, blue). <i>NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate</i>

Freeform Comments:

(b)(4)

4.1.2.1 ☐ CONTAINER LABEL FOR PARENTERAL SOLUTIONS

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4.1.2.2 ☒ CONTAINER LABEL FOR SOLID INJECTABLE

Reviewer Assessment:

☒	☐	Strength is expressed in terms of the total amount of drug per vial
☐	☒	Container label includes instructions for reconstitution and resultant concentration provided, if space permits
☐	☒	Quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)

Freeform Comments:

(b)(4)

(b)(4)

Please see standard comment below.

Standard Comments:

Revise the strength statement to express the strength in terms of the total amount of drug per vial. For example: XX mg/vial or XX mg per vial.

4.1.2.3 ☐ CONTAINER LABEL FOR PHARMACY BULK PACKAGE

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4.2 ☒ CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Reviewer Assessment:

☒	☐	The answers to the Container Label questions are the same for the Carton Labeling.
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Freeform Comments:

Along with the Container comments, we will request the following:

Revise (b)(4) on the side labels to read "PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE."

4.3 PRESCRIBING INFORMATION

Reviewer Assessment:

☐	☒	Prescribing Information is the same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8) .
☐	☒	Patent/exclusivity carve out is acceptable.
☐	☒	Manufacturer/Distributor/Packager statement is acceptable and has address listed correctly
☐	☒	STIC requirements addressed appropriately

☐	☒	Intent to join the Antiretroviral Pregnancy Registry (APR) upon full approval
☐	☒	Pregnancy registry information is appropriately included/excluded as required for the RLD.
HIGHLIGHTS:		
☐	☒	Contact information for applicant and FDA are listed correctly
☐	☒	Revision date appears at end of HIGHLIGHTS section
DESCRIPTION/INACTIVE INGREDIENTS:		
☐	☒	Appropriate warning/precaution statements for inactive ingredients are present (21 CFR 201): Sulfite (21 CFR 201.22) Yellow #5 (Tartrazine) (21 CFR 201.20) Phenylalanine/aspartame (21 CFR 201.21) Latex (21 CFR 801.437).
☐	☒	Alcohol is properly listed [21 CFR 201.10(d)(2)]
☐	☒	Gluten statement is appropriately stated.
☒	☐	Sterile product statement [21 CFR 201.57(c)(12)(D)]
HOW SUPPLIED/STORAGE and HANDLING:		
☐	☒	All submitted labels and labeling are consistent with the HOW SUPPLIED section
☐	☒	Physical description (e.g. scoring, color, imprint, capsule size, nozzle tip, cap color) of the finished product in the HOW SUPPLIED section are appropriately displayed
☐	☒	NDC numbers are present
☐	☒	Drug product is the same color as the RLD's drug product as required (e.g. warfarin, levothyroxine, enoxaparin)
☐	☒	Storage or dispensing statement is acceptable compared to the RLD/USP monograph.
☐	☒	"Discard unused portion" for single-dose products

Freeform Comments:

(b)(4)

Standard Comments:

DESCRIPTION: Include "Sterile", as required for the proposed drug product. Refer to 201.57(c)(12)(D).

4.3.1 ☐ MEDICATION GUIDE

4.3.2 ☒ **OTHER PATIENT LABELING**

Reviewer Assessment:

☐ ☒ Other patient labeling is the same as the model labeling except for allowable differences.

Freeform Comments:

The applicant's IFU is in line with the RLD except for the following:

(b)(4)

The DCR review is pending.

We note a stand-alone IFU is listed as a separate labeling piece in all AR but not provided on drugs@FDA. The content of the stand-alone IFU is the same as what is provided in section 2.8 of the Prescribing Information. An email was sent to OND to provide this labeling piece to drugs@FDA.

4.3.3 ☒ **STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS**

Table 8: ANDA Tablet/Capsule Size and Imprint

Tablet/Capsule Strength	ANDA Tablet/Capsule Size (mm) and imprint code from SPL	ANDA Tablet/Capsule Size (mm) and imprint code (Cite source: e.g., Drug Product Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)
NA	Click here to enter text.	Click here to enter text.

Reviewer Assessment:

☐ ☒ Applicant submitted SPL

☒ ☐ Data elements (strength, inactive ingredients, product characteristics, packaging etc.) are consistent with the information submitted in the ANDA labeling.

Freeform Comments:

(b)(4)

Standard Comments:**5 ☐ COMMENTS/CONSULTS FOR OTHER DISCIPLINES****6 OVERALL ASSESSMENT OF MATERIALS REVIEWED****Table 9: Review Summary of Container Label and Carton Labeling**

	Final or Draft or NA	Packaging Sizes	Submission Received Date	Recommendation
Container	Draft	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	12/16/2019	Revise
Blister	NA			
Carton	Draft	One vial and one pre-filled syringe with diluent	12/16/2019	Revise
Diluent (in pre-filled syringe)	Draft	2 mL	12/16/2019	Revise

Table 13 Review Summary of Prescribing Information and Patient Labeling

	Final or Draft or NA	Revision Date and/or Code	Submission Received Date	Recommendation
Prescribing Information	Draft	Revised: 10/2019	12/16/2019	Revise
Medication Guide	NA			
Instructions for Use	NA	Iss. 10/2019	12/16/2019	Revise
SPL Data Elements		Revised: 10/2019	12/16/2019	Revise



Esther
Kim

Digitally signed by Esther Kim

Date: 4/22/2020 12:27:04PM

GUID: 5423006c00721ec9406da22c031498a2



Lisa
Kwok

Digitally signed by Lisa Kwok

Date: 4/22/2020 01:41:58PM

GUID: 508da70800028c5cddf24c815a550d26

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208336

MEDICAL REVIEW(s)

CLINICAL CONSULTATION REVIEW
Division of Clinical Review (DCR)
Office of Bioequivalence (OB), Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Drug Product:	Risperidone (b) (4) Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial
ANDA#/Applicant:	214068, Teva Pharmaceuticals USA Inc.
RLD#/Approval Date: Sponsor:	Risperdal Consta® (Risperidone) (b) (4) Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial. NDA 021346, approved 10/29/2003, Janssen Pharmaceuticals Inc.
Clinical Primary Reviewer:	Mary Lee, MD Medical Officer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)
Clinical Secondary Reviewer:	Andrew Fine, PharmD Team Leader DCR/OB/OGD
To:	Zakaria Wahba, Ph.D, Through April C. Braddy, PhD., RAC Acting Director, Division of Bioequivalence III Office of Generic Drugs
Reason for Consult:	1) Does the two serious adverse (SAEs) for patients # (b) (6) (low hemoglobin) and patient # (b) (6) (pneumonia), with the test product treatment during the pivotal BE study indicate any safety concerns for the test product? In addition, please evaluate if the SAEs observed in patients # (b) (6) and # (b) (6) were related to the drug product. 2) Is there any additional information that DBIII needs to communicate to the applicant concerning these SAEs?
Date of Submission:	12/16/2019: Original Submission
GDUFA Goal Date:	10/15/2020
Date Consult Received:	05/13/2020
Date of Completion:	08/05/2020
Conclusion:	DCR concludes that the serious adverse event (SAE) of anemia in Subject (b) (6) and pneumonia in Subject (b) (6) were unlikely related to the administration of the test product (Risperdal Consta®). Anemia and pneumonia are listed as adverse reactions for the RLD (Risperdal Consta®). The occurrence of these adverse events does not indicate a safety or quality concern for the test product compared to the RLD, and no additional information is needed from the Applicant.
Deficiency Classification:	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 Executive Summary:

On 12/16/2019, Teva Pharmaceuticals USA Inc. (“Applicant”) submitted ANDA 214068, which contains the results of a multiple-dose, multi-national, multi-center, open-label, two-way crossover steady-state Bioequivalence (BE) study (#CAC15003) in patients.

Pivotal BE study #CAC15003 followed the Product Specific Guidance (PSG) for risperidone injection, intramuscular. A total of 98 subjects were dosed in this study, that was conducted in 14 clinical sites, located in three different countries (Bulgaria, Moldova and Poland). Each subject received four deep intramuscular injection of strength 25 mg/vial, test or RLD products, given one injection every 2 weeks (14 days) on Day 0, 14, 28 and 42 in each period. Based on the Applicant’s submitted results, the 90% Confidence Intervals (CIs) for pharmacokinetic (PK) parameters, C_{max}(SS) and AUC(Tau), pass the BE acceptance criteria. Fifty-one (51) adverse events (AEs) (including 2 serious adverse events; SAEs) were reported from 25 subjects following administration of test product and 29 AEs (including 1 SAE) were reported from 10 subjects after administration of reference product during the study. The Applicant also submitted a pilot single dose, parallel BE study (#PHA-RIP.I-01.15-208/147) in healthy adults under fasting conditions, with no SAEs reported.

In the pivotal BE study (#CAC15003), subject (b) (6) had decreased hemoglobin after test product treatment (last dose given on (b) (6)), and was hospitalized from (b) (6) to (b) (6) due to mild anemia. Subject (b) (6) showed breathing difficulty on (b) (6), after test product treatment (last dose given on (b) (6)) and was hospitalized from (b) (6) to (b) (6). Subject (b) (6) was diagnosed with pneumonia. The Principal Investigator (PI) claimed that the mild anemia for subject (b) (6) and pneumonia for subject (b) (6), were not related to the administration of the test product. Both Subject (b) (6) and (b) (6) adverse reactions resolved after hospitalization.

The Division of Bioequivalence III (DBIII) is seeking advice from the Division of Clinical Review (DCR) on the following two questions:

- 1) Do the aforementioned serious adverse events (SAEs) for patients (b) (6) and (b) (6), with the test product treatment during the pivotal BE study indicate any safety concerns for the test product? In addition, please evaluate if the serious adverse events observed in patient (b) (6) and (b) (6) were related to the drug product.
- 2) Is there any additional information that DBIII needs to communicate to the applicant concerning these serious adverse events?

The RLD (Risperdal Consta®) label includes adverse reactions to the drug, and categorizes it according to the occurrence of the adverse reactions in clinical trials.¹ Anemia and pneumonia were adverse reactions observed in < 2% of a schizophrenia double-blind, placebo-controlled trial and in < 2% in two bipolar double-blind, placebo-controlled studies.

A search in PubMed did not show studies linking anemia and pneumonia to risperidone.

¹ Drugs@FDA, search for “Risperdal Consta”, label approved 02/05/2020, accessed 08/06/2020.

The most recent Periodic Adverse Drug Experience Report, covering the duration of June 1, 2019 to May 31, 2020, for Risperdal Consta® showed that anemia and pneumonia were still listed as adverse reactions.

Based on the review of available information, DCR finds that the adverse events of anemia and pneumonia were not related to the test product administration. In addition, the Q1/Q2 sameness of the test and reference formulations, the rarity of this SAE further supports that it is unlikely that a difference between the RLD and test product caused or contributed to these SAEs. The occurrence of these adverse events does not indicate a safety or quality concern for the test product compared to the RLD.

2 Internal Recommendation:

The Division of Bioequivalence III (DBIII) is seeking advice from the Division of Clinic Review (DCR) on the following two questions:

- 1) Do the aforementioned serious adverse events (SAEs) for patients (b) (6) and (b) (6), with the test product treatment during the pivotal BE study indicate any safety concerns for the test product? In addition, please evaluate if the serious adverse events observed in patient (b) (6) and (b) (6) were related to the drug product.
- 2) Is there any additional information that DBIII needs to communicate to the applicant concerning these serious adverse events?

DCR's response:

Based on our review of information provided by the applicant related to Subjects # (b) (6) and (b) (6) RLD labeling, post-marketing adverse drug reports data from NDA 021346, and medical literature, from a clinical perspective:

- It is unlikely that a difference between the RLD and test product contributed to this occurrence of anemia in Subject (b) (6) and pneumonia in Subject (b) (6)
- The occurrence of these adverse events does not indicate a safety or quality concern for the test product compared to the RLD.
- DCR has no comments to convey to the applicant at this time.

3 Regulatory Background:

Risperdal Consta® (risperidone) (b) (4) Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial., was approved on 10/29/2003 (NDA 021346; Sponsor Janssen Pharmaceuticals Inc.) for the treatment of schizophrenia.

3.1 Current or Draft Guidance

There is a draft product specific guidance (PSG) for risperidone intramuscular injectable, posted February 2010, and most recently revised August 2016.² To demonstrate BE, the PSG recommends two studies. The first study is an in vitro drug release study using the 25 mg/vial.

The second study is an in vivo, two-period, crossover steady-state study using the 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial strengths in male and nonpregnant female patients with schizophrenia or bipolar I disorder, who are already receiving a stable regimen of risperidone (b) (4) injection via the intramuscular route. Patients who are receiving any dosage regimen of risperidone (b) (4) injection every two weeks would be eligible to participate in the study by continuing their established maintenance dose. BE of the multiple dose study would be proven by evaluation of pharmacokinetic (PK) data. A waiver for in vivo testing of the 12.5 mg/vial, 37.5 mg/vial and 50 mg/vial based on acceptable in vitro and in vivo BE studies on the 25 mg/vial, proportional similarity of the formulations across all strengths, and acceptable in vitro drug release testing of all strengths.

3.2 Orange Book Information

The RLD, Risperdal Consta® injectable, intramuscular, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial are listed in the Orange Book as the RLD. The 25 mg/vial strength is listed as the RS. There are no approved ANDAs referencing NDA 21346.

3.3 Formulation Comparison: Reference Listed Drug, Risperdal Consta®, vs. Test Drug

According to the DBIII's consult, the proposed generic drug formulation is Q1/Q2 the same as the RLD.³

Reviewer comment:

The qualitatively (Q1) and quantitatively (Q2) sameness between the proposed generic formulation to the RLD, gives support that these AEs are unlikely caused by the proposed generic product (test product).

4 Labeling:

FDA approved the current labeling for Risperdal Consta® on 2/05/2020 (Source: Drugs@FDA).⁴ Labeling includes Prescribing Information (PI) and Instructions for Use.

² Fda.gov search for FDA Product Specific Guidances, accessed 07/06/2020.

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

³ CDER Informatics "ANDA-214068-ORIG-1", Document "A214068N000DCR_ConultRequest01-DCR.04272020.doc" by Sylvia Park, added on May 13, 2020.

⁴ Drugs@FDA, search for Risperdal Consta. Accessed 07/30/2020.

<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>

4.1 Boxed Warning

**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)

4.2 Indications and Usage

Risperdal Consta® is an atypical antipsychotic indicated for the treatment of schizophrenia and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder.

4.3 Dosage and Administration

Patient need to have established tolerability with oral Risperdal® prior to initiating treatment with Risperdal Consta®. Each injection is deep intramuscular (IM) deltoid or gluteal, and 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. Administer 25 mg IM every 2 weeks. Patients not responding to 25 mg may benefit from a higher dose of 37.5 or 50 mg. The maximum dose should not exceed 50 mg every 2 weeks.

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®. 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.

4.4 Contraindications

- Known hypersensitivity to risperidone, paliperidone or to any excipients in Risperdal Consta®

4.5 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.
- Neuroleptic malignant syndrome: manage with immediate discontinuation and close monitoring.

- Tardive dyskinesia: discontinue treatment if clinically appropriate.
- Metabolic changes: increase cardiovascular/cerebrovascular risks. Metabolic changes include hyperglycemia, dyslipidemia and weight gain.
- Hyperprolactinemia : risperidone treatment may elevate prolactin levels.
- Orthostatic hypotension: associated with dizziness, tachycardia, bradycardia and syncope can occur, especially during initial dose titration with oral risperidone.
- Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including Risperdal Consta®. Patients with history of clinically significant low white blood cell count (WBC) or 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.
- Potential for cognitive and motor impairment.
- Seizures: may potentially lower the seizure threshold
- Dysphagia: esophageal dysmotility and aspiration can occur. Use cautiously in patients at risk for aspiration pneumonia.
- Priapism: has been reported.
- Thrombotic thrombocytopenic purpura (TTP): has been reported.
- Avoid inadvertent administration into a blood vessel.
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies. Manifestations include mental status changes, motor impairment, extrapyramidal symptoms and features consistent with Neuroleptic Malignant Syndrome.
- Disease or conditions that could affect metabolism or hemodynamic responses.

4.6 Adverse Reactions

Common adverse reactions (>5%) in clinical trials were:

- Headache, parkinsonism, dizziness, akathisia, fatigue
- Constipation, dyspepsia
- Sedation, weight increased
- Pain in extremity
- Dry mouth

Other Adverse reactions observed during the clinical trials⁵ evaluation of Risperidone (<2%)

- anemia, neutropenia
- cardiac adverse events including tachycardia, atrioventricular block first degree, palpitations, bundle branch blocks
- diarrhea, vomiting abdominal pain
- Infections including nasopharyngitis, influenzas, bronchitis, urinary tract infection, rhinitis, respiratory tract infection, ear infection, pneumonia, lower respiratory tract infection
- Psychiatric disorders including insomnia, anxiety, sleep disorder, depression

⁵ Drugs@FDA, Risperdal Consta RLD label. Clinical trials: 12-week double-blind Risperdal Consta in schizophrenia subjects, 54week double-blind Risperdal Consta trial in bipolar subjects.

Common adverse reactions that were associated with discontinuation from clinical trials in patients with schizophrenia

- Agitation, depression, anxiety and akathisia

Common adverse reactions that were associated with discontinuation from clinical trials in patients with bipolar disorder

- Hyperglycemia, hypokinesia and tardive dyskinesia

4.7 Use in Specific Populations

- Pregnancy: may cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure.
- Pediatrics: safety and effectiveness not established in patients less than 18 years of age.
- Geriatrics: dosing for otherwise healthy elderly patients is the same as for healthy nonelderly. Elderly patients may be more predisposed to orthostatic effects than nonelderly.
- Renal or hepatic impairment: dose appropriately with oral Risperdal prior to initiating treatment with Risperdal Consta®.

4.8 Mechanism of Action and Pharmacodynamics

Mechanism of action of risperidone in schizophrenia is unclear. The drug's therapeutic activity in schizophrenia could be mediated through a combination of dopamine T2 (D2) and serotonin Type 2 (5 HT2) receptor antagonism. The clinical effect from risperidone results from the combined concentrations of risperidone and its major active metabolite, 9-hydroxyrisperidone (paliperidone). Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Reviewer's Comments: The subjects reviewed in this consult response, had serious adverse events of anemia and pneumonia. These events were reported in the RLD labeling Adverse Reaction section. The inclusion of these adverse events in the RLD labeling demonstrates that these events have occurred in the trials evaluating Risperdal Consta®.

5 Discussion:

5.1 Consult Question

On 05/13/2020, the Division of Bioequivalence III (DBIII) consulted the Division of Clinical Review (DCR) regarding serious adverse events that occurred in two subjects who participated in a multiple-dose, multi-national, multi-center, open-label, two-way crossover steady-state BE study (#CAC15003) conducted to support ANDA 214068 for Teva Pharmaceuticals USA Inc.'s proposed Risperidone (b) (4) injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

In the pivotal BE study (#CAC15003), subject (b) (6) had decreased hemoglobin after test product treatment (last dose given on (b) (6)), and was hospitalized from (b) (6) to (b) (6) due to mild anemia. Subject (b) (6) had chronic obstructive pulmonary disease (COPD) after test product treatment (last dose given on (b) (6)) and was hospitalized from (b) (6) to

(b) (6) The Principal Investigator (PI) claimed that the mild anemia for subject (b) (6) and COPD for subject (b) (6), were not related to the administration of the test product.

The Division of Bioequivalence III (DBIII) is seeking advice from the Division of Clinical Review (DCR) on the following two questions:

- 1) Do the aforementioned serious adverse events (SAEs) for patients (b) (6) and (b) (6), with the test product treatment during the pivotal BE study indicate any safety concerns for the test product? In addition, please evaluate if the serious adverse events observed in patient (b) (6) and (b) (6) were related to the drug product.
- 2) Is there any additional information that DBIEI needs to communicate to the applicant concerning these serious adverse events?

5.2 Summary of Key Study Design Elements and Procedures.

In order to address the consult question, this review includes assessment of the ANDA 214068 pivotal BE Study (#CAC15003), and the RLD Risperdal Consta® labeling.

Teva conducted Study #CAC15003, an open label, randomized, multiple-dose, multinational, multi-center, two-way crossover pharmacokinetic BE study of Risperidone (b) (4) Injection 12.5, 25, 37.5 and 50 mg, manufactured by Pharmathen International S.A. for Actavis Group PTC, compared to Risperdal Consta® (risperidone) (b) (4) injection, 12.5, 25, 37.5 and 50 mg, manufactured by Janssen Pharmaceuticals, Inc., USA. The study was conducted at 21 clinical centers in Bulgaria, Poland and Moldova. The study start date was 01-September-2017, and the study completion date was 29-May-2019.

The objective of Study #CAC15003 was to assess the bioequivalence (BE) of the Applicant's test preparation containing 12.5, 25, 37.5 and 50 mg risperidone (b) (4) injection, compared to the reference standard, administered to subjects as a multiple dose, under fasting conditions in two different periods. Subjects received the same dosage strength in both periods, which was also their current risperidone dosing regimen prior to study entry. In order to assess BE, the pre-defined confidence intervals (CI) were calculated for the ratios (test/reference) of the pharmacokinetic endpoints AUC(Tau) and Cmax (SS) of risperidone. These CI were then compared with the corresponding acceptance ranges.

The secondary objective was to investigate the safety of the proposed product on the basis of clinical and laboratory examinations.

Study Design

The study enrolled 104 subjects, diagnosed with schizophrenia, and 80 subjects completed the study. Each subject randomly received four deep intramuscular gluteal injections every 2 weeks (14 days) of 25 mg risperidone (either test product or the RLD) in each of the two study periods. Subjects received the same dosage strength in both periods. There was no wash-out period between the two study periods.

Blood Sampling

The Blood sampling time points were specified in the protocol so that all the PK parameters could be adequately characterized. This included intensive sampling in period 2. The blood sampling schedule in each study period is shown in Figure 1. The total amount of blood taken from each subject was 462 mL per subject (n=72 plasma samples for analysis for risperidone and n=2 blood samples for the initial and for the final safety laboratory examination, 10 mL each).⁶

Figure 1: Blood Sampling Schedule for Study CAC15003

In the first study period 0 h (pre-dose) and 4h, 8h, 1d and 3d after the first, 0 h (pre-dose) and 8h, 1d and 3d after the second and the third and pre-dose (0h) and 4h, 8h, 24h, 36h, 2d, 3d, 4d, 5d, 6d, 7d, 8d, 9d, 10d, 11d, 12d, 13d and 14 days after the fourth administration.

In the second study period the same samples as in the first period and additional samples 2d, 4d, 5d, 6d, 7d, 8d, 9d, 10d, 11d, 12d and 13d after the third administration were taken.

Source: Applicant's Study CAC15003 Synopsis.

Subject Disposition

In Study CAC15003, 104 subjects enrolled. Of the 104 subjects enrolled, 98 were randomized and treated with study medication at least once. Eighteen subjects dropped out without replacement. Subject (b) (6) was not one of these eighteen subjects who dropped out, and Subject #64 was included as a drop out. Eighty subjects completed both study periods and 77 of them completed according to the protocol without major protocol deviations.

Safety Evaluation

Of these 104 subjects, 80 subjects completed the study and were exposed to multiple doses of deep intramuscular (IM) gluteal injection of either 25 mg of the test product or 25 mg of the RLD on 8 single occasion. Therefore, the total exposure for the 80 subjects was 200 mg risperidone per subject. A total of 86 adverse events (AEs) were registered in 30 subjects. Twenty-nine treatment emergent adverse events (TEAS) were observed in 10 subjects after administration of the RLD. Of these 29 TEAS after administration of the RLD, one TEA was bronchitis which was deemed as unrelated. All 29 TEAS recovered or resolved. There were 51 TEAEs observed in 25 subjects after administration of the Test product.

The Applicant reported four serious AEs (SAEs). The SAEs of Subjects (b) (6) and (b) (6) were included amongst these four SAEs. Subjects (b) (6) and (b) (6) were administered the test product, and both SAEs were considered by the Investigator as not treatment related. The other two SAEs: one SAE (salpingo-oophoritis) observed before dosing with any investigational product, one SAE reported as "hallucinations", observed after administration of the reference product and judged by the Investigator as not related to treatment.

There was no death reported in this study.

5.3 Summary of Case Report Forms (CRF) for Subjects #19 and #64

⁶ Global Submit 214068. Module 5.3.1.2. CAC15003- CAC 15003. Study Repot Body. Section 9.5.4. Drug Concentration Measurements.

Both subjects (b) (6) and (b) (6) received the test product. Subject (b) (6) was at Site 02, located at 8800 Sliven, Bulgaria, and a total of 12 subjects participated at this site (0 subject drop-out). The study dates at Site 02 ranged from (b) (6) to (b) (6). Subject (b) (6) was at Site 09, located at 4002 Plovdiv, Bulgaria, and a total of 7 subjects participated at this site (2 drop-outs). The study dates at Site 09, ranged from (b) (6) to (b) (6).

Subject (b) (6)

Subject (b) (6) is a 45-year-old Caucasian female, normal BMI (19.0 kg/m²), with past medical history of only schizophrenia. Past medications include oral risperidone 25 mg daily. Subject's concomitant medication was aripiprazole 15 mg daily, since (b) (6). Subject's entry examination was conducted on (b) (6) and showed normal vital signs (afebrile, normal heart rate and blood pressure). Subject's ECG was normal and physical exam was normal. Subject's entry examination labs showed hemoglobin 91 g/L (9.1 g/dl), hematocrit 0.31 L/L, shown in Figure 3. The urinalysis showed trace blood (ca.250 dry/μl) which was deemed not clinically relevant. Pregnancy test (urine) was negative. On the CRF, the fulfillment of all criteria for inclusion in the trial was checked "yes". Period I began (Day 0) (b) (6).

Day 0 in Period II (Day 56 in Period I) was (b) (6), and included blood assessments of basic metabolic panel and complete blood cell count, shown in Figure 4. Urine analysis showed blood ca. 250 ery/μl, erythrocytes 0, leukocytes 2-3, epithelia 0, bacteria 0. Urine pregnancy test was negative. Blood hemoglobin was 92 g/L (9.2 g/dl).

The final examination date was (b) (6). Vitals were normal, urine pregnancy test was negative, and physical exam was reported as normal. ECG on (b) (6) is normal. Blood lab values on final exam date still showed low hemoglobin (74 g/L or 7.4 g/dl) and low hematocrit. Urine analysis showed blood (ca. 250 ery/μl), erythrocytes 10-12, leukocytes 2-4, epithelia 10-12, 0 bacteria.

The "Report of Adverse Event", stated low hemoglobin levels. The start date for this adverse report was (b) (6). The CRF had "unrelated" box check for causal relationship between study medication and AE. the subject was treated with Iron solution 100mg/5 mL, famotidine 40 mg, "hemotransfusion 500 mL". The subject's SAE was then recorded as resolved.

Figure 2: Laboratory Reference Ranges

MEDICAL LABORATORY RAMUS Ltd REFERENCE RANGES Valid for 2017 Haematology		
Name of the test	Method	Reference range
Hemoglobin Hb	Cian-methaemoglobin method	Female: 115-160 g/l Male: 130-180 g/l
Red Blood Cells (RBC)	Conductometric method	Female: 3,7-5,4 T/l Male: 4,2-6,2 T/l
Hematocrit HCT	Indirectly based on Conductometric method	Female: 0,35-0,44 L/L Male: 0,37-0,55 L/L

Source: Global Submit 214068. Study Report. P. 114/232.

Figure 3: Subject (b) (6), Day 0 in Period I, Entry Examination Lab Values, dated December 7, 2017.

Date of blood sample taken:		(b) (6) DD MMM YYYY		not done ☐
Parameter	Value	Unit	Reference range	Clinical relevance for out of range values (considering patient's main disease) (NCR = not clinically relevant CR = clinically relevant IPV = implausible value)
Sodium	145	mmol/l	see list of reference ranges	☐ NCR ☐ CR ☐ IPV
Potassium	6	mmol/l		☒ NCR ☐ CR ☐ IPV
Calcium	2.4	mmol/l		☐ NCR ☐ CR ☐ IPV
Chloride	103	mmol/l		☐ NCR ☐ CR ☐ IPV
Creatinine*	68.1	umol/l		☐ NCR ☐ CR ☐ IPV
Total protein*	78	g/l		☐ NCR ☐ CR ☐ IPV
Total bilirubin*	4.5	umol/l		☐ NCR ☐ CR ☐ IPV
Glucose (fasting)*	4.65	mmol/l		☐ NCR ☐ CR ☐ IPV
Urea*	3.8	mmol/l		☐ NCR ☐ CR ☐ IPV
Uric acid*	288.7	umol/l		☐ NCR ☐ CR ☐ IPV
ALT*	15	U/l		☐ NCR ☐ CR ☐ IPV
AST*	18	U/l		☐ NCR ☐ CR ☐ IPV
GGT*	26	U/l		☐ NCR ☐ CR ☐ IPV
ALP*	79	U/l		☐ NCR ☐ CR ☐ IPV
Hemoglobin	91	g/L		☒ NCR ☐ CR ☐ IPV
Hematocrit	0.31	L/L		☒ NCR ☐ CR ☐ IPV
Leukocytes	7.3	G/L		☐ NCR ☐ CR ☐ IPV
Erythrocytes	4.14	T/L		☐ NCR ☐ CR ☐ IPV
Platelet count	361	G/L		☐ NCR ☐ CR ☐ IPV

Source: Global Submit 214068. Case Report Form Subject (b) (6). Page 45/182.

Figure 4: Subject (b) (6), Day 0 in Period II, Entry Lab Values, dated (b) (6).

Hemoglobin	92	g/L	☒ NCR ☐ CR ☐ IPV
Hematocrit	0.32	L/L	☒ NCR ☐ CR ☐ IPV
Leukocytes	5.5	G/L	☐ NCR ☐ CR ☐ IPV
Erythrocytes	4.4	T/L	☐ NCR ☐ CR ☐ IPV
Platelet count	421	G/L	☐ NCR ☐ CR ☐ IPV

Source: Global Submit 214068. Case Report Form Subject (b) (6). Page 89/182.

Figure 5: Subject (b) (6), Final Day (Day 56 of Period II) Lab Values, dated (b) (6).

Hemoglobin	34	g/L	☒ NCR ☒ CR ☐ IPV
Hematocrit	0.26	L/L	☒ NCR ☐ CR ☐ IPV
Leukocytes	5.1	G/L	☐ NCR ☐ CR ☐ IPV
Erythrocytes	3.66	T/L	☒ NCR ☐ CR ☐ IPV
Platelet count	337	G/L	☐ NCR ☐ CR ☐ IPV

Source: Global Submit 214068. Case Report Form Subject (b) (6). Page 138/182.

Reviewer comment:

The Day 0 study entry examination laboratory results for Subject (b) (6) showed that the subject had underlying anemia. Subject's entry laboratory results showed hemoglobin 91 g/L. The hemoglobin normal reference ranges are different for men and women. The Applicant's laboratory normal range for women's hemoglobin is 115-160 g/L. According to the WHO criteria, the lower limit of normal range for women is hemoglobin of 120 g/L.⁷ The revised WHO/National Cancer Institute's criteria for anemia in women is < 120 g/L.⁸ The multiple blood sampling taken during the study (total blood loss of approximately 462 mL) is the likely explanation for the subject's decreased hemoglobin of 74 g/L reported on Day 56 of the Period II. The subject was appropriately treated with blood transfusion. The Case Report Form stated "hemotransfusion 500 mL", which was probably the English translation of blood transfusion. This reviewer agrees that the anemia was not related to risperidone. It should be noted that the Risperdal Consta® RLD labeling includes anemia as an adverse reaction.

Subject (b) (6)

Subject (b) (6) is a 61year old Caucasian male, normal BMI (18.9 kg/m²), with past medical history of only schizophrenia, diagnosed in (b) (6). According to the Applicant's Study Report Appendix, Table 17 "Report of serious adverse events-Comments" and Section 12.3.1.12, Subject (b) (6) was reported to show "breathing deficiency...later redirected to the pulmonary clinic with pneumonia." However, other sections of the Applicant's study report and subject's Case Report Form (CRF) stated a diagnosis of "chronic obstructive pulmonary disease" for this serious adverse event. . This reviewer listed below the relevant information from the subject's CRF in order to determine the diagnosis, treatment, and outcome of this subject's serious adverse event.

The CRF showed that the subject's past medications include risperidone 3 mg ((b) (6) (b) (6)) and Moditen 25 mg (fluphenazine derivative, (b) (6)), both for schizophrenia. Subject's concomitant medications were depakin 300 mg daily (since (b) (6)) and Akinestat 2 mg PO (anticholinergic antiparkinson agent) twice daily (since (b) (6)). The subject's inclusion date for the study was (b) (6) and entry exam was (b) (6). Entry examination showed normal vital signs (e.g., afebrile, normal heart and blood pressure) and physical exam, including respiratory system was normal. The ECG was normal. Period I began (Day 0) on (b) (6). The subject did not return for Day 14 of Period 1. The Case report form's "Drop-out sheet" states that "subject did not come for second application of

⁷ Buttarello M. "Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how". International Journal of Laboratory Hematology. Volume 38. Issue S1. May 2016. P. 123-132.

⁸ UpToDate, search "Anemia", accessed 08/04/2020.

study medication', and date of discontinuation was (b) (6). The initial "Report for Adverse Event", stated report of pneumonia on (b) (6), and. The report stated that the last administration study medication before AE onset was (b) (6). The "Report for Adverse Event" had several check -boxes and the following were checked: "in-subject hospitalization or prolongation of existing hospitalization needed", "for this moderate severity". The report stated "unrelated" causal relationship between study medication and AE and that the study medication did not change.⁹ The follow-up "Report for Adverse Event" stated diagnosis as "chronic obstruction pulmonary disease" with start date (b) (6) and end date as (b) (6). The second page of "Report for Adverse Event" states that study medication was "drug permanently withdrawn".¹⁰

Reviewer comment:

The description of Subject (b) (6) serious adverse event (SAE) in the Applicant's report was inconsistently reported as pneumonia and COPD. The initial "Report of Adverse Event" stated a diagnosis of pneumonia while the follow-up report stated diagnosis of chronic obstructive pulmonary disease, which was treated and resolved. According to the World Health Organization (WHO), chronic obstruction pulmonary disease is defined as a disease with persistent respiratory symptoms due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases" (e.g. smoking).¹¹ This study was conducted at 21 clinical centers in Bulgaria, Poland and Moldova. Although the CRF was translated in English, this reviewer believes that the chronic obstruction pulmonary disease diagnosis for the "Serious Adverse Event" could also have been a mistake in translation. Chronic obstructive pulmonary disease is often diagnosed in a subject with a smoking history, and would have been recorded in a subject's medical history. The CRF states that there was no past medical history of chronic obstructive pulmonary disease, but the CRF shows positive smoking history, with no start date and check to plan to continue during the study.

Chronic obstructive pulmonary disease is not listed in the RLD label as an adverse reaction. However, the RLD label listed respiratory tract infection and pneumonias under "other adverse reactions observed during the clinical trials, <2%". Although there was incongruence of the diagnosis for Subject (b) (6), the SAE between the Applicant study report and the CRF, DCR hypothesizes that most likely Subject (b) (6) had an exacerbation of his chronic obstructive pulmonary disease, caused by pneumonia. Notwithstanding the limited and conflicting information, this reviewer acknowledges a temporal relationship between test product administration and this reported adverse event, but agrees with the Investigator's statement that it was unlikely that administration of the risperidone medication was the cause of or related to this the subject's respiratory adverse event. Justification for this assessment include the Q1 and quantitatively Q2 sameness between the proposed generic formulation to the RLD, inclusion of respiratory tract infections as adverse reactions in the RLD labeling, and chronic use of risperidone (oral) prior to enrollment and administration of the test product.

⁹Global Submit 214068. Module 5.3.7. Case Report Forms. page 148/182.

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¹⁰ Global Submit 214068. Module 5.3.7. Case Report Forms. page 149/182.

¹¹ UpToDate, search "chronic obstruction pulmonary disease", accessed 08/04/2020.

6 Conclusions:

The serious adverse events of anemia in Subject (b) (6) and chronic obstructive pulmonary disease in Subject (b) (6) are both labeled adverse events in the RLD labeling, and the test formulation is Q1/Q2 the same as the RLD. From a clinical safety perspective:

- It is unlikely that any difference between the RLD and test product caused or contributed to the occurrence of these adverse events.
- The occurrence of this adverse event does not indicate any safety or quality concern for the test product compared to the RLD. No additional information is requested.



Mary
Lee

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Andrew
Fine

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Date: 8/23/2020 04:31:28PM
GUID: 50174afb000001af8e1e5e9e9cb6265d

**Clinical Review of Comparative (Threshold) Analyses
for Drug-Device Combination Products**

Division of Clinical Review (DCR)

Office of Bioequivalence (OB), Office of Generic Drugs (OGD)

Center for Drug Evaluation and Research (CDER)

ANDA	214068
Drug Product/Strength(s)	Risperidone for Extended-Release Intramuscular (IM) Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial
ANDA Applicant	Teva Pharmaceuticals
RLD/Reference Standard#/Product Name	NDA 021346 Approved 10/29/03 Risperdal Consta® (risperidone) Intramuscular Injection 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial
RLD/RS Sponsor	Janssen Pharms
Primary Reviewer	Jennifer Hammer, M.D. Medical Officer Division of Clinical Review (DCR) Office of Bioequivalence (OB) Office of Generic Drugs (OGD)
Secondary Reviewer	Andrew Fine, Pharm.D. Team Leader, DCR/OB/OGD
Submission Date(s)	12/16/19: Original Submission 03/27/20: Clinical/Response to Information Request 05/12/20: Clinical/Response to Information Request 6/09/20: Clinical/Response to Information Request
Date of Review	06/12/20
GDUFA Goal Date	10/15/20
Comparative Threshold Analyses Conclusion	☐ No Design Differences - Acceptable ☒ Minor Design Differences ☒ Acceptable ☐ Not acceptable ☐ Other Design Differences ☐ Acceptable ☐ Not acceptable
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)

1 INTRODUCTION AND BACKGROUND

1.1 Summary of Drug Product Information Pertinent to Review

Risperdal Consta[®] (risperidone) IM Injection 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial is a drug-device combination product, approved October 29, 2003. Risperdal Consta[®] is an atypical antipsychotic indicated for the treatment of schizophrenia and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder. Each injection is administered by a health care professional and is given as a deep intramuscular (IM) deltoid or gluteal injection. The recommended dose is 25 mg 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 is 50 mg every 2 weeks.

The reference listed drug (RLD) Risperdal Consta[®] IM Injection is supplied as a dose pack consisting of a vial containing risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter and two Terumo SurGuard[®] 3 needles for intramuscular injection (a 21 G 1-inch needle with needle protection device for deltoid administration and a 20 G 2-inch needle with needle protection device for gluteal administration). The RLD label, approved on 02/05/20, includes a patient information sheet and Instructions for Use (IFU).¹

Teva Pharmaceuticals (Teva or the Applicant) submitted an abbreviated new drug application (ANDA 214068) on December 16, 2019 for Risperidone IM Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial. The proposed product is also supplied as a dose pack consisting of a vial containing risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter and two Terumo SurGuard[®] 3 needles for intramuscular injection (a 21 G 1-inch needle with needle protection device for deltoid administration and a 20 G 2-inch needle with needle protection device for gluteal administration).

DCR sent an information request (IR) letter to the Applicant on March 3, 2020 requesting the Applicant submit high resolution photographs of the drug product and the results of their threshold analyses comparing their proposed Risperidone for IM Injection to the RLD Risperdal Consta[®]. The Applicant provided their response to DCR on March 27, 2020. Additionally, DCR sent a second IR letter to the Applicant on May 5, 2020 to clarify the cap color of the 12.5 mg/vial and the Applicant provided their response on May 12, 2020. DCR sent a third IR letter to the Applicant on June 3, 2020 to ask for justification for additional language in the proposed IFU compared to the RLD and the Applicant provided their response on June 9, 2020. The responses to all IRs will be assessed in this review.

This review evaluates the delivery device constituent part of the combination product intended to administer the drug product and any associated product labeling and packaging. This review focuses on the analysis of the user interface² for the drug-device combination product (drug and a delivery device intended to administer a drug) comparing the proposed generic and the RLD.

¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021346s0631bl.pdf

² User interface refers to all components of the combination product with which a user interacts.

1.2 Other Relevant Information

ANDA 214068 is the first ANDA to be submitted for Risperidone IM Injection.

2 COMPARATIVE (THRESHOLD) ANALYSES REVIEW AND DISCUSSION

DCR conducted comparative analyses of the user interface of the proposed generic combination product and its RLD Risperdal Consta[®] (NDA 021346). DCR also reviewed the comparative analyses provided by the Applicant.³

2.1 Physical comparison of the product samples: RLD vs. Proposed

DCR examined the delivery device constituent part of the RLD and proposed generic product using samples provided by the applicant.

Table 1: Comparison of Actual Samples (carton) – Photos of RLD Risperdal Consta[®] (NDA 021346) and Proposed Risperidone for IM Injection (ANDA 214068) provided by Applicant.

RLD Risperdal Consta [®] (NDA 021346)	Proposed (ANDA 214068)
Carton 12.5 mg	
	
Carton 25 mg	

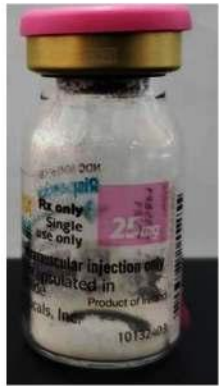
³ ANDA 214068 Applicant submission. Module 5.3.5.4 Threshold Analysis.

<\\cdsesub1\evsprod\anda214068\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\threshold-analysis\5354-other-stud-rep\reprd001\thran-risp\threshold-analysis.pdf>

RLD Risperdal Consta® (NDA 021346)	Proposed (ANDA 214068)
 25 mg Dose Pack Risperdal CONSTA risperidone Long-Acting Injection DOSE PACK CONTENTS: • One 25 mg vial of risperidone extended-release microspheres for injection • One pre-filled syringe containing 2 mL of diluent • One Vial Adapter • One 21-gauge 1.5" Insulin SureGuard® 3 safety needle for deltoid injection • One 20-gauge 1.5" Insulin SureGuard® 3 safety needle for gluteal injection Do not substitute any components of the dose pack. For deltoid or gluteal intramuscular injection only Each injection should be administered by a healthcare professional. PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.	(b) (4)
Carton 37.5 mg	
 37.5 mg Dose Pack Risperdal CONSTA risperidone Long-Acting Injection DOSE PACK CONTENTS: • One 37.5 mg vial of risperidone extended-release microspheres for injection • One pre-filled syringe containing 2 mL of diluent • One Vial Adapter • One 21-gauge 1.5" Insulin SureGuard® 3 safety needle for deltoid injection • One 20-gauge 1.5" Insulin SureGuard® 3 safety needle for gluteal injection Do not substitute any components of the dose pack. For deltoid or gluteal intramuscular injection only Each injection should be administered by a healthcare professional. PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.	(b) (4)
Carton 50 mg	
 50 mg Dose Pack Risperdal CONSTA risperidone Long-Acting Injection DOSE PACK CONTENTS: • One 50 mg vial of risperidone extended-release microspheres for injection • One pre-filled syringe containing 2 mL of diluent • One Vial Adapter • One 21-gauge 1.5" Insulin SureGuard® 3 safety needle for deltoid injection • One 20-gauge 1.5" Insulin SureGuard® 3 safety needle for gluteal injection Do not substitute any components of the dose pack. For deltoid or gluteal intramuscular injection only Each injection should be administered by a healthcare professional. PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE.	(b) (4)
<u>Reviewer Comments:</u> <i>The different colors for each strength of the proposed product match the colors for the RLD.</i>	

Table 2: Comparison of Actual Samples (contents of dose pack) – Photos of RLD Risperdal Consta® (NDA 021346) and Proposed Risperidone for IM Injection (ANDA 214068) provided by Applicant.

RLD Risperdal Consta® (NDA 021346)	Proposed (ANDA 214068)
Contents of Dose Pack	

	
<u>Reviewer Comments:</u> <i>The layout of the components inside the dose pack is different between the RLD and proposed product. The Applicant stated that these differences do not affect the operation. DCR agrees that this difference is minor and acceptable as all the necessary components are included in the dose pack of the proposed product.</i>	
Vial 12.5 mg	
	
Vial 25 mg	
	
Vial 37.5 mg	

	
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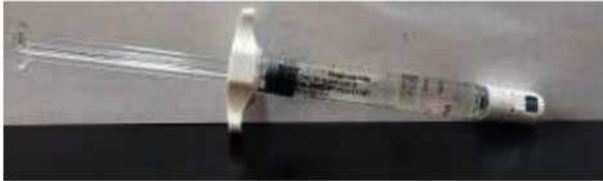
Vial 50 mg

	
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Reviewer Comments:

The Applicant's initial IR response included photos of the proposed 12.5mg vial (b) (4) while the RLD cap is considered violet. The photos included in the Applicant's threshold analysis, however, showed a violet cap. An IR was sent to the Applicant asking for new photos and clarification of the cap color. The Applicant responded⁴ that the photos in the original IR was for the exhibit batch (b) (4) but that the proposed cap for commercial use is the color that is in the threshold analysis (violet). The different color of the vial tops for each strength of the proposed product match the colors for each strength of the RLD

Prefilled Syringe

	
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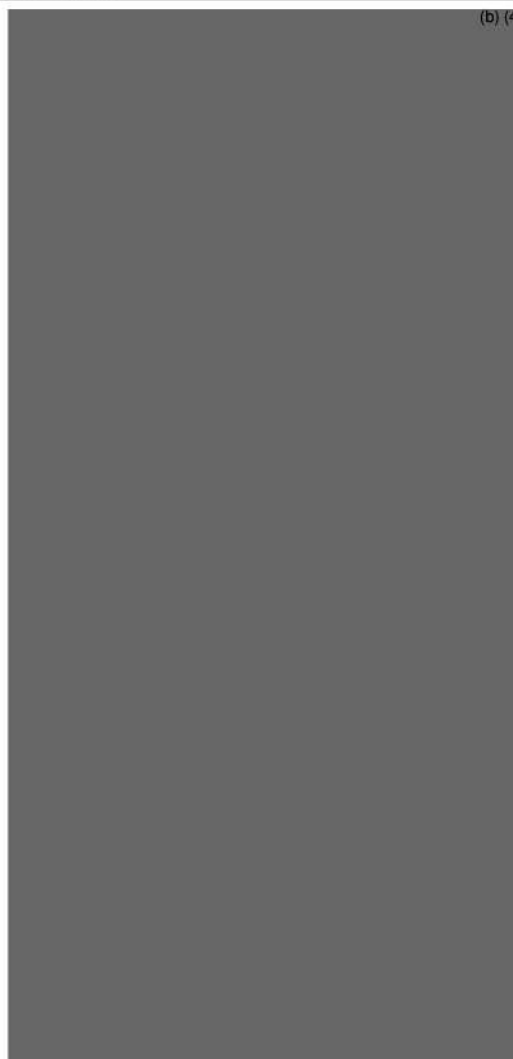
Reviewer Comments:

Both syringes have the same dimensions with 3 mL barrels. The Applicant notes that the RLD plunger rod is transparent (b) (4). Additionally, the RLD backstop is white and opaque while the proposed backstop (b) (4). These

⁴ [\\cdsesub1\evsprod\anda214068\0009\m1\us\teva-ir-resp.pdf](#)

are minor and acceptable differences as the color of the plunger rod, flange, cap, and backstop do not impact critical tasks.

Vial Adapter in Blister Pack



Reviewer Comments:

The RLD vial adapter is packaged in a hard blister pack that is sealed with a paper lid while the proposed vial adapter is packaged (b) (4). The hard blister pack is designed so that the vial adapter can be attached to the vial while still in the blister pack to maintain the sterility of the adapter. The proposed vial adapter (b) (4)

Vial Adapter

	(b) (4)
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Reviewer Comments:

The (b) (4) proposed adapter is (b) (4) compared to the (b) (4) the RLD. The differences do not alter the use of the vial adapter and are a minor difference and acceptable.

Needles

 	(b) (4)
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Reviewer Comments:

The Applicant found no design difference between the needles. DCR agrees with this assessment.

Photos source: ANDA 214068 Applicant submission. Module 1.11.4 Multiple Module Information Amendment.
[Application 214068 - Sequence 0004 - 1.11.4 Multiple Module Information Amendment -](#)

2.2 Comparative Task Analysis

The Applicant provided a tabular comparison of the administration procedures between the proposed generic product and the RLD.⁵ Table 3 below shows the relevant excerpts from the Applicant's Comparative Task Analysis.

Table 3. Applicant's Comparative Task Analysis



(b) (4)

2 Pages have been withheld in full as b4 immediately following this page

⁵ [\\cdsesub1\evsprod\anda214068\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\threshold-analysis\5354-other-stud-rep\reprd001\thran-risp\threshold-analysis.pdf](#)

(b) (4)

Source: ANDA 214068 Applicant submission. Module 5.3.5 Threshold Analysis.

<\\cdsesub1\evsprod\anda214068\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\threshold-analysis\5354-other-stud-rep\reprd001thran-risp\threshold-analysis.pdf>

Reviewer Comments:

- The Applicant notes differences in [REDACTED] (b) (4). The RLD's vial adapter is packaged in a hard blister pack. It is designed so that the vial adapter can be attached to the vial while still in the blister pack to keep the adapter sterile. The proposed vial adapter [REDACTED] (b) (4)

(b) (4)

The Applicant determined this an acceptable difference because the product is intended to be administered by a health care professional who should have experience with abiding by sterile procedures, no additional training is required. Octreotide Acetate for Injectable Suspension is a product with a similar kit for injection. The RLD (Sandostatin®) uses a similar vial adapter and hard blister pack which is used to keep the vial adapter sterile when it is attached to the vial. (b) (4)

. A comparative analysis was done⁶ in which these design differences were found to be acceptable because the end-user is a health care professional. DCR recommended labeling changes to emphasize that the tip of the vial adapter must be cleaned with alcohol. The Applicant included that recommended language in this submission as well (See Section 2.3). Therefore, DCR finds this design difference in preparing the vial adapter and removing the sterile blister as unlikely to impact a critical task and is acceptable.

- The RLD includes an additional step to remove the blister pack once the vial adapter is attached to the vial. This step is not needed for the Applicant's product. This additional step was also not necessary for ANDA 210317 ((Octreotide Acetate for Injectable Suspension). DCR finds this difference, removal of step to dispose blister pack, acceptable.
- Aside from the differences noted above due to the different vial adapter packaging, the Applicant noted no design difference in the step of connecting the vial adapter to the vial, and ensuring it's connected.

2.3 Labeling comparison of the delivery device constituent part: RLD vs. Proposed

The latest product labeling for the RLD, Risperdal Consta®, was approved on February 5, 2020 (Supplement 63). In addition to the Prescribing Information insert, the RLD labeling also includes Patient Information and Instructions for Use. The RLD labeling is available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021346s0631b1.pdf

For the threshold analyses of this drug-device combination product, the comparison of the product labeling focuses on the Dosage and Administration, Dosage Forms and Strengths, and How Supplied/Storage and Handling sections of the Prescribing Information (PI) and the Instructions for Use (IFU). Expected changes such as substituting the Brand name, the list of inactive ingredients, and manufacturing information will not be mentioned. Because container and carton labels are reviewed in detail by the Division of Labeling Review (DLR), detailed comparisons of the bottle and carton label are not performed in this review; however, any part of the label that affects the use of the device is assessed in this section, the Physical Comparison, and the Comparative Task Analysis sections of the review, where applicable.

Table 1: Applicant's Proposed Labeling Status

⁶ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b3e00e>

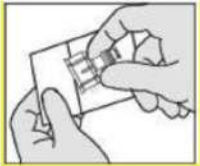
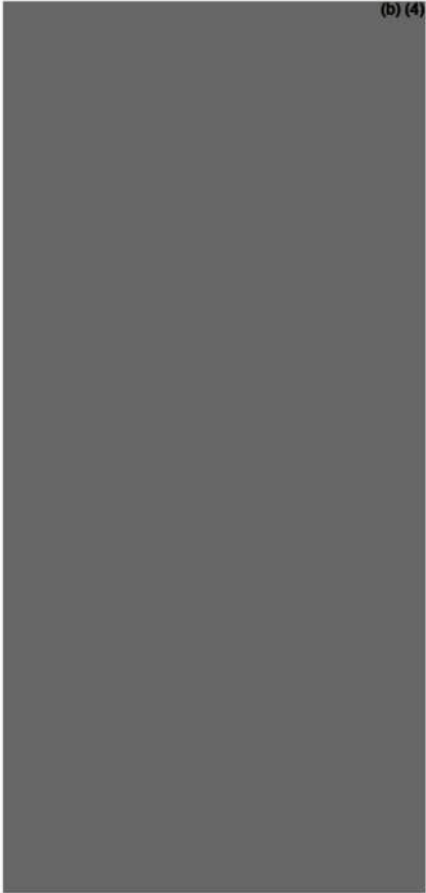
Milestone for DLR Discipline	Yes/No (if yes include date)
Labeling DRL/IR sent?	Yes (4/27/20)
Applicant replied to DRL/IR with modified proposed labeling?	Yes (5/11/20)
Submission Date of proposed labeling used for this review: 05/11/2020	

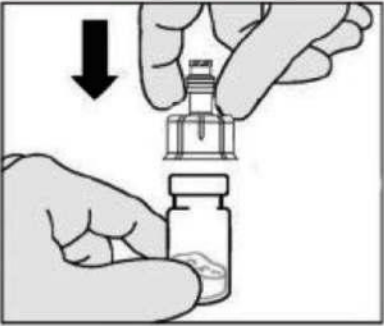
Aside from the expected changes such as proprietary name and manufacturing information, the original Applicant labeling contains differences compared to the RLD which was revised February 5, 2020. As a result, the Division of Labeling (DLR) sent a deficiency letter (DRL) to the Applicant on 4/27/20 including the following comments:

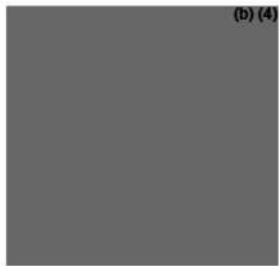
1. "GENERAL COMMENT
 - a. Revise the name of your drug product to read "Risperidone for Extended-Release Injectable Suspension" to comply with USP nomenclature guidelines from USP General Chapter, General Information <1121> Nomenclature, on your labels and labeling.
 - b. Comment as to whether text appears on your (b) (4). Ensure your proposed (b) (4) are in compliance with the requirements (b) (4)
2. CONTAINER LABEL (Drug Product)
 - a. Refer to comment 1a above.
 - b. Revise the strength statement to express the strength in terms of the total amount of drug per vial. For example: XX mg/vial or XX mg per vial.
3. CONTAINER LABEL (Diluent)
Refer to comment 1a above.
4. CARTON LABELING
 - a. Refer to comments 1a and 2b above.
 - b. Revise (b) (4) on the side labels to read "PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE."
5. PRESCRIBING INFORMATION
 - a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Risperdal Consta, NDA 021346/S-063 approved on February 5, 2020 found on the Drugs@FDA website.
 - b. Refer to comment 1a above.
 - c. DESCRIPTION: Include "Sterile", as required for the proposed drug product. Refer to 201.57(c)(12)(D).
6. INSTRUCTIONS FOR USE
Refer to comment 1a above.
7. STRUCTURED PRODUCT LABELING (SPL)
 - a. DATA ELEMENTS: Provide the data elements for the 25 mg, 37.5 mg, and 50 mg strengths.
 - b. (b) (4)

The Applicant responded with revised labeling on 5/11/20.

Table 3: Comparison of IFU Labels – RLD Risperdal Consta® (NDA 021346) and Proposed Product Risperidone IM Injection (ANDA 214068)

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
 Prepare vial adapter Hold sterile blister as shown. Peel the blister film from backing and remove the vial adapter from its packaging by holding between the white luer cap and the skirt. Do not touch spike tip and luer tip connector of the vial adapter at any time. This will result in contamination.	(b) (4) 

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
 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, confirmed by an audible "click". CLEAN the luer tip of the vial adapter with an alcohol wipe	(b) (4) 
Do not shake. Do not touch exposed luer tip connector on vial adapter. This will result in contamination.	(b) (4) 

Proposed Risperidone IM Injection (ANDA 214068)	RLD Risperdal Consta® (NDA 021346)
Hold syringe by white collar then insert tip into the luer tip connector of the vial adapter.	 (b) (4)

Reviewer Comments: Although the proposed product contains similar components, the vial adapter has design differences when compared to the RLD and the Applicant has modified the Instructions for Use (IFU) to align with these design differences. These differences are:

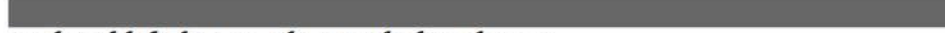
-
-
-
-
-



As discussed in Section 2.2, these modifications to the IFU regarding the vial adapter are consistent with those recommended by DCR for another Teva product⁷, Octreotide Acetate for Injectable Suspension. Therefore, these differences in the IFU are acceptable.

There was one additional difference between the IFUs of the proposed product and RLD. The connection of the vial adapter to the vial is confirmed by an “audible click” (highlighted by Applicant) for the proposed product while this language is not included in the RLD’s IFU. This audible confirmation was not included in the Applicant’s Comparative Analysis (Section 2.2). An IR was sent on 6/3 to the Applicant asking for clarification as to why this language is included. The Applicant responded⁸ on 6/9, stating

 (b) (4)

. Teva also submitted updated labeling to align with this change.

⁷ <http://panorama.fda.gov/PanoramaDocMgmt/webhooks/viewdownload?id=090026f881b3e00e>

⁸ <\\cdsesub1\evsprod\anda214068\0011\m1\us\response.pdf>

3 CONCLUSION

From a clinical safety perspective, the differences in luer tip of the vial adapter, syringe, blister pack removal, as well as additions to the IFU to account for these physical differences between the RLD and proposed product are minor and unlikely to impact the safe and effective use of the proposed product as a substitute for the RLD. DCR finds the proposed risperidone IM injection acceptable.

4 RECOMMENDATION

The Clinical Discipline has completed its review of the comparative (threshold) analyses and has no comments at this time.

- ☐ Major
- ☐ Minor
- ☒ N/A (Review is Adequate)



Jennifer
Hammer

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Andrew
Fine

Digitally signed by Andrew Fine
Date: 6/12/2020 03:57:02PM
GUID: 50174afb000001af8e1e5e9e9cb6265d

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 214068

CHEMISTRY REVIEW(s)

ANDA Executive Summary

1. Application/Product Information

ANDA Number.	214068
Review Cycle #	03
Applicant Name	Teva Pharmaceuticals USA, Inc.
Drug Product Name	Risperidone (b) (4) Injection
Dosage Form. (click (+) for more than one)	Suspension, extended release Injectable
Proposed Strength(s)	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Route of Administration (click (+) for more than one)	Intramuscular
Maximum Daily Dose	50 mg
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of schizophrenia
Drug Product Description	The proposed test product Risperidone for Injectable Suspension for (b) (4) injection (b) (4) is a complex and combination drug product. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability. For the leachables (b) (4) detected in the diluent of the injection kit, the applicant provided toxicology assessment, for which P/T consult review is deemed adequate. (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)
Co-packaged product information	Risperidone for Extended-Release Injectable Suspension is provided as a single-dose pack, consisting of a vial

	containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent for Risperidone for Extended-Release Injectable Suspension, a 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).		
Device information, if any:	Prefilled syringe, vial adapter and needles.		
Storage Temperature/ Conditions	The entire dose pack should be stored in the refrigerator (36° to 46°F; 2° to 8°C) and protected from light.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Greg Huang	Jin Xu
	<i>Drug Product/ Labeling</i>	Greg Huang	Jin Xu
	<i>Manufacturing</i>	Raeann Wu	Cassandra Abellard
	<i>Biopharmaceutics</i>	Jia Leo	N/A
	<i>Microbiology</i>	Dacie Bridge	Yan Zheng
	<i>Other (specify):</i>		
	<i>RBPM</i>	Suzan Ghodasara	
	<i>ATL</i>	Jin Xu	
Consults	Discipline Consulted	Recommendation	Date
	P/T consult from OLDP	Adequate	6/20/2023
	P/T consult from OMPA	Adequate	8/8/2023

2. Submission Document(s) Reviewed

Submission(s) Assessed	Documents Date	Disciplines Affected
Original Submission	12/16/2019	All

Amendment-Quality Response to IR	04/09/2020	Manufacturing
Amendment-Quality Response to IR	04/29/2020	CDRH
Amendment-Quality Response to IR	07/24/2020	CDRH
Amendment-Quality Response to IR	08/04/2020	Facility
Resubmission-Response to CRL	05/27/2021	Drug Substance, Drug Product, Manufacturing, Biopharmaceutics, Microbiology
Amendment-Quality Response to IR	08/19/2021	Facility
Amendment-Quality Response to IR	12/07/2021	Microbiology
Resubmission-Response to CRL	02/27/2023	Drug Product, Manufacturing, Pharm/Tox
Unsolicited Amendment	03/23/2023	Drug Substance, Facility
Amendment-Quality Response to IR	07/06/2023	Drug Product, Microbiology
Amendment-Quality Response to IR	09/06/2023	Manufacturing

3. Related/Supporting Documents

a. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Risperidone USP	Adequate	4/20/2023	Review #14
	III	(b) (4)	(b) (4)			

(b) (4)		(b) (4)			
	III				
	III				
	III				
	III				
	IV				
	V				
	V				
	Other				
	Other				

b. Other Documents: *IND, RLD, RS, Approved ANDA*

Document	Application Number	Description
	NDA 021346	RLD

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4. Final Overall recommendation – Approval

Deficiencies (if applicable):

Overall Quality Deficiencies - Optional *(Deficiencies that affect multiple sub-disciplines; for subheadings use the format shown, for all deficiencies.)*

None

Drug Substance Deficiencies

None

Drug Product Deficiencies

None

Labeling Deficiencies *(Please contact OGD if you identify any Labeling deficiencies with your comments)*

None

Manufacturing Deficiencies

None

Biopharmaceutics Deficiencies

None

Microbiology Deficiencies

None

Other Deficiencies *(Specify discipline, such as Environmental. For consults such as Biostatistics, PharmTox, CDRH, Clinical, etc., include consult type and specify Quality discipline – example: **Pharm/Tox consult for Drug Product**)*

None

Additional Comments:

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response: None

5. Basis for Recommendation

a. Summary of Rationale for Recommendation:

The ANDA has been assessed by DS, DP, Process, Facility, Biopharmaceuticals, and Microbiology. All CMC related issues have been satisfactorily resolved.

NDSRI Impacted Application: No

The ANDA is approvable from a CMC perspective.

b. Recommendation by Subdiscipline:

Drug Substance: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Drug Product: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Quality Labeling: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Manufacturing: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Biopharmaceutics: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Microbiology: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

Environmental: ADEQUATE

Provide justification(s) (for major deficiencies only):
(Click link to view [Justification Statements](#))

1.

6. Life-Cycle Considerations

**Established Conditions per ICH Q12: No
Comments:**

**Comparability Protocols (PACMP): No
Comments:**

Additional Comments: None



Jin
Xu

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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Risperidone
ANDA Number	214068
Applicant Name	Teva Pharmaceuticals USA, Inc.
Assessment Cycle Number	3a
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Risperidone drug substance is assessed for control critical quality attributes. DMF# (b) (4) is adequate as of 10/19/2021 and LoA is provided. The drug substance remains adequate from the quality perspective per Review#3a.

List Submissions being assessed (Table):

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019
Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020

Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020
Seq.008 Multiple Categories/Subcategories ((b) (4) LOA)	05/07/2020
Seq. 0007 Response to IR from CDRH	04/29/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021
Seq.0018 Response to IR (Microbiology)^	12/07/2021
Seq.0019 Post-CR Meeting Request^	04/01/2022
Seq.0020 General Correspondence for additional DS skid^	06/08/2022
Seq.0021 Response to CR-Major^	02/27/2023
Seq.0022 Amendment to CR Response (Reintroducing an API source of Jubilant)^	03/23/2023

*Review #2

^Review#3

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*): NA

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

INN Name

Risperidone

Chemical Abstract Service (CAS) Number

106266-06-2

Chemical Name(s)

4H-Pyrido[1,2- α]pyrimidin-4-one,3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl

Or

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2- α]pyrimidin-4-one (Source: DMF: (b) (4))

USAN Name

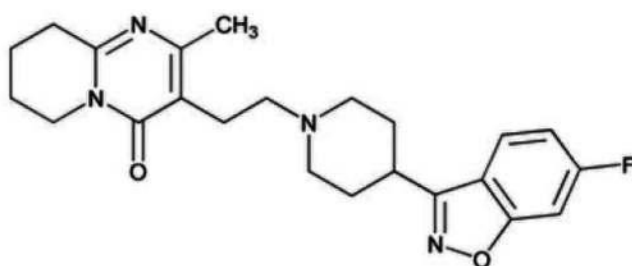
Risperidone

IUPAC Name

(3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (Source: PubChem¹)

¹URL: <https://pubchem.ncbi.nlm.nih.gov/compound/5073#section=Crystal-Structures>

Structural Formula



Molecular Formula

C₂₃H₂₇FN₄O₂

Relative Molecular Mass

410.48

Pharmacological Class

Antipsychotic

Physical Description: White or almost white powder.

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R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: NA

Lifecycle Management Considerations: NA

DRUG SUBSTANCE LIST OF DEFICIENCIES: None

Primary Drug Substance Assessor Name and Date: Greg Huang 05/01/2020, 06/01/2020 (#1), 02/11/2022 (#2)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/26/2020 (Review 1); 2/17/2022 (Review #2)

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Risperidone for Injectable Suspension contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The product is a combination of extended-release microspheres for injection and diluent for parenteral use. The product is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles.
ANDA Number	214068
Assessment Cycle Number	3a
Drug Product (DP) Name / Strength	12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial
Route of Administration	Intramuscular deltoid or gluteal injection.
Drug Product Manufacturer	Pharmathen International S.A
RLD/RS Information (Brand Name of Product, Applicant)	RISPERDAL CONSTA® (risperidone) (b) (4) injection in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone by Janssen Pharmaceuticals Inc.
RLD/RS Number	N021346
Proposed Indication	Risperidone for Injectable Suspension is indicated for the treatment of schizophrenia. It should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection.

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

The proposed Risperidone for Injectable Suspension for (b) (4) injection (LAI) is a complex and combination drug product, with no generic drug product approved so far. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability. For the leachables (b) (4), the applicant provided toxicology assessment, for which P/T consult review is deemed adequate. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #3a	Comments
Chemical Stability (All CQAs)	45 Medium	(b) (4)	Low	(b) (4)

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	36 Medium		Low	
Other CQAs	36 Medium		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019

Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020
Seq.0008 Multiple Categories/Subcategories (DMF (b) (4) LOA)	05/07/2020
Seq. 0007 Response to IR from CDRH	04/29/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021
Seq.0018 Response to IR (Microbiology)^	12/07/2021
Seq.0019 Post-CR Meeting Request^	04/01/2022
Seq.0020 General Correspondence for additional DS skid^	06/08/2022
Seq.0021 Response to CR-Major^	02/27/2023
Seq.0022 Amendment to CR Response (Reintroducing an API source of Jubilant)^	03/23/2023
Seq.0024 IR Response\$	07/06/2023

* Review #2

^ Review#3

\$ Review#3a

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: N/A
- Dissolution status: specifications are/are not finalized with Biopharmaceuticals, and implemented, and stability data complies with

*revised specifications (if applicable) to confirm shelf life proposal:
(Refer to Biopharmaceutic Assessment)*

- *Elemental impurity compliance with ICH Q3D – status: **Adequate***
- *Number of Comparability protocols included: **0***

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Risperidone (b) (4) Injection is an extended-release microspheres formulation which 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. The diluent for parenteral use is a clear, colorless solution.

The current formulation was deemed Qualitatively and Quantitatively the same by the OGD through responses to controlled correspondences, 1524801, 1524802, 1524803, 1524804 and 02407. A copy of the controlled correspondences is included in Module 1.2.

Table 1: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 12.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial)	RLD formulation (mg/vial)	RLD formulation (% w/w)	Proposed formulation (mg/vial)	Proposed formulation (mg/vial)	Proposed formulation (% w/w)	Function
Risperidone (base)	12.5 mg (label claim)	(b) (4)	(b) (4)	12.5 mg	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	
Total weight - risperidone microspheres	(b) (4)	41.0 mg (label claim)	100.0	(b) (4)	43.0 mg ⁽⁵⁾	100	--

(b) (4)

(b) (4) (b) (4)

Table 6: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 25 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w)	Function
Risperidone (base)	25.0 mg (label claim)	(b) (4)	(b) (4)	25 mg	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)							
Total weight - risperidone microspheres		78.0 mg (label claim)	100.0		81.0 mg ⁽⁵⁾	100	--

(b) (4)

Table 11: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 37.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	37.5 mg (label claim)	(b) (4)	(b) (4)	37.5 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		116.0 mg (label claim)	100.0		120.0 mg ⁽⁵⁾	100	--

(b) (4)

Table 16: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 50 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w)	Function
Risperidone (base)	50.0 mg (label claim)	(b) (4)	(b) (4)	50 mg	(b) (4)	Active Substance
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		152.0 mg (label claim)	100.0	156.0 mg ⁽³⁾	100	--

(b) (4)

Table 21: Quantitative Composition and Function of the Microspheres and Diluent

Ingredient	Quality Standards	Function	12.5 mg/ vial				25 mg/vial				37.5 mg/vial				50 mg/vial			
			mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)
Microspheres in vial			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
Risperidone			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
75:25 Polylactide co-glycolide			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
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(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
(b) (4)			(b) (4)				(b) (4)				(b) (4)				(b) (4)			
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(b) (4)			(b) (4)				(											

Ingredient	Quality Standards	Function	12.5 mg/ vial			25 mg/vial			37.5 mg/vial			50 mg/vial		
			mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)
Citric acid anhydrous														(b) (4)
Sodium chloride														
Sodium hydroxide														
Water for injection														
Total Diluent (mg)	-	-	(b) (4)	100.0			(b) (4)	100.0	-		(b) (4)	100.0	-	
Total Weight of reconstituted suspension (mg)	-	-	-	2,064.8	-	100.0	-	2,097.6	-	100.0	-	2,163.2	-	100.0
														(b) (4)

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R REGIONAL INFORMATION

Environmental

Assessment: Adequate
Refer to Module 1.12.14.

Methods Validation or Verification Package

Assessment: Adequate
Refer to 3.2.R.

Comparability Protocols

Assessment: N/A
No comparability protocol proposed.

Lifecycle Management Consideration

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/03/2020 (Review#1), 09/15/2020 (#1b), 02/16/2021 (#2), 04/04/2023 (#3), 08/17/2023 (#3a)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/29/2020 (Review 1); 2/19/2022 (Review 2); 8/18/2023

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/01/2020

Secondary Drug Product Assessor Name and Date: Jin Xu, 5/29/2020



Jin
Xu

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Greg
Huang

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MANUFACTURING INTEGRATED ASSESSMENT

Review #3

Application ID	ANDA 214068
Drug Product Name	Risperidone (b) (4) Injection
Strengths	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Dosage Form	Injectable
Administration Route	Intramuscular
Indication	• Schizophrenia • Bipolar Disorder
Applicant Name	Teva Pharmaceuticals USA, Inc.
RLD Number	21346
Primary Reviewer	Raeann Wu
Secondary Reviewer	Ying Zhang/Cassandra Abellard

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Risperidone (b) (4) Injection, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular injection. The risperidone 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. The diluent for parenteral use is a clear, colorless solution. The microspheres are suspended in the diluent prior to injection.

The manufacturing of diluent includes the following (b) (4)

[REDACTED]

The manufacturing of the risperidone microspheres (powder) includes the following (b) (4)

[REDACTED]

The manufacturing of kit includes the following (b) (4)

[REDACTED]

[REDACTED] (b) (4)
[REDACTED]. Justification is provided in the process development report and is adequate.

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V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Yong Wu 2/6/2020 5/8/2020 5/28/2020 6/9/2020 8/27/2020 9/10/2020	Yubing Tang 2/14/2020 5/25/2020 5/31/2020 6/9/2020 09/07/2020 9/10/2020	9/10/2020	CR Major	Withheld
2	Raeann Wu	Ying Zhang	3/10/2022	CR Major	Withheld
3a	Raeann Wu	Cassandra Abellard	8/28/2023	IR	Approve
3b	Raeann Wu	Cassandra Abellard	10/17/2023	Adequate	Approve



Raeann
Wu

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Cassandra
Abellard

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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 214068-ORIG-1-AMEND-21
Product Name/Strengths	Risperidone (b) (4) Injection/ 12.5mg, 25mg, 37.5mg, and 50mg
Applicant	Teva Pharmaceuticals USA Inc
Dosage Form /Route of Administration	Powder for Injection/intramuscular injection
Indication for Use	1) Treatment of schizophrenia. 2) Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
RLD	NDA 021346 Risperdal Consta® (risperidone) (b) (4) Injection (12.5mg, 25mg, 37.5mg, and 50mg)
Submission Date	2/27/2023
Primary Reviewer	Jia Leo, Ph.D.
Recommendation	ADEQUATE

REVIEW SUMMARY

This amendment provides response to the Complete Response Letter (CRL) dated 3/25//2022. In the last review cycle, Biopharmaceutics is adequate. However, in this amendment, the Applicant provide additional information, adding an additional manufacturing (b) (4) (b) (4).¹ To support the proposed change, the Applicant provided comparative in vitro dissolution profile data for the pre-change (b) (4) (b) (4)) and the post-change (b) (4) (b) (4) drug products.²

The dissolution profiles of the pre-change drug product, including the pivotal BE batch, are similar to that of the post-change drug product under both accelerated (b) (4) and real time (b) (4) dissolution conditions (**Appendix 1**). The provided in vitro dissolution profile data support the proposed manufacturing change.

Conclusion and Recommendation: From a Biopharmaceutics perspective, ANDA 214068-ORIG-1-AMEND-21 for Risperidone (b) (4) Injection is ADEQUATE.

¹ [\\CDSESUB1\EVSPROD\anda214068\0021\m1\us\resp-fda-crl-25mar2022.pdf](#)

² [\\CDSESUB1\EVSPROD\anda214068\0021\m2\27-clin-sum\skid1-skid2-comp-disso.pdf](#)

Appendix 1: Supporting Data

Approved dissolution method and acceptance criteria

Apparatus	Medium/ Temperature	Volume (mL)	Acceptance Criteria
Cylinder bottle	HEPES buffer pH 7.4 /37°C (normal) and 45°C (accelerated) water bath	200	At 37 °C: NMT (b) (4) % in day 1 NMT (b) (4) % in day 21 At 45 °C: (b) (4) % in 120 hr (b) (4) % in 160 hr NLT (b) (4) % in 210 hr

(b) (4)

Summary of f₂ values for pre-change (Sample 1) and post-change (Sample 2) drug products using the accelerated dissolution method (45°C)

Dissolution method water bath at 45°C ±0.3°C		
Sample 1	Sample 2	f ₂
(b) (4)	(b) (4)	
LOT 4000381	LOT 4201234	51.3
Test Product 12.5mg LOT 4000381A	Test Product 12.5mg LOT 4201234A	62.5
Test Product 25mg* LOT 4700023B	Test Product 25mg LOT 4201234B	73.7
Test Product 25mg LOT 4000381B	Test Product 25mg LOT 4201234B	54.6
Test Product 37.5mg LOT 4000381C	Test Product 37.5mg LOT 4201234C	53.4
Test Product 50mg LOT 4000381D	Test Product 50mg LOT 4201234D	53.2

* BE Batch



Jia
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CHAPTER VII: MICROBIOLOGY

[IQA ANDA Assessment Guide Reference](#)

Product Information	
ANDA Number	214068
Assessment Cycle Number	MR03
Drug Product Name / Strength	Risperidone (b) (4) Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Route of Administration	Intramuscular Injection
Applicant Name	Teva Pharmaceuticals USA, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: view justification statements found at: [Justification Statements](#)

N/A
Other (Requires Division Director Approval) – Assessor writes-in justification here if “other” selected as theme.

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0021	2/27/2023
0022	3/23/2023
0024	7/6/2023

Highlight Key Issues from Last Cycle and Their Resolution: A complete response letter (CRL) was issued on March 25, 2022 regarding deficiencies related to drug product, the DS manufacturing facility following Agency inspection, manufacturing process, labeling, and pharmacology/toxicology. Quality Microbiology was previously adequate.

Remarks: The 2/27/23 ANDA amendment is a response to the CRL dated 3/25/22 and references a post-CRL preliminary response dated 4/21/22 and an Agency email correspondence dated 7/8/22. A subsequent amendment to the CRL response was submitted on 3/23/23.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): Not applicable

Supporting Documents:

A214068MR01.docx (dated 5/21/2020; Overall inadequate, A214068MR02.docx (dated 12/23/2021; adequate) for original ANDA reviews.

Select Number of Approved Comparability Protocols: 0

Product Quality Microbiology Assessment

The proposed drug product, Risperidone (b) (4) Injection 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a 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). The product (b) (4)

(b) (4). The provided diluent is (b) (4).

The ANDA was previously adequate for Quality Microbiology.

The 2/27/23 ANDA amendment is a response to the CRL dated 3/25/22. The amendment proposes a change (b) (4)

(b) (4)
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(b) (4) There are no changes to the manufacturing process parameters or DP manufacturing facility.

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R REGIONAL INFORMATION

- **Executed Batch Records**

(b) (4)

Assessment: Adequate

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable

Primary Microbiology Assessor Name and Date: Dacie R. Bridge, July 7, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yan Zheng, Ph.D., July 7, 2023



Dacie
Bridge

Digitally signed by Dacie Bridge
Date: 7/11/2023 07:45:48AM
GUID: 5a994d0c0051111bec366cf8880c9f85



Yan
Zheng

Digitally signed by Yan Zheng
Date: 7/11/2023 07:42:52AM
GUID: 58ca9ce301e697996a209b08cf0d70b6



Jin
Xu

Digitally signed by Jin Xu
Date: 11/02/2023 11:48:04AM
GUID: 544fe030000ef07a52f9f2ca8154764c

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Risperidone
ANDA Number	214068
Applicant Name	Teva Pharmaceuticals USA, Inc.
Assessment Cycle Number	3a
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Risperidone drug substance is assessed for control critical quality attributes. DMF (b) (4) is adequate as of 10/19/2021 and LoA is provided. The drug substance remains adequate from the quality perspective per Review#3a.

List Submissions being assessed (Table):

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019
Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020

Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020
Seq.008 Multiple Categories/Subcategories (DMF (b) (4) LOA)	05/07/2020
Seq. 0007 Response to IR from CDRH	04/29/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021
Seq.0018 Response to IR (Microbiology)^	12/07/2021
Seq.0019 Post-CR Meeting Request^	04/01/2022
Seq.0020 General Correspondence for additional DS skid^	06/08/2022
Seq.0021 Response to CR-Major^	02/27/2023
Seq.0022 Amendment to CR Response (Reintroducing an API source of Jubilant)^	03/23/2023

*Review #2

^Review#3

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*): NA

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

INN Name

Risperidone

Chemical Abstract Service (CAS) Number

106266-06-2

Chemical Name(s)

4H-Pyrido[1,2- α]pyrimidin-4-one,3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidiny]ethyl]-6,7,8,9-tetrahydro-2-methyl

Or

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Source: DMF: (b) (4))

USAN Name

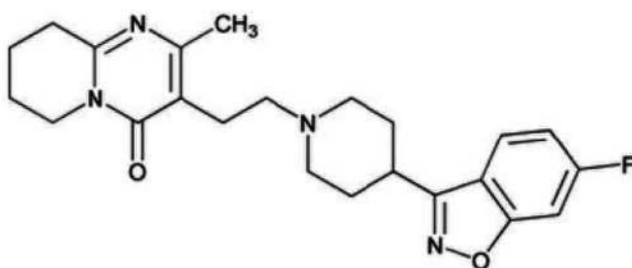
Risperidone

IUPAC Name

(3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one (Source: PubChem¹)

¹URL: <https://pubchem.ncbi.nlm.nih.gov/compound/5073#section=Crystal-Structures>

Structural Formula



Molecular Formula

C₂₃H₂₇FN₄O₂

Relative Molecular Mass

410.48

Pharmacological Class

Antipsychotic

Physical Description: White or almost white powder.

(b) (4)

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R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: NA

Lifecycle Management Considerations: NA

DRUG SUBSTANCE LIST OF DEFICIENCIES: None

Primary Drug Substance Assessor Name and Date: Greg Huang 05/01/2020, 06/01/2020 (#1), 02/11/2022 (#2)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/26/2020 (Review 1); 2/17/2022 (Review #2)

CHAPTER II: DRUG PRODUCT

IQA ANDA Assessment Guide Reference

Product Information	Risperidone for Injectable Suspension contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The product is a combination of extended-release microspheres for injection and diluent for parenteral use. The product is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles.
ANDA Number	214068
Assessment Cycle Number	3a
Drug Product (DP) Name / Strength	12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial
Route of Administration	Intramuscular deltoid or gluteal injection.
Drug Product Manufacturer	Pharmathen International S.A
RLD/RS Information (Brand Name of Product, Applicant)	RISPERDAL CONSTA® (risperidone) (b) (4) injection in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone by Janssen Pharmaceuticals Inc.
RLD/RS Number	N021346
Proposed Indication	Risperidone for Injectable Suspension is indicated for the treatment of schizophrenia. It should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection.

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

The proposed Risperidone for Injectable Suspension for (b) (4) injection (LAI) is a complex and combination drug product, with no generic drug product approved so far. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability. For the leachables (b) (4) the applicant provided toxicology assessment, for which P/T consult review is deemed adequate. (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #3a	Comments
Chemical Stability (All CQAs)	45 Medium	(b) (4)	Low	(b) (4)

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	36 Medium		Low	
Other CQAs	36 Medium		Low	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019

Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) ((b) (4) LOA)	04/27/2020
Seq.0008 Multiple Categories/Subcategories (DMF (b) (4) LOA)	05/07/2020
Seq. 0007 Response to IR from CDRH	04/29/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021
Seq.0018 Response to IR (Microbiology)^	12/07/2021
Seq.0019 Post-CR Meeting Request^	04/01/2022
Seq.0020 General Correspondence for additional DS skid^	06/08/2022
Seq.0021 Response to CR-Major^	02/27/2023
Seq.0022 Amendment to CR Response (Reintroducing an API source of Jubilant)^	03/23/2023
Seq.0024 IR Response\$	07/06/2023

* Review #2

^ Review#3

\$ Review#3a

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): None

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- USP monograph for Drug Product and compliance (current USP) – status: N/A
- Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data complies with

*revised specifications (if applicable) to confirm shelf life proposal:
(Refer to Biopharmaceutic Assessment)*

- *Elemental impurity compliance with ICH Q3D – status: **Adequate***
- *Number of Comparability protocols included: **0***

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Risperidone (b) (4) Injection is an extended-release microspheres formulation which 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. The diluent for parenteral use is a clear, colorless solution.

The current formulation was deemed Qualitatively and Quantitatively the same by the OGD through responses to controlled correspondences, 1524801, 1524802, 1524803, 1524804 and 02407. A copy of the controlled correspondences is included in Module 1.2.

Table 1: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 12.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	12.5 mg (label claim) (b) (4)	(b) (4)	(b) (4)	12.5 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		41.0 mg (label claim)	100.0		43.0 mg ⁽⁵⁾	100	--

Table 6: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 25 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	25.0 mg (label claim)	(b) (4)	(b) (4)	25 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)							
Total weight - risperidone microspheres		78.0 mg (label claim)	100.0		81.0 mg ⁽⁵⁾	100	--
(b) (4)							

Table 11: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 37.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w)	Function
Risperidone (base)	37.5 mg (label claim)	(b) (4)	(b) (4)	37.5 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		116.0 mg (label claim)	100.0		120.0 mg ⁽⁵⁾	100	--

(b) (4)

Table 16: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 50 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	50.0 mg (label claim) (b) (4)	(b) (4)	(b) (4)	50 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)							
Total weight - risperidone microspheres		152.0 mg (label claim)	100.0		156.0 mg ⁽³⁾	100	-- (b) (4)

Table 21: Quantitative Composition and Function of the Microspheres and Diluent

Ingredient	Quality Standards	Function	12.5 mg/ vial				25 mg/vial				37.5 mg/vial				50 mg/vial			
			mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)
Microspheres in vial																		
Risperidone			USP		API													
75:25 Polylactide co-glycolide (b) (4)																		

Ingredient	Quality Standards	Function	12.5 mg/ vial			25 mg/vial			37.5 mg/vial			50 mg/vial		
			mg/ unit ²	mg injected ³	%/ unit	% reconstituted Inject ed (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Inject ed (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Inject ed (w/w)
Citric acid anhydrous														(b) (4)
Sodium chloride														
Sodium hydroxide														
Water for injection														
Total Diluent (mg)	-	-	(b) (4)	100.0			(b) (4)	100.0	-	-	(b) (4)	100.0	-	-
Total Weight of reconstituted suspension (mg)	-	-	-	2,064.8	-	100.0	-	2,097.6	-	100.0	-	2,163.2	-	100.0
														(b) (4)

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R REGIONAL INFORMATION

Environmental

Assessment: Adequate
Refer to Module 1.12.14.

Methods Validation or Verification Package

Assessment: Adequate
Refer to 3.2.R.

Comparability Protocols

Assessment: N/A
No comparability protocol proposed.

Lifecycle Management Consideration

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

None

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/03/2020 (Review#1), 09/15/2020 (#1b), 02/16/2021 (#2), 04/04/2023 (#3), 08/17/2023 (#3a)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/29/2020 (Review 1); 2/19/2022 (Review 2); 8/18/2023

CHAPTER IV: LABELING

[IQA ANDA Assessment Guide Reference](#)

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/01/2020

Secondary Drug Product Assessor Name and Date: Jin Xu, 5/29/2020



Jin
Xu

Digitally signed by Jin Xu
Date: 10/27/2023 10:50:28AM
GUID: 544fe030000ef07a52f9f2ca8154764c



Greg
Huang

Digitally signed by Greg Huang
Date: 10/27/2023 10:55:26AM
GUID: 531549bf000057f8a3471efdb18b5d7f

MANUFACTURING INTEGRATED ASSESSMENT

Review #3

Application ID	ANDA 214068
Drug Product Name	Risperidone (b) (4) Injection
Strengths	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Dosage Form	Injectable
Administration Route	Intramuscular
Indication	• Schizophrenia • Bipolar Disorder
Applicant Name	Teva Pharmaceuticals USA, Inc.
RLD Number	21346
Primary Reviewer	Raeann Wu
Secondary Reviewer	Ying Zhang/Cassandra Abellard

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

Risperidone (b) (4) Injection, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular injection. The risperidone 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. The diluent for parenteral use is a clear, colorless solution. The microspheres are suspended in the diluent prior to injection.

The manufacturing of diluent includes the following (b) (4)

The manufacturing of the risperidone microspheres (powder) includes the following (b) (4)

The manufacturing of kit includes the following unit operations: (b) (4)

(b) (4). Justification is provided in the process development report and is adequate.

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V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Yong Wu 2/6/2020 5/8/2020 5/28/2020 6/9/2020 8/27/2020 9/10/2020	Yubing Tang 2/14/2020 5/25/2020 5/31/2020 6/9/2020 09/07/2020 9/10/2020	9/10/2020	CR Major	Withheld
2	Raeann Wu	Ying Zhang	3/10/2022	CR Major	Withheld
3a	Raeann Wu	Cassandra Abellard	8/28/2023	IR	Approve
3b	Raeann Wu	Cassandra Abellard	10/17/2023	Adequate	Approve



Raeann
Wu

Digitally signed by Raeann Wu
Date: 10/17/2023 05:05:32PM
GUID: 5d39e659001a3e5cf21357e71e829161



Cassandra
Abellard

Digitally signed by Cassandra Abellard
Date: 10/17/2023 05:25:57PM
GUID: 564f42da0022c9f20052124ea8956e48

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☐ Complete Response-Minor + Travel Comment
☒ Complete Response-Major
☐ Complete Response-Major + Travel Comment
☐ Complete Response-Major-Facilities Only
☐ Complete Response-Deferred-Travel Restriction-COVID19 <i>Choose this option when both of the following apply:</i> • <i>Quality is Adequate except for inspection deferred due to travel restriction</i> <u>AND</u> • <i>OGD has deficiencies (e.g., Bioequivalence, Labeling, etc.)</i>

ANDA #214068 Assessment #2

Drug Product Name	Risperidone
Dosage Form	Injectable
Strength	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0018	12/07/2021	Quality
eCTD 0017	08/19/2021	Quality
eCTD 0016	05/27/2021	Quality
eCTD 0014	08/04/2020	Quality
eCTD 0013	07/24/2020	Quality
eCTD 0012	07/20/2020	Quality
eCTD 0008	05/07/2020	Quality
eCTD 0007	04/29/2020	Quality
eCTD 0005	04/09/2020	Quality
eCTD 0002	02/03/2020	Quality
eCTD 0001	12/16/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Greg Huang	Jin Xu
Drug Product	Greg Huang	Jin Xu
Manufacturing	Raeann Wu	Ying Zhang
Microbiology	Jennifer Sykora	Yan Zheng
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Suzan Ghodasara	
Application Technical Lead	Jin Xu	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

*If Active Pharmaceutical Ingredient (API) data is provided as part of ANDA submission, list Division of Lifecycle API (DLAPI) Assessor

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the ANDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Risperidone USP	Adequate	10/19/2021	
	III		(b) (4)			
	III					
	III					
	III					
	III					
	IV					

(b) (4)	V	(b) (4)			
	V				
	Other				
	Other				

B. Other Documents: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
NDA	N021346	RLD

4. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology	Complete	Inadequate - Major	2/14/2022	Chanchal Gupta
CDRH				
Clinical				
Other				

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

For more details about the items in this template, please see the [Abbreviated Executive Summary \(CR Only\) chapter of the ANDA IQA Guide](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete Response-Major

The ANDA has been assessed by DS, DP, Process and Facilities, and Microbiology. There are still issues pending resolution in DP, Process and Facilities. The Facilities and the DP deficiencies are classified as Major.

II. QUALITY ASSESSMENT OVERVIEW

III. A. DP OVERALL RECOMMENDATION: Inadequate-Major

Drug Substance: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Drug Product: Inadequate-Major

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

The drug product deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractable and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

2. Insert additional **Major** justification below (if necessary)

Insert brief summary of Drug Product assessment and deficiencies.

Labeling: N/A

B. Manufacturing:**a. Process: Inadequate-Minor**

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

Summary:**b. Facilities: Inadequate-Major**

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

2. Insert additional **Major** justification below (if necessary)

Summary:

Insert brief summary of Manufacturing Facilities assessment and deficiencies.

C. Biopharmaceuticals: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

D. Microbiology: Adequate

1. Provide Justification, if **Major**: (Click link to view [Justification Statements](#))

2. Insert additional **Major** justification below (if necessary)

E. List of Deficiencies for Complete Response

Overall Quality Deficiencies - Optional (*Deficiencies that affect multiple sub-disciplines*)

N/A

Drug Substance Deficiencies

N/A

Drug Product Deficiencies

1. (b) (4)
2. (b) (4)

Labeling Deficiencies (*Please contact OGD if you identify any Labeling deficiencies with your comments*)

N/A

Manufacturing Deficiencies

Facility:

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Process:

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
2. [REDACTED] (b) (4)
[REDACTED]
3. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
4. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

Biopharmaceutics Deficiencies -None

Microbiology Deficiencies -None

Pharm/Tox Consult for Drug Product

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

(b) (4)

[Redacted text block]

a. (b) (4)

[Redacted text block]

b. (b) (4)

[Redacted text block]

c. (b) (4)

[Redacted text block]

The acceptability of your safety assessment will be a review issue upon submission.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment(s) in your response:

N/A

Application Technical Lead Name and Date: Jin Xu, 3/14/2022



Jin
Xu

Digitally signed by Jin Xu
Date: 3/14/2022 05:06:55PM
GUID: 544fe030000ef07a52f9f2ca8154764c

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 214068
Drug Product Name	Risperidone (b) (4) Injection
Strengths	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Dosage Form	Injectable
Administration Route	Intramuscular
Indication	- Schizophrenia - Bipolar Disorder
Applicant Name	Teva Pharmaceuticals USA, Inc.
RLD Number	21346
Primary Reviewer	Raeann Wu
Secondary Reviewer	Ying Zhang

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

THEME: Inadequate Facility - cGMP Withhold

JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary:

Risperidone (b) (4) Injection, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular injection. The risperidone 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. The diluent for parenteral use is a clear, colorless solution. The microspheres are suspended in the diluent prior to injection.

The manufacturing of diluent includes the following (b) (4)

[REDACTED]

The manufacturing of the risperidone microspheres (powder) includes the following (b) (4)

[REDACTED]

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(b) (4)

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Yong Wu 2/6/2020 5/8/2020 5/28/2020 6/9/2020 8/27/2020 9/10/2020	Yubing Tang 2/14/2020 5/25/2020 5/31/2020 6/9/2020 09/07/2020 9/10/2020	9/10/2020	CR Major	Withheld
2	Raeann Wu	Ying Zhang	3/10/2022	CR Major	Withheld
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.



Raeann
Wu

Digitally signed by Raeann Wu
Date: 3/10/2022 10:57:39AM
GUID: 5d39e659001a3e5cf21357e71e829161



Ying
Zhang

Digitally signed by Ying Zhang
Date: 3/10/2022 05:21:38PM
GUID: 508da70d000290426d6c95419a1f4c28

CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Risperidone
ANDA Number	214068
Applicant Name	Teva Pharmaceuticals USA, Inc.
Assessment Cycle Number	2
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Adequate

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Risperidone drug substance is assessed for control critical quality attributes. DMF# (b) (4) is adequate as of 10/19/2021 and LoA is provided. The drug substance is adequate from the quality perspective.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019
Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020

Seq.0007 Response to IR from CDRH	04/29/2020
Seq.0008 Multiple Categories/Subcategories (DMF (b) (4) LOA)	05/07/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021

*covered under current Review #2

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): NA

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

INN Name

Risperidone

Chemical Abstract Service (CAS) Number

106266-06-2

Chemical Name(s)

4H-Pyrido[1,2- α]pyrimidin-4-one,3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl

Or

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2- α]pyrimidin-4-one (Source: DMF: (b) (4))

USAN Name

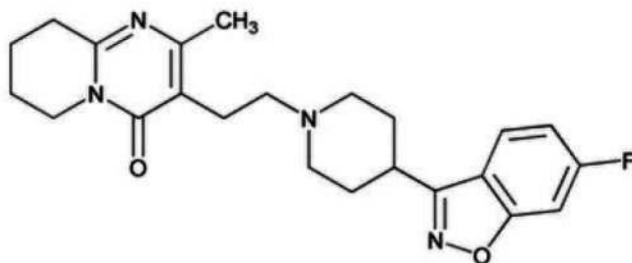
Risperidone

IUPAC Name

(3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2- α]pyrimidin-4-one (Source: PubChem¹)

¹URL: <https://pubchem.ncbi.nlm.nih.gov/compound/5073#section=Crystal-Structures>

Structural Formula



Molecular Formula

C₂₃H₂₇FN₄O₂

Relative Molecular Mass

410.48

Pharmacological Class

Antipsychotic

Physical Description: White or almost white powder.

(b) (4)

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R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: NA

Lifecycle Management Considerations: NA

DRUG SUBSTANCE LIST OF DEFICIENCIES: None

Primary Drug Substance Assessor Name and Date: Greg Huang 05/01/2020, 06/01/2020 (#1), 02/11/2022 (#2)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/26/2020 (Review 1); 2/17/2022 (Review #2)

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Risperidone for Injectable Suspension contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The product is a combination of extended-release microspheres for injection and diluent for parenteral use. The product is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles.
ANDA Number	214068
Assessment Cycle Number	2
Drug Product (DP) Name / Strength	12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial
Route of Administration	Intramuscular deltoid or gluteal injection.
Drug Product Manufacturer	Pharmathen International S.A
RLD/RS Information (Brand Name of Product, Applicant)	RISPERDAL CONSTA® (risperidone) long-acting injection in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone by Janssen Pharmaceuticals Inc.
RLD/RS Number	N021346
Proposed Indication	Risperidone for Injectable Suspension is indicated for the treatment of schizophrenia. It should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection.

Assessment Recommendation: Inadequate - Major

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

The proposed Risperidone for Injectable Suspension for (b) (4) injection (LAI) is a complex and combination drug product, with no generic drug product approved so far. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability. A

deficiency (b) (4)

(b) (4)

Pharm/Tox review cited major deficiencies in

(b) (4)

.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #2	Comments
Chemical Stability (All CQAs)	45 Medium	(b) (4)	Low	(b) (4)

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	36 Medium		Low	
Other CQAs	36 Medium		High	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.0001 Original Submission	12/16/2019
Seq.0002 Response to filing IR	02/03/2020
Seq.0004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.0005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.0006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020
Seq.0008 Multiple Categories/Subcategories (DM (b) (4) LOA)	05/07/2020
Seq. 0007 Response to IR from CDRH	04/29/2020
Seq.0012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.0013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.0014 Response to the Discipline Review Letter – Facility	08/04/2020
Seq.0015 Post CR Meeting Request*	10/23/2020
Seq.0016 CR Response*	05/27/2021
Seq.0017 Response to IR (Facility)*	08/19/2021
*covered under current Review #2	

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): Deficiencies in the leachables exceeding AET and Pharm/Tox assessment.

Select Number of Approved Comparability Protocols:

0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A*
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: (Refer to Biopharmaceutic Assessment)*
- *Elemental impurity compliance with ICH Q3D – status: Adequate*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Risperidone (b) (4) Injection is an extended-release microspheres formulation which 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. The diluent for parenteral use is a clear, colorless solution.

The current formulation was deemed Qualitatively and Quantitatively the same by the OGD through responses to controlled correspondences, 1524801, 1524802, 1524803, 1524804 and 02407. A copy of the controlled correspondences is included in Module 1.2.

Table 1: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 12.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial)	RLD formulation (mg/vial)	RLD formulation (mg/vial)	RLD formulation (% w/w)	Proposed formulation (mg/vial)	Proposed formulation (mg/vial)	Proposed formulation (% w/w)	Function
Risperidone (base)	12.5 mg (label claim)	(b) (4)	(b) (4)	(b) (4)	12.5 mg	(b) (4)	(b) (4)	Active Substance
7525 polylactide-co-glycolide (PLG)		(b) (4)	(b) (4)	(b) (4)		(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres			41.0 mg (label claim)	100.0		43.0 mg ⁽⁵⁾	100	--
(b) (4)								

Table 6: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 25 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	25.0 mg (label claim) (b) (4)	(b) (4)	(b) (4)	25 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres	(b) (4)	78.0 mg (label claim)	100.0	(b) (4)	81.0 mg ⁽⁵⁾	100	--

Table 11: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 37.5 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial) (b) (4)	RLD formulation (mg/vial) (b) (4)	RLD formulation (% w/w) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (mg/vial) (b) (4)	Proposed formulation (% w/w) (b) (4)	Function
Risperidone (base)	37.5 mg (label claim) (b) (4)	(b) (4)	(b) (4)	37.5 mg (b) (4)	(b) (4)	(b) (4)	Active Substance (b) (4)
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		116.0 mg (label claim)	100.0		120.0 mg ⁽⁵⁾	100	--

(b) (4)

Table 16: Qualitative and Quantitative Comparison between the RLD's and Teva's proposed 50 mg/ vial Microsphere formulation

Ingredients	RLD formulation (mg/vial)	RLD formulation (mg/vial)	RLD formulation (% w/w)	Proposed formulation (mg/vial)	Proposed formulation (mg/vial)	Proposed formulation (% w/w)	Function
Risperidone (base)	50.0 mg (label claim)	(b) (4)	(b) (4)	50 mg	(b) (4)	(b) (4)	Active Substance
7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Total weight - risperidone microspheres		152.0 mg (label claim)	100.0		156.0 mg ⁽³⁾	100	--

(b) (4)

Table 21: Quantitative Composition and Function of the Microspheres and Diluent

Ingredient	Quality Standards	Function	12.5 mg/ vial			25 mg/vial			37.5 mg/vial			50 mg/vial			% reconstituted Injected (w/w)
			mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	mg/unit ²	mg injected ³	%/unit	% reconstituted Injected (w/w)	
Microspheres in vial															
Risperidone	USP	API												(b) (4)	
75:25 Polylactide co-glycolide														(b) (4)	
Total		--	43.0 ⁽⁵⁾		100.0	--	81.0 ⁽⁵⁾		100.0-	--	120.0 ⁽⁵⁾		100.0	--	
Diluent															
Carboxymethyl cellulose sodium salt ⁴	(b) (4)													(b) (4)	
Polysorbate 20															
Disodium hydrogen phosphate dihydrate															

Ingredient	Quality Standards	Function	12.5 mg/ vial			25 mg/vial			37.5 mg/vial			50 mg/vial		
			mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ³	%/ unit	% reconstituted Injected (w/w)
Citric acid anhydrous			(b) (4)											
Sodium chloride			(b) (4)											
Sodium hydroxide			(b) (4)											
Water for injection			(b) (4)											
Total Diluent (mg)	-	-			100.0				100.0	-			100.0	-
Total Weight of reconstituted suspension (mg)	-	-	-	2,064.8	-	100.0	-	2,097.6	-	100.0	-	2,163.2	-	100.0
(b) (4)														

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R REGIONAL INFORMATION

Environmental

Assessment: Adequate
Refer to Module 1.12.14.

Methods Validation or Verification Package

Assessment: Adequate
Refer to 3.2.R.

Comparability Protocols

Assessment: N/A
No comparability protocol proposed.

Lifecycle Management Consideration

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

1.	(b) (4)
2.	(b) (4)
3.	(b) (4)
	(b) (4)

The acceptability of your safety assessment will be a review issue upon submission.

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/03/2020 (Review#1), 09/15/2020 (#1b), 02/16/2021 (#2)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/29/2020 (Review 1); 2/19/2022 (Review 2)

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/01/2020

Secondary Drug Product Assessor Name and Date: Jin Xu, 5/29/2020



Greg
Huang

Digitally signed by Greg Huang
Date: 2/25/2022 08:42:46AM
GUID: 531549bf000057f8a3471efdb18b5d7f



Jin
Xu

Digitally signed by Jin Xu
Date: 2/25/2022 08:45:23AM
GUID: 544fe030000ef07a52f9f2ca8154764c

RECOMMENDATION

☐ Approval
☐ Complete Response-Minor
☒ Complete Response-Major
☐ Complete Response-Major-Facilities Only

ANDA #214068 Assessment #1

Drug Product Name	Risperidone
Dosage Form	Injectable
Strength	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Route of Administration	Intramuscular
Rx/OTC Dispensed	Rx
Applicant	Teva Pharmaceuticals USA, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0014	08/04/2020	Quality
eCTD 0013	07/24/2020	Quality
eCTD 0012	07/20/2020	Quality
eCTD 0008	05/07/2020	Quality
eCTD 0007	04/29/2020	Quality
eCTD 0005	04/09/2020	Quality
eCTD 0002	02/03/2020	Quality
eCTD 0001	12/16/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Anjali Bain	Benjamin Lim
Drug Product	Greg Huang	Jin Xu
Manufacturing	Yong Wu	Yubing Tang
Microbiology	Renee Marcsisin	Jesse Wells
Biopharmaceutics	Jia Yin	Ta-Chen Wu
Regulatory Business Process Manager	Temitope Oriola	
Application Technical Lead	Jin Xu	
Laboratory (OTR)		
Environmental		

QUALITY ASSESMENT DATA SHEET

[IQA ANDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Risperidone USP	Adequate	05/12/2020	Reviewe3d by Anjali Bain
	III		(b) (4)			
	III					
	III					
	III					
	III					
	IV					

(b) (4)	V	(b) (4)			
	V				
	Other				
	Other				

B. OTHER DOCUMENTS: IND, RLD, RS, Approved ANDA

Document	Application Number	Description
NDA	N021346	

4. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	Complete	Adequate	5/11/2020	Yongcheng Huang
CDRH-ODE	Complete	Adequate	9/16/2020	Shawn Shermer
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

ABBREVIATED EXECUTIVE SUMMARY (CR ONLY)

[IQA ANDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Major

One or more facilities were found inadequate at the time of action due to inspectional deficiencies. FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

II. QUALITY ASSESSMENT OVERVIEW

A. Drug Substance: Inadequate-Minor

1. Primary Justification:

N/A

2. Secondary Justification (if necessary):

N/A

3. Tertiary Justification (if necessary):

N/A

4. Insert additional justification below (if necessary)

N/A

Risperidone drug substance is assessed for control critical quality attributes. A minor deficiency regarding the drug substance storage needs to be addressed. DMF (b) (4) is adequate as of 05/12/2020 and LoA is provided.

Drug Product: Inadequate-Minor

1. Primary Justification:

N/A

2. Secondary Justification (if necessary):

N/A

3. Tertiary Justification (if necessary):

N/A

4. Insert additional justification below (if necessary)

N/A

The proposed Risperidone for Injectable Suspension for (b) (4) injection (LAI) is a complex and combination drug product. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability, which have deficiencies to be addressed (refer to the List of Deficiencies at the end of the assessment document).

Labeling: Choose an item.

N/A

B. Manufacturing: Inadequate-Major

1. Primary Justification:

The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

2. Secondary Justification (if necessary)

N/A

3. Tertiary Justification (if necessary):

N/A

4. Insert additional justification below (if necessary)

N/A

Manufacturing Summary:

Risperidone Long Acting Injection, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular injection. The risperidone 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. The diluent for parenteral use is a clear, colorless solution. The microspheres are suspended in the diluent prior to injection.

The manufacturing of diluent includes (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Information Request regarding manufacturing process deficiencies were sent on DRL. (b) (4)

[REDACTED]

(b) (4)

Therefore, ANDA 214068 is NOT recommended for approval in its present form from process and facility review perspective.

C. Biopharmaceutics: Inadequate-Minor

1. Primary Justification:

N/A

2. Secondary Justification (if necessary):

N/A

3. Tertiary Justification (if necessary):

N/A

4. Insert additional justification below (if necessary)

N/A

The reference listed drug (RLD) for the proposed drug product is Risperdal Consta® (risperidone) (b) (4) Injection under NDA 021346 held by Janssen Pharmaceuticals Inc. The proposed formulation is deemed by Office of Generic Drug (OGD) to be qualitatively and quantitatively same as the RLD.

The proposed drug product is provided as a dose pack, consisting of a vial containing the risperidone powder (risperidone encapsulated in poly-(d,l-lactide-co-glycolide) acid (PLGA) microspheres), a pre-filled syringe containing 2 mL of diluent for extended-release injectable suspension of risperidone, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular (IM) injection. The risperidone powder needs to be suspended in the diluent prior to IM injection. (b) (4)

(b) (4)

The Applicant adopted the dissolution method in the product specific guidance (PSG) for risperidone IM injection and investigated the discriminating ability of the method against several process parameters

(b) (4)

The Biopharmaceutics deficiencies will be conveyed to the Applicant in Complete Response Letter (CRL).

D. Microbiology: Inadequate-Minor

1. Primary Justification:

N/A

2. Secondary Justification (if necessary):

N/A

3. Tertiary Justification (if necessary):

N/A

4. Insert additional justification below (if necessary)

N/A

The drug product is (b) (4)

(b) (4)

Microbiology review is inadequate.

E. List of Deficiencies for Complete Response

1) Overall Quality Deficiencies - Optional (Deficiencies that affect multiple sub-disciplines)

N/A

2) Drug Substance Deficiencies

1. (b) (4)

3) Drug Product Deficiencies

1. (b) (4)
2. (b) (4)
3. (b) (4)
4. (b) (4)

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18. [REDACTED] (b) (4)
19. [REDACTED] (b) (4)
20. [REDACTED] (b) (4)
21. [REDACTED] (b) (4)
22. [REDACTED] (b) (4)
23. [REDACTED] (b) (4)
24. [REDACTED] (b) (4)
25. [REDACTED] (b) (4)
26. [REDACTED] (b) (4)

4) Labeling Deficiencies (Please contact OGD if you identify any Labeling deficiencies with your comments)

N/A

5) Manufacturing Deficiencies
a. Process

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[REDACTED] (b) (4)
[REDACTED]

33. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

34. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

35. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

b. Facility

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

6) Biopharmaceutics Deficiencies

1. Provide the aqueous solubility data for the drug substance, risperidone, in your drug product over the (b) (4) to support your claim regarding the solubility.
2. We acknowledge that you have adopted the dissolution method in the product specific guidance (PSG) for risperidone intramuscular injection for your proposed drug product. It is noted that for 12.5 mg strength, 100 mL medium volume is proposed, while for the other strengths (25 mg, 37.5 mg, and 50 mg), 200 mL medium volume is proposed. Unless you have convincing or appropriate rationale and justification for using different medium volumes for different strengths, we request that optimize the dissolution method using the same medium volume for all strengths of your product.
3. We acknowledge that you have evaluated the discriminating ability of your proposed dissolution method. However, the changes of the tested critical process parameters (CPPs) are beyond what the Agency typically recommended range, i.e., $\pm 20\%$ of target value, without appropriate justification. Re-evaluate the discriminating ability of your proposed dissolution method against critical material attributes (CMAs) and CPPs that affect dissolution of your product. Submit the following information and data to demonstrate the discriminating ability of the dissolution method:
 - a) A list of CMAs and CPPs affecting the dissolution of your product.
 - b) Percentage change of CMAs and CPPs of the tested aberrant batches.
 - c) Complete in vitro dissolution data (individual, mean, SD, RSD) and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference/target drug products.
 - d) If available, data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference/target drug product.

Note that, if different dissolution medium volume is used for different strengths of your product, discriminating ability of the dissolution method needs to be demonstrated for each dissolution medium volume.

4. In your Table 34 of Pharmaceutical Development Report, one of the tested dissolution (b) (4). In Table 35, Table 36, Figure 26, and Figure 27 of the same document, (b) (4). Clarify your tested dissolution medium pH and update the information in your Pharmaceutical Development Report.

7) Microbiology Deficiencies

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]:
 - a. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
 - i. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].
 - ii. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].
 - b. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
 - i. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
 - c. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
 - i. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
 - d. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
 - i. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

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8. [REDACTED] (b) (4)
- a. [REDACTED] (b) (4)
- b. [REDACTED] (b) (4)

8) Other Deficiencies (Specify discipline, such as Environmental)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

An inspection of [REDACTED] (b) (4)

[REDACTED]

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>

Application Technical Lead Name and Date: Jin Xu, 9/21/2020



Jin
Xu

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CHAPTER I: DRUG SUBSTANCE

[IQA ANDA Assessment Guide Reference](#)

Drug Substance Name	Risperidone
ANDA Number	214068
Applicant Name	Teva Pharmaceuticals USA, Inc.
Assessment Cycle Number	1b
DMF Number (If Applicable)	(b) (4)
DMF Status	Adequate
DMF Holder	(b) (4)

Assessment Recommendation: Inadequate - Minor

Theme:

☒ N/A	☐ Other (Requires Division Director Approval)
☐ DMF	☐ Due to Consult
☐ New DS Batch	

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

Risperidone drug substance is assessed for control critical quality attributes. A minor deficiency regarding the drug substance storage needs to be addressed. DMF# (b) (4) is adequate as of 05/12/2020 and LoA is provided.

List Submissions being assessed (Table):

Document(s) Assessed	Date Received
Seq.001 Original Submission	12/16/2019
Seq.002 Response to filing IR	02/03/2020
Seq.004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020
Seq.005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): NA

Select Number of Approved Comparability Protocols: 0

S.1 GENERAL INFORMATION

INN Name

Risperidone

Chemical Abstract Service (CAS) Number

106266-06-2

Chemical Name(s)

4H-Pyrido[1,2- α]pyrimidin-4-one,3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidiny]ethyl]-6,7,8,9-tetrahydro-2-methyl

Or

3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2- α]pyrimidin-4-one (Source: DMF: (b) (4))

USAN Name

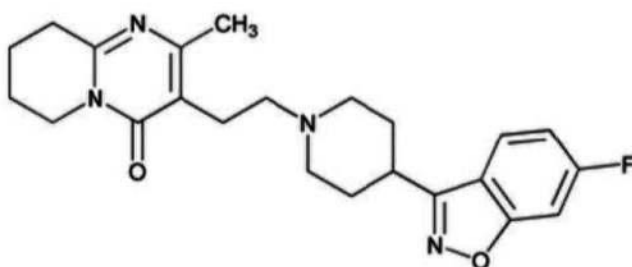
Risperidone

IUPAC Name

(3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2- α]pyrimidin-4-one (Source: PubChem¹)

¹URL: <https://pubchem.ncbi.nlm.nih.gov/compound/5073#section=Crystal-Structures>

Structural Formula



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R REGIONAL INFORMATION

Comparability Protocols: None

Assessment: NA

Lifecycle Management Considerations: NA

DRUG SUBSTANCE LIST OF DEFICIENCIES

1. (b) (4)

Primary Drug Substance Assessor Name and Date: Greg Huang 05/01/2020, 06/01/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/26/2020

CHAPTER II: DRUG PRODUCT

[IQA ANDA Assessment Guide Reference](#)

Product Information	Risperidone for Injectable Suspension contains risperidone, an atypical antipsychotic belonging to the chemical class of benzisoxazole derivatives. The product is a combination of extended-release microspheres for injection and diluent for parenteral use. The product is provided as a dose pack, consisting of a vial containing the microspheres, a pre-filled syringe containing the diluent, a vial adapter, and two Terumo SurGuard® 3 Needles.
ANDA Number	214068
Assessment Cycle Number	1b
Drug Product (DP) Name / Strength	12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone per vial
Route of Administration	Intramuscular deltoid or gluteal injection.
Drug Product Manufacturer	Pharmathen International S.A
RLD/RS Information (Brand Name of Product, Applicant)	RISPERDAL CONSTA® (risperidone) long-acting injection in dosage strengths of 12.5 mg, 25 mg, 37.5 mg, or 50 mg risperidone by Janssen Pharmaceuticals Inc.
RLD/RS Number	N021346
Proposed Indication	Risperidone for Injectable Suspension is indicated for the treatment of schizophrenia. It should be administered every 2 weeks by deep intramuscular (IM) deltoid or gluteal injection.

Assessment Recommendation: Inadequate - Minor

Theme:

☒ N/A	☐ Unacceptable Analytical Methods
☐ Unqualified Impurity	☐ Application Quality
☐ New DP Batch	☐ Pharmaceutical Equivalence
☐ Product Design	☐ Product Safety
☐ Failing Stability Data	☐ Other (Requires Division Director Approval)
☐ Application Completeness	☐ Due to Consult

Justification: view justification statements found at: [Justification Statements](#)

Paste appropriate justification statement(s) here or insert "N/A" if not applicable.
Other (Requires Division Director Approval)- Assessor writes justification here if "other" selected as theme.

Assessment Summary:

The proposed Risperidone for Injectable Suspension for long-acting injection (LAI) is a complex and combination drug product, with no generic drug product approved so far. Quality assessment is conducted for the formulation and product development, critical quality attributes of Excipients, Diluent, Microsphere Drug Powder and Injection Administration Kit, Specifications of Excipients and Finished Drug Product, CCS Components and Stability, which have deficiencies to be addressed (refer to the List of Deficiencies at the end of the assessment document).

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking After Assessment Cycle #1	Comments
Chemical Stability (All CQAs)	45 Medium	(b) (4)	Medium	(b) (4)

		(b) (4)		(b) (4)
Meeting USP <1> Requirement	36 Medium		Medium	
Other CQAs	36 Medium		Medium	

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Seq.001 Original Submission	12/16/2019
Seq.002 Response to filing IR	02/03/2020
Seq.004 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples)	03/27/2020

Seq.005 Multiple Categories/Subcategories (Process/Facility IR Request, including High Resolution Photos of Test and RLD Samples)	04/09/2020
Seq.006 Multiple Categories/Subcategories (Clinical IR Request, including High Resolution Photos of Test and RLD Samples) (DMF (b) (4) LOA)	04/27/2020
Seq.008 Multiple Categories/Subcategories (DMF (b) (4) LOA)	05/07/2020
Seq.012 Response to the Discipline Review Letter – Bioequivalence	07/20/2020
Seq.013 Response to the Discipline Review Letter – CDRH	07/24/2020
Seq.014 Response to the Discipline Review Letter – Facility	08/04/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List Bullet Points with Key Information and Update as Needed): Refer to List of Deficiencies

Select Number of Approved Comparability Protocols: 0

List Current Quality Endorsement Status:

- *USP monograph for Drug Product and compliance (current USP) – status: N/A*
- *Dissolution status: specifications are/are not finalized with Biopharmaceutics, and implemented, and stability data complies with revised specifications (if applicable) to confirm shelf life proposal: (Refer to Biopharmaceutic Assessment)*
- *Elemental impurity compliance with ICH Q3D – status: Inadequate*
- *Number of Comparability protocols included: 0*

P.1 DESCRIPTION AND COMPOSITION

Component/Composition Table

Risperidone Long Acting Injection is an extended-release microspheres formulation which 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. The diluent for parenteral use is a clear, colorless solution.

The current formulation was deemed Qualitatively and Quantitatively the same by the OGD through responses to controlled correspondences, 1524801, 1524802, 1524803, 1524804 and 02407. A copy of the controlled correspondences is included in Module 1.2.

Table 2: Quantitative Composition and Function of the Microspheres and Diluent

Ingredient	Quality Standards	Function	12.5 mg/ vial			25 mg/vial			37.5 mg/vial			50 mg/vial						
			mg/ unit ²	mg injected ¹	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ¹	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ¹	%/ unit	% reconstituted Injected (w/w)	mg/ unit ²	mg injected ¹	%/ unit	% reconstituted Injected (w/w)
Risperidone	USP	API	(b) (4)															
75:25 Polylactide-co-glycolide	Non-compendial		(b) (4)															
(b) (4)			(b) (4)															
Total		--	43.0	(b) (4)	--	100.0	81.0	(b) (4)	100.0	--	120.0	(b) (4)	100.0	--	156.0	(b) (4)	100.0	--
			Diluent															

Environmental

Assessment: Adequate

Refer to Module 1.12.14.

Methods Validation or Verification Package

Assessment: Adequate

Refer to 3.2.R.

Comparability Protocols

Assessment: N/A

No comparability protocol proposed.

Lifecycle Management Consideration

N/A

DRUG PRODUCT LIST OF DEFICIENCIES

1.	(b) (4)
2.	(b) (4)
3.	(b) (4)
4.	(b) (4)
5.	(b) (4)
6.	(b) (4)
7.	(b) (4)
8.	(b) (4)

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	(b) (4)
23.	(b) (4)
24.	(b) (4)
25.	(b) (4)
26.	(b) (4)

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/03/2020 (Review#1), 09/15/2020 (#1b)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jin Xu, 5/29/2020

CHAPTER IV: LABELING

IQA ANDA Assessment Guide Reference

R REGIONAL INFORMATION

1.14 Labeling

Labeling & Prescribing Information

DESCRIPTION (Rx insert or Active Ingredient(s), and Inactive Ingredients in DRUG FACTS for OTC):

Is the information accurate? ☒ Yes ☐ No

If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No

If "Yes," does labeling have accurate USP statement in the DESCRIPTION (for Rx) or Other Information section of DRUG FACTS (for OTC)?

☐ Yes ☐ No ☐ Statement not needed

If NO, what is/are the needed statement(s)? _____

HOW SUPPLIED section (Rx insert) or Storage (in DRUG FACTS for OTC)

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Is tamper evident feature provided in the container/closure for the OTC products or Controlled Substance (CII – CIV) products? ☐ Yes ☐ No
☒ N/A (NOT OTC or Controlled Substance)

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es): N/A

ANDA Strength	Length (MM)	Imprint Code

Send issue to the Labeling assessor through the Platform with a list of quality-related labeling deficiencies and also record reference number or link for all the issues: N/A

Issue Description	Issue Reference Number or Link

LABELING LIST OF DEFICIENCIES

N/A

Primary Drug Product Assessor Name and Date: Greg Huang, 05/20/2020, 06/01/2020

Secondary Drug Product Assessor Name and Date: Jin Xu, 5/29/2020



Jin
Xu

Digitally signed by Jin Xu
Date: 9/15/2020 01:56:03PM
GUID: 544fe030000ef07a52f9f2ca8154764c



Greg
Huang

Digitally signed by Greg Huang
Date: 9/15/2020 01:51:25PM
GUID: 531549bf000057f8a3471efdb18b5d7f

MANUFACTURING INTEGRATED ASSESSMENT

Application ID	ANDA 214068
Drug Product Name	Risperidone (b) (4) Injection
Strengths	12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial
Dosage Form	Injectable
Administration Route	Intramuscular
Indication	- Schizophrenia - Bipolar Disorder
Applicant Name	Teva Pharmaceuticals USA, Inc.
RLD Number	21346

I. Manufacturing Summary

Facility Assessment Recommendation: Inadequate - Major

#1 THEME: Inadequate Facility - cGMP Withhold

#1 JUSTIFICATION: The facilities deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

#2 THEME: Other "pending inspection due to travel restrictions"

Process Assessment Recommendation: Inadequate - Minor

Assessment Summary:

Risperidone (b) (4) Injection, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular injection. The risperidone 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. The diluent for parenteral use is a clear, colorless solution. The microspheres are suspended in the diluent prior to injection.

The manufacturing of diluent includes the following (b) (4)

[REDACTED]

The manufacturing of the risperidone microspheres (powder) includes the following (b) (4)

[REDACTED]



VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Yong Wu 2/6/2020 5/8/2020 5/28/2020 6/9/2020 8/27/2020 9/10/2020	Yubing Tang 2/14/2020 5/25/2020 5/31/2020 6/9/2020 09/07/2020 9/10/2020	9/10/2020	CR Major	Withheld
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.
Choose an item.			Click to enter a date.	Choose an item.	Choose an item.



Yong
Wu

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Date: 9/10/2020 03:35:13PM
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Yubing
Tang

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Date: 9/10/2020 10:45:12PM
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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: October 2, 2020

TO: Bing Li, Ph.D.
Director (Acting)
Office of Bioequivalence
Office of Generic Drugs

FROM: Amanda Lewin, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

Li-Hong Yeh, Ph.D.
DNDSI/OSIS

Erin McDowell, B.S., B.A.
DNDSI/OSIS

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Remote Record Review (RRR) of multiple clinical sites
in support of ANDA (b) (4) and ANDA 214068

1. RRR Summary

OSIS conducted a Remote Record Review (RRR) of the clinical portion of studies (b) (4) and CAC15003 (ANDA 214068, risperidone) conducted at the following clinical sites:

- Site 1: State Psychiatric Hospital - Pazardzhik, Pazardzhik, Bulgaria
- Site 2: Department - Psychiatry, "MHAT Dr. Ivan Selimski" JSC, Sliven, Bulgaria
- Site 3: IMSP Clinical Psychiatric Hospital, Chisinau, Moldova

An onsite inspection was not possible due to the disruption of inspectional activities by COVID-19 global pandemic.

We did not observe any objectionable findings during the Remote Record Reviews of all three clinical sites that impact reliability of study data.

1.1. Recommendation

Based on our review of the Remote Record Review findings, we conclude the data from the audited studies are reliable.

2. Reviewed Studies



Study CAC15003 (ANDA 214068)

"Randomized, multiple-dose, multi-national, multi-center, open-label, two-way crossover pharmacokinetic study to assess the bioequivalence of Risperidone Long-Acting Injection, 12.5, 25, 37.5 and 50 mg, manufactured by Pharmathen International S.A. for Actavis Group PTC ehf (TEST) compared to RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION, 12.5, 25, 37.5 and 50 mg, Janssen Pharmaceuticals, Inc., USA (REFERENCE), in patients"

Study Period: 09/01/2017 – 05/29/2019



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(b) (4)

4. RRR Findings

At the conclusion of the RRRs, we did not observe any objectionable findings that impact the reliability of study data. We did not have any other findings to discuss with the clinical sites' management during the RRR close-out meetings.

5. Conclusion

After review of the RRR findings, we conclude that data from the audited studies are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Chen/Lewin/Yeh
/McDowell
OTS/OSIS/DGDSI/Cho/Benson/Choi/Skelly/Au

Draft: AL 09/29/2020

Edit: PY 09/29/2020; EM 09/29/2020; GB 09/30/2020; AD 10/02/2020

ECMS:

Site 1:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839da645>

Site 2:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839da669>

Site 3:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839da68d>

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8839da6b1>

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f8841aa004>

OSIS File #: BE 8834 (ANDA 214068) and (b) (4) (ANDA (b) (4))

Amanda E. Lewin -S Digitally signed by Amanda E. Lewin -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2002000530,
cn=Amanda E. Lewin -S
Date: 2020.10.02 12:31:55 -04'00'

Amanda Lewin, Ph.D.

Li-hong P. Yeh -S Digitally signed by Li-hong P.
Yeh -S
Date: 2020.10.02 13:10:59 -04'00'

Li-Hong Yeh, Ph.D.

Erin M. McDowell -S Digitally signed by Erin M. McDowell -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
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cn=Erin M. McDowell -S
Date: 2020.10.02 13:16:23 -04'00'

Erin McDowell, B.S., B.A.

Gopa Biswas -S Digitally signed by Gopa Biswas -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Gopa Biswas -S,
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Date: 2020.10.02 13:33:15 -04'00'

Gopa Biswas, Ph.D., Lead Pharmacologist

Ruben C. Ayala -S Digitally signed by Ruben C. Ayala -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Ruben C. Ayala -S,
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Date: 2020.10.02 13:41:36 -04'00'

Ruben Ayala, Pharm.D., Lead Pharmacologist

Zhou Chen -S Digitally signed by Zhou Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Zhou Chen -S, 0.9.2342.19200300.100.1.1=1300130439
Date: 2020.10.02 13:38:26 -04'00'

Zhou Chen, Ph.D., Lead Pharmacologist

Arindam Dasgupta -S Digitally signed by Arindam Dasgupta -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=0012329705, cn=Arindam Dasgupta -S
Date: 2020.10.02 13:54:56 -04'00'

Arindam Dasgupta, Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/3/2020

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: ANDA 214068

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

OSIS inspected the sites in September 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4).

The final classification for the inspection was No Action Indicated (NAI).

Please note that the (b) (4) site is permanently closed.

Therefore, based on the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	
Analytical		

Folaremi
Adeyemo

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DN: cn=Folaremi Adeyemo, o, ou,
email=folaremi.adeyemo@fda.hhs.gov,
c=US
Date: 2020.02.03 10:44:25 -05'00'

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/3/2020

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct biopharmaceutical inspection**

RE: ANDA 214068

The Division of Generic Drug Study Integrity (DGDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below.

Rationale

Military Medical Academy, Sofia: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site:

State Psychiatric Hospital – Tsarev brod, Tsarev Brod: OSIS recommends that a clinical inspection will not be needed because only 7 subjects (7% of total subjects) were randomized at the site.

Center for Mental Health – Sofia District, Sofia: OSIS recommends that a clinical inspection will not be needed because only 6 subjects (6% of total subjects) were randomized at the site.

Center for Mental Health – Vratsa EOOD, Vratsa: OSIS recommends that a clinical inspection will not be needed because only 6 subjects (6% of total subjects) were randomized at the site.

State Psychiatric Hospital – Lovech, Lovech: OSIS recommends that a clinical inspection will not be needed because only 6 subjects (6% of total subjects) were randomized at the site.

State Psychiatric Hospital "Sveti Ivan Rilski", Novi Iskar: OSIS recommends that a clinical inspection will not be needed because only 8 subjects (8% of total subjects) were randomized at the site.

Center for Mental Health – Plovdiv EOOD, Plovdiv: OSIS recommends that a clinical inspection will not be needed because only 7 subjects (7% of total subjects) were randomized at the site.

MHAT - Levski EOOD, Levski: OSIS recommends that a clinical inspection will not be needed because only 6 subjects (6% of total subjects) were randomized at the site.

Instytut Psychiatrii i Neurologii, Warsaw: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Zespół Poradni Zdrowia Psychicznego, Toruń: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Uniwersyteckie Centrum Kliniczne, Gdańsk: OSIS recommends that a clinical inspection will not be needed because only 2 subjects (2% of total subjects) were randomized at the site.

Centrum Badań Klinicznych, Jagiellońskie Centrum Innowacji, Krakow: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Milickie Centrum Medyczne, sp. z o.o., Milicz: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Rodzinne Centrum Medyczne LUBIMED, Lublin: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ, Krakow: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Podlaskie Centrum Psychogerii, Białystok: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

IMSP Clinical Psychiatric Hospital, Chisinau: OSIS recommends that a clinical inspection will not be needed because only 3 subjects (3% of total subjects) were randomized at the site.

IMSP Psychiatry Hospital Balti, Balti: OSIS recommends that a clinical inspection will not be needed because only 5 subjects (5% of total subjects) were randomized at the site.

Hospital of Psychiatry and Phthisiopulmonology, Orhei: OSIS recommends that a clinical inspection will not be needed because no subjects were randomized at the site.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Military Medical Academy	3 Sveti Georgy Sofiyski Street, 1000 Sofia, Bulgaria
Clinical	State Psychiatric Hospital – Tsarev brod	30 Hristo Botev Street, 9747 Tsarev Brod, Bulgaria
Clinical	Center for Mental Health – Sofia District	309 Slivnitsa Boulevard, 1000 Sofia, Bulgaria
Clinical	Center for Mental Health – Vratsa EOOD	1 Belasitsa Street, 3000 Vratsa, Bulgaria
Clinical	State Psychiatric Hospital – Lovech	1 Aleksander Batenberg Street, 5500 Lovech, Bulgaria
Clinical	State Psychiatric Hospital "Sveti Ivan Rilski"	140 Hristo Botev Street, 1282 Novi Iskar, Bulgaria
Clinical	Center for Mental Health – Plovdiv EOOD	68 Peshtersko Shose Boulevard, 4002 Plovdiv, Bulgaria
Clinical	MHAT - Levski EOOD	5 Nikola Vaptsarov Street, 5900 Levski, Bulgaria
Clinical	Instytut Psychiatrii i Neurologii	ul. Jana III Sobieskiego 9, 02-957 Warsaw, Poland)

Facility Type	Facility Name	Facility Address
Clinical	Zespół Poradni Zdrowia Psychicznego	ul. Adama Mickiewicza 24/26, 87-100 Toruń, Poland
Clinical	Uniwersyteckie Centrum Kliniczne.	Klinika Chorób Psychiczych i Zaburzeń Nerwicznych, ul. Dębinki 7, 80-952 Gdańsk, Poland
Clinical	Centrum Badań Klinicznych, Jagiellońskie Centrum Innowacji	Life Science Park, ul. Michała Bobrzyńskiego 14, 30-348 Krakow, Poland
Clinical	Milickie Centrum Medyczne, sp. z o.o.	ul. Grzybowa 1, 56-300 Milicz, Poland
Clinical	Rodzinne Centrum Medyczne LUBIMED	ul. Jacka Woronieckiego 11, 20-492 Lublin, Poland
Clinical	Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ	ul. Józefa Babińskiego 29, 30-393 Krakow, Poland)
Clinical	Podlaskie Centrum Psychogeriatrici	ul. Swobodna 38/9, 15-756 Białystok, Poland
Clinical	IMSP Clinical Psychiatric Hospital	Department of Psychiatry, Narcology, and Medical Psychology, 3 Costiujeni Street, Chisinau, MD2011, Republic of Moldova
Clinical	IMSP Psychiatry Hospital Balti	114 Gagarin Street, Balti, MD 3110, Republic of Moldova
Clinical	Hospital of Psychiatry and Phthisiopulmonology	2 Dubasari Street, Orhei, MD 3500, Republic of Moldova

Folaremi
Adeyemo

Digitally signed by Folaremi Adeyemo
DN: cn=Folaremi Adeyemo, o, ou,
email=folaremi.adeyemo@fda.hhs.gov,
c=US
Date: 2020.02.03 10:51:46 -05'00'

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#: 214068

Drug Product: RISPERIDON INJECTION, SUSPENSION

DMF#: (b) (4)

DMF Subject (API name): RISPERIDONE-USP

Note: If the DMF is for a mixture of the API and excipient(s) (e.g. stabilizer, buffer), email DMF OGD Mailbox (DMFOGD@fda.hhs.gov) and include the URL to the project; example "this TCIR is for an API excipient mixture".). Note to reviewer: Do not archive the TCIR document as changes may need to be made.

1. Are there any **secondary DMFs** referenced by this DMF? ☐ Yes ☒ No

If yes, fill in the following table.

Secondary DMF #	Subject of the DMF	Intermediate/Starting material?

Note: If the secondary DMF is for a regulatory starting material, a review of the secondary DMF may not be needed.

2. Are there any intermediate facilities **listed in the 356h**? ☐ Yes ☒ No

If yes, determine if the intermediate facility is critical.

Facility Name and Address	FEI/DUNS	Intermediate critical (Y/N)	Justification*

* If an intermediate facility is identified, please select justification(s) from the following:

1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.

3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
 4. Intermediate is not deemed critical because the criteria above do not apply.
 5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre-existing facility and was not evaluated for other applications.
3. Does the Type II API DMF list any manufacturing facilities, intermediate facilities, or testing facilities for routine release or stability testing that are **not listed in the facility profile and/or on the 356h** form for the referencing ANDA? ☐ Yes ☒ No

If yes, include the information identifying each facility and its function below:

Facility Name and Address [#]	Function ^{\$}	Justification if Intermediate facility*	FEI/DUNS [#]

- * If an intermediate facility is identified, please select justification(s) from the following:
1. The intermediate is not separated by an adequate number of steps from the final API. The risk to DS quality cannot be adequately mitigated through the intermediate specification and thereby the facility warrants evaluation.
 2. The intermediate route of synthesis involves unusual or complex chemistry which presents a risk to DS quality that cannot be adequately mitigated through the intermediate specification.
 3. The drug substance is very complex, and the intermediate route of synthesis introduces the most critical structural features and the risk to DS quality cannot be adequately mitigated through the intermediate specification.
 4. Intermediate is not deemed critical because the criteria above do not apply.
 5. The intermediate would be deemed critical if new, but the current intermediate facility was a pre-existing facility and was not evaluated for other applications.

^{\$} Facility function codes for hidden and critical intermediate facilities:

CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
LCP: Laboratory, Chemical/Physical Testing
LBI: Laboratory, Biological Testing
LMS: Laboratory, Microbiological – Sterility Testing
LMN: Laboratory, Microbiological – Non-Sterility Testing
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation
CRU: API Non-Sterile/Intermediate

Note: Add “-Critical Intermediate” to the appropriate manufacturing code if the site manufactures a critical intermediate.

#Note: *Not for FOI boxes (refer to SOP for format)* need to be used if the facility information is submitted in a secondary DMF.

RBPM to include the following comment in the early-IR sent to the applicant:

“Please note that there are [manufacturing facilities] [manufacturing facility (critical intermediate)] [and/or] [testing facilities performing routine release or stability testing] that are included in DMF [DMF#] for [API name] that were not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or new facilities may result in an extension of the performance goal date for your submission.”

RBPM to include the following modified comment in the early-IR sent to the applicant if the facility information is submitted in a secondary DMF:

“Please note that there is a manufacturing facility (critical intermediate) that is included in a DMF referenced by [Primary DMF#] for [API name] that was not included on your form 356h. Please contact your DMF holder to resolve any discrepancies and clarify which DMF related facilities support your application. Please note that a revised 356h form will be required to add any new facilities to your application. The addition of a new facility or new facilities may result in an extension of the performance goal date for your submission.”

3. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?

☐ Yes ☒ No

If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

4. After examining the labelling for the drug product:

Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐ Yes ☒ No

Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐ Yes ☒ No

The following question applies to drug products indicated for the treatment of cancer.

Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐ Yes ☒ No

Is a DCR consult required to determine that the drug substance is carcinogenic? ☐ Yes ☒ No

If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

Consult form date:



Jayani
Perera

Digitally signed by Jayani Perera
Date: 1/21/2020 11:46:11PM
GUID: 534c0e2600067da8fcb366ee6a6d78a9

ANDA: 214068

Company: Teva Pharmaceuticals USA, Inc.

Drug Product: Risperidone Long Acting Injection, 12.5mg/vial, 25mg/vial, 37.5mg/vial and 50mg/vial
RLD: 021346

Other Approved Applications: None.

Indication: Schizophrenia; Bipolar Disorder

Risk Profile Performed By: Jin Xu

PRODUCT PROPERTY/CQAS	PROBABILITY OF OCCURRENCE (O)	SEVERITY OF EFFECT (S)	DETECTABILITY (D)	RPN	COMMENTS
Chemical Stability (All CQAs)	3	5	3	45 Moderate	(b) (4)
Meeting USP <1> Requirement	3	4	3	36 Moderate	
Other CQAs	3	4	3	36 Moderate	

Risk ranking criteria:

- RPN < 25 are considered as low risk; 25 < RPN < 60 are considered as moderate risk; RPN > 60 are considered as high risk.

Following Table can be copied in the IQA Template under Risk Assessment Section:

Product Property/ CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Cycle #	Comments
Chemical Stability (All CQAs)	Medium	(b) (4)		

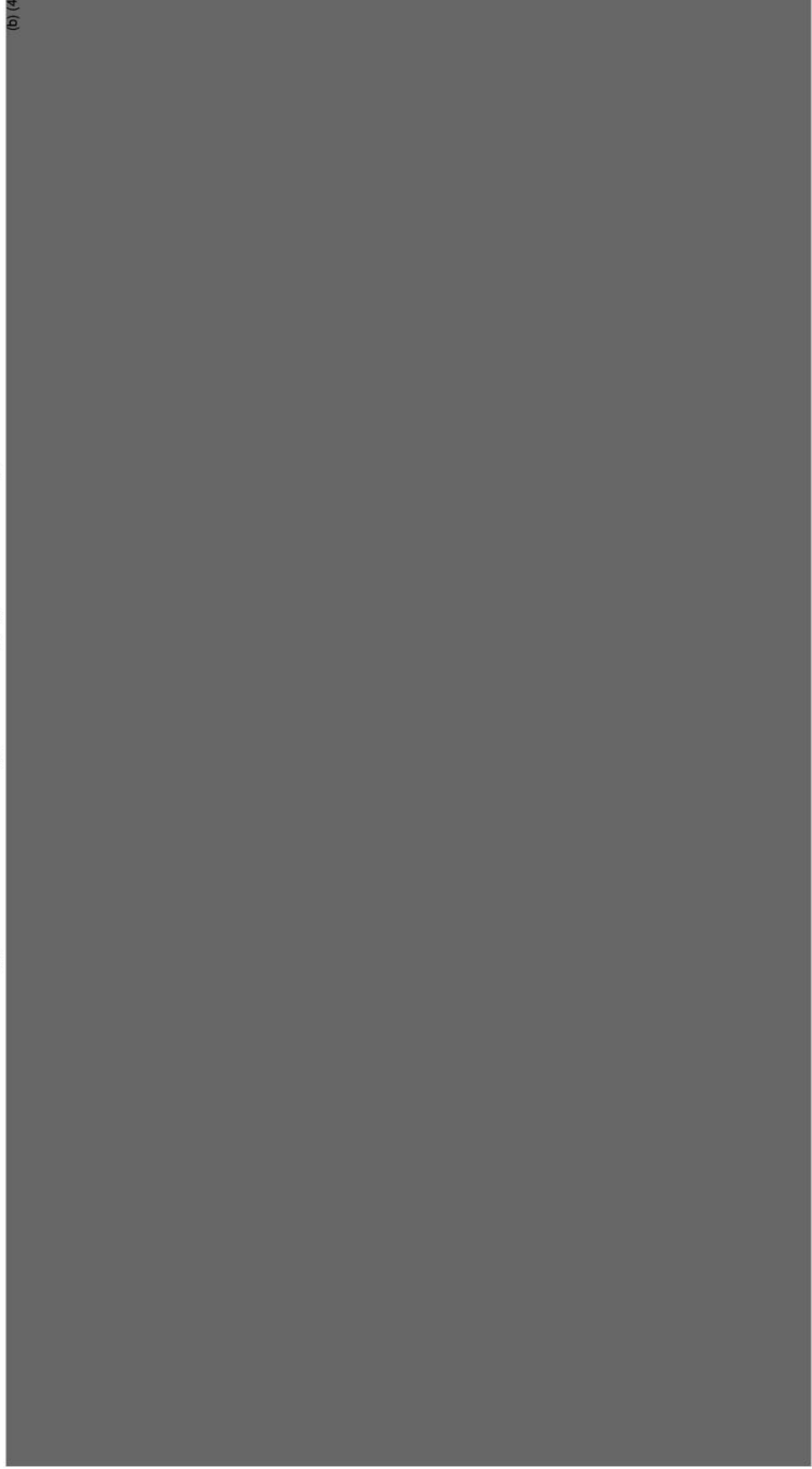
(b) (4)	

Risk ranking criteria:

- Product properties or CQAs that fall under a RPN of 25 are considered as low risk.
- Product properties or CQAs at or above RPN 25 but below 60 are considered as moderate risk.
- Product properties or CQAs at or above an RPN 60 are considered as high risk.

Appendix 1 – List of High Risk Drugs (as of 9/26/2013)

(b) (4)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208336

BIOPHARM/TOX REVIEW(s)

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Risperidone (b) (4), 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
DMF#/ANDA#:	ANDA 214068
Applicant:	Teva Pharmaceuticals USA Inc.
RLD#/Approval Date:	Risperdal Consta® (NDA 021346), approved on 10/29/2003
Sponsor:	Janssen Pharmaceuticals Inc.
Pharmacology-Toxicology Primary Reviewer:	Wei Ding, PhD, DABT Pharmacologist
Pharmacology-Toxicology Secondary Reviewer:	Melanie Mueller, PharmD, PhD Lead Toxicologist
Tertiary Reviewer:	N/A
To:	Raeann Wu, PhD Division of Post-Marketing Activities (DPMA) Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	OPQ asked DPTR to evaluate the acceptability of the daily exposure of (b) (4) in the generic risperidone for injectable suspension under ANDA 214068.
Impurity Chemical Name:	(b) (4)
Date of Submission:	ANDA 214068 was submitted on 12/16/2019; the documents under current review were submitted on 02/27/2023
Date Consult Received:	06/29/2023
Date of Completion:	08/08/2023
Conclusion:	Pharm/Tox concludes that the maximum daily exposure of (b) (4) in the generic risperidone for injectable suspension product under ANDA 214068 is acceptable from a Pharm/Tox perspective. See Section 2 for Internal Recommendations.

1 Memorandum:

Background

This Pharmacology/Toxicology review addresses a consult request from the Division of Post-Marketing Activities (DPMA)/Office of Pharmaceutical Quality (OPQ), regarding safety evaluation of (b) (4) of the proposed risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial under ANDA 214068. The proposed drug product is the first generic of risperidone long-acting injection.

The reference listed drug (RLD) is Risperdal Consta® (NDA 021346), marketed by Janssen Pharmaceuticals Inc. and approved on 10/29/2003. Risperidone is an atypical antipsychotic indicated for the treatment of schizophrenia; and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder. Per the RLD label, risperidone long-acting injection is administered every two weeks by deep intramuscular deltoid or gluteal injection. According to the RLD labeling, the maximum daily dose (MDD) is 50 mg/day.

(b) (4) used as (b) (4) to manufacture risperidone (b) (4). The applicant proposed to (b) (4). The applicant submitted a safety/toxicology assessment of (b) (4) and (b) (4). DPMA consulted DPTR to evaluate the submitted toxicological assessment report to address the safety of (b) (4) in the proposed drug product.⁵

Review and Risk Assessment

DPTR previously reviewed the safety of (b) (4) in several generic products. Notably, (b) (4)

(b) (4)

[NOT FOR FOIA]: Table 1:

(b) (4)

(b) (4)

(b) (4)



Conclusion

Exposure to (b) (4) from the generic risperidone for injection suspension drug product under ANDA 214068 does not raise safety concern from a Pharm/Tox perspective.

1.1 Context of Use Summary based on RLD Labeling

Drug Product Name	Risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
Route(s) of Administration	Intramuscular injection
Maximum Daily Dose (MDD)	50 mg intramuscular (IM) every two weeks ^{9,10}
Treatment Duration	>1 – 10 years ^{11,12}

2 Internal Recommendation:

The maximum daily exposure of (b) (4) in the generic risperidone for injectable suspension product under ANDA 214068 is acceptable from a Pharm/Tox perspective.

3 Comments to be conveyed by the RPM to the ANDA applicant as written:

N/A





Wei
Ding

Digitally signed by Wei Ding
Date: 8/08/2023 10:21:57AM
GUID: 5c61b72a0022b4ac80b903674d2d2090



Melanie
Mueller

Digitally signed by Melanie Mueller
Date: 8/08/2023 10:47:05AM
GUID: 54653ac0003bbe59a54d6c91b731724a

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Product:	Risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
DMF#/ANDA#:	ANDA #214068
Applicant:	Teva Pharmaceuticals USA Inc.
RLD#/Approval Date:	Risperdal Consta® (NDA #021346), approved on 10/29/2003
Sponsor:	Janssen Pharmaceuticals Inc.
Pharmacology-Toxicology Primary Reviewer:	Wei Ding, PhD, DABT Pharmacologist
Pharmacology-Toxicology Secondary Reviewer:	Melanie Mueller, PharmD, PhD Lead Toxicologist
Tertiary Reviewer:	Sruthi King, PhD Deputy Director
To:	Greg Huang, PhD Division of Liquid Based Products (DLBP) Raeann Wu, PhD Division of Post-Marketing Activities (DPMA) Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	OPQ asked DPTR to evaluate the detection limit of the leachables (b) (4) in the generic risperidone for injectable suspension under ANDA 214068.
Impurity Chemical Name:	(b) (4)
Date of Submission:	ANDA 214068 was submitted on 12/16/2019; the documents under current review were submitted on 02/27/2023
Date Consult Received:	03/28/2023 (received original consult form) 04/05/2023 (received updated consult form)
Date of Completion:	06/20/2023
Conclusion:	Pharm/Tox concludes that the leachables detected in the generic risperidone for injectable suspension product under ANDA 214068, at their proposed MDEs, are acceptable from a Pharm/Tox perspective. See Section 2 for Internal Recommendations.

Deficiency Classification:

- ☐ Major
☐ Minor
☒ N/A

1 Executive Summary:

This Pharmacology/Toxicology review addresses a consult request from the Office of Pharmaceutical Quality (OPQ), regarding safety evaluation of leachables originating from the reconstituted suspension of the proposed risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial. The proposed drug product is the first generic of risperidone long-acting injection.

The reference listed drug (RLD) is Risperdal Consta® (NDA 021346), marketed by Janssen Pharmaceuticals Inc. and approved on 10/29/2003. Risperidone is an atypical antipsychotic indicated for the treatment of schizophrenia; and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder. Per the RLD label, risperidone long-acting injection is administered every two weeks by deep intramuscular deltoid or gluteal injection. According to the RLD labeling, the maximum daily dose (MDD) is 50 mg/day.

Teva Pharmaceuticals USA Inc. submitted ANDA 214068 on 12/16/2019. Upon original submission, the applicant evaluated leachables identified in the drug product (Study #1611_2021) and provided a toxicological assessment report on 05/27/2021, which was updated on 01/18/2021. In the submitted leachable report, the applicant (b) (4)

Therefore, DPTR review issued as deficiency requesting the applicant to 1) identify and fully characterize all leachable compounds (b) (4) with a CAS # and/or structure, 2) address the irritation/sensitization potential and general toxicity of leachable compounds (b) (4) and 3) address the mutagenicity of all leachable compounds (b) (4)

In response to FDA's request, the applicant submitted toxicological assessment reports to justify the safety of leachables with CAS number and/or chemical structure on 03/23/2023. The toxicology of all the leachables detected (b) (4) was evaluated in the current review.

Based on publicly available toxicological information, (Q)SAR analysis, and data available for structurally similar surrogate compounds suggested by CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS), the genetic toxicity, skin irritation potential, and general toxicity of the leachables at their detected MDEs were assessed. There was no safety concern identified. Therefore, the MDEs for these chemicals are acceptable from the Pharm/Tox perspective.

2 Internal Recommendation:

The leachables detected in the generic risperidone for injectable suspension product under ANDA 214068, at their proposed MDEs, are acceptable from a Pharm/Tox perspective.

3 Comments to be conveyed by the RBPM/RPM to the DMF Holder/ANDA applicant as written:

N/A

4 Regulatory Background:

Teva Pharmaceuticals USA Inc. submitted ANDA 214068 on 12/16/2019.¹ The reference listed drug (RLD) is Risperdal Consta® (NDA #021346), marketed by Janssen Pharmaceuticals Inc. and approved on 10/29/2003.

Upon original submission, the applicant evaluated leachables identified in the drug product (Study #1611_2021) and provided a toxicological assessment report on 05/27/2021, which was updated on 01/18/2021. In the submitted leachable report, the applicant did not identify all leachables exceeding the analytical evaluation threshold (AET) with CAS number and/or structure. Therefore, DPTR review² requested the applicant to 1) identify and fully characterize all leachable compounds exceeding a maximum daily exposure (MDE) of (b) (4) a CAS # and/or structure, 2) address the irritation/sensitization potential and general toxicity of leachable compounds with (b) (4) considering the context of use of your drug product, which is a long-acting injection administered intramuscularly. If grouping and/or use surrogate compounds for safety assessment, to provide a rationale for grouping and for the choice of surrogates, and 3) address the mutagenicity of all leachable compounds with (b) (4), using approaches described in ICH M7(R1) guidance. Mutagenic compounds should be limited to not-more-than (b) (4).

The applicant conducted leachable study in the drug product in the actual container closure system (CSS) (b) (4)

The applicant submitted toxicological reports to justify the levels of these leachables.^{4,5,6} DLBP and DPMA consulted DPTR to evaluate the submitted toxicological assessment reports to address the safety of leachables in the proposed drug product.⁷

¹ ANDA 214068 docuBridge section 1.2 Cover Letter at: [ANDA214068 \(214068 - 0022 - \(22\) - 2023-03-23 - ORIG-1 /Multiple Categories/Subcategories\) - Cover Letter 16Dec2019 - Original Application](#)

² Dr. Chanchal Gupta A214068N000DPTR-Consult Review-01_leachables_memoandum.pdf at: <https://panorama.fda.gov/document/view?ID=6209b445008dba2a061c37f9486808d0>

³ ANDA 214068 docuBridge section 3.2.P.2 Leachable study (entrapped compounds) at: [ANDA214068 \(214068 -](#) (b) (4)

above 10 mcg

⁷ A214068 OPQ-SafetyConsultForm.v3_updated 4-4-2023.pdf at: <https://panorama.fda.gov/document/view?ID=642d6c930025fbd5a03866c61363b5b2>

4.1 Orange Book Information

The RLD is the only approved risperidone for injectable suspension in the current market.⁸

5 Labeling:

The current product label for Risperdal Consta was approved on 02/12/2021.⁹ There is a black box warning:

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

5.1 Indications (excerpted from RLD labeling)

RISPERDAL® is an atypical antipsychotic indicated for:

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

5.2 Dosage and Administration (excerpted from RLD labeling)

The maximum daily dose was determined to be 50 mg intramuscular (IM) every two weeks.¹⁰

5.3 Nonclinical Information of API (Labeling Section 13.1)

N/A

⁸ Searched by Wei Ding on 04/11/2023 at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

⁹ RLD (NDA 021346, Risperdal Consta) labeling at:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020272Orig1s083,020588Orig1s071,021444Orig1s057,021346Orig1s061lbl.pdf

¹⁰

(b) (4)

5.4 Context of Use Summary based on RLD Labeling

Drug Product Name	Risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
Route(s) of Administration	Intramuscular injection
Maximum Daily Dose (MDD)	50 mg intramuscular (IM) every two weeks ^{11,12}
Treatment Duration	>1 – 10 years ^{13,14}

6 Discussion:

This review evaluates the of the acceptability of the detected level of the leachables (b) (4)

(b) (4) in the generic risperidone for injectable suspension under ANDA 214068. The leachables identified in risperidone for injectable suspension are summarized in Table 1 below. For those chemicals that do not have publicly available toxicological information, we reached out to DARS for (Q)SAR and surrogate analysis (Appendix).

Table 1: Leachables Identified in Risperidone for Injectable Suspension:

Leachable	MDE (µg/day)	DARS Recommended Surrogate	Mutagenicity Assessment
(b) (4)			

*Previously reviewed by DPTR (see Section 6.2)

¹¹ Dr. Chanchal Gupta A214068N000DPTR-Consult Review-01_leachables_memorandum.pdf at: <https://panorama.fda.gov/task/view?ID=618a96c5004c9491dfc3fd8be7d415b6>

¹² (b) (4)

¹³ (b) (4)

¹⁴ Dr. Chanchal Gupta A214068N000DPTR-Consult Review-01_leachables_memorandum.pdf at: <https://panorama.fda.gov/task/view?ID=618a96c5004c9491dfc3fd8be7d415b6>

6.1 ANDA Applicant's Justification

The applicant calculated an analytical evaluation threshold (AET) of (b) (4) using a safety concern threshold (SCT) of (b) (4) and the weight of the reconstituted suspension at the MDD of 50 mg/day of risperidone as (b) (4).¹⁵ The applicant's SCT and MDD are adequate from a Pharm/Tox perspective. Based on the duration of treatment, the threshold for (b) (4). Leachables exceeding the SCT are listed in Table 1.

The applicant submitted toxicological report to justify the detection levels of these leachables.^{16,17,18}

6.2 [NOT FOR FOIA]: Prior Review Experience of the Review Issue

(b) (4)

(b) (4)

(b) (4)

(b) (4)

6.3.1 Acute Toxicology

N/A

6.3.2 Absorption, Distribution, Metabolism and Excretion

N/A

6.3.3 Genetic Toxicology

N/A

6.3.4 General Toxicology

N/A

6.3.5 Reproductive Toxicology

N/A

6.4 Integrated Risk Assessment

The leachables identified above AET in the generic risperidone for injectable suspension product under ANDA 214068 were reviewed and results summarized in the table below. The genetic toxicity, skin irritation potential, and general toxicity of the leachables at their detected MDEs were assessed and there was no safety concern identified. Therefore, the MDEs for these leachables are acceptable from the Pharm/Tox perspective.

Table 1: Summarization of safety Assessment of leachables:

Leachable	MDE (µg/day)	Genotoxicity	Skin Irritation	Support for general safety	Acceptable (yes or no)
(b) (4)					

7 Conclusion:

The leachables detected in the generic risperidone for injectable suspension product under ANDA 214068, at their proposed MDEs, are acceptable from a Pharm/Tox perspective.

2 Pages have been withheld in full as b4 immediately following this page

³³ * The decision is based on the risk assessment of the leachable compound.

³⁴ # The decision is based on the risk assessment of the surrogate chemicals of the leachable compound.



Wei
Ding

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Melanie
Mueller

Digitally signed by Melanie Mueller
Date: 6/20/2023 02:23:29PM
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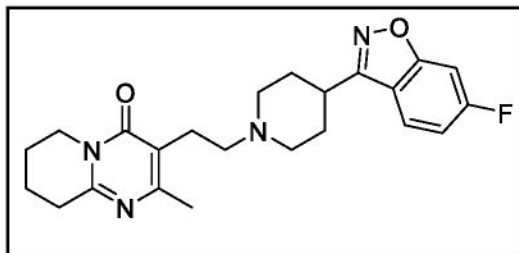


Sruthi
King

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To: Wei Ding (CDER/OGD/OSCE/DPTR)
cc: Melanie Mueller (CDER/OGD/OSCE/DPTR)
From: CDER/OTS/OCP/DARS: Computational Toxicology Consultation Service
Re: ANDA 214068
Date: May 16, 2023

Summary



Risperidone (API)

A leachables study was conducted by the applicant for the drug product risperidone (API), (b) (4)

[REDACTED]

Therefore, the CDER/OTS/OCP/DARS Computational Toxicology Consultation Service (CTCS) was consulted to:

- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]

CTCS concludes the following:

- [REDACTED] (b) (4)
- [REDACTED]

PHARMACOLOGY-TOXICOLOGY CONSULTATION REVIEW
Division of Pharmacology/Toxicology Review (DPTR)
Office of Safety and Clinical Evaluation (OSCE), Office of Generic Drugs (OGD)
Center for Drug Evaluation & Research (CDER)

Drug Substance/Product:	Risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
DMF#/ANDA#:	ANDA #214068
Applicant:	Teva Pharmaceuticals USA Inc.
RLD#/Approval Date:	Risperdal Consta® (NDA #021346), approved on 10/29/2003
Sponsor:	Janssen Pharmaceuticals Inc.
Pharmacology-Toxicology Primary Reviewer:	Chanchal Gupta, PhD Staff Fellow
Pharmacology-Toxicology Secondary Reviewer:	Melanie Mueller, PharmD, PhD Lead Toxicologist
Tertiary Reviewer:	Robert Dorsam, PhD Division Director
To:	Greg Huang, PhD Division of Liquid Based Products (DLBP) II Office of Pharmaceutical Quality (OPQ)
Reason for Consult:	To evaluate the safety of leachables originating from the reconstituted suspension of the proposed risperidone long-acting injection.
Impurity Chemical Name:	Not applicable
Date of Submission:	05/27/2021
Date Consult Received:	11/18/2021 (received original consult request form) 01/18/2022 (received updated consult request form)
Date of Completion:	02/14/2022
Conclusion:	DPTR concludes that a comprehensive safety review of leachables in the proposed risperidone long-acting injection could not be conducted due to lack of adequate characterization and identification of leachables exceeding the analytical evaluation threshold. Hence, the proposed container closure system is not qualified for safety. See Section 2 for Internal Recommendations and Section 3 for Comments to be conveyed to the Applicant by the RPM.
Deficiency Classification:	☒ Major ☐ Minor ☐ N/A
Justification for Major Designation: The deficiency requires justification or nonclinical studies that support the safety of the proposed drug product. As described in Appendix A, Section B, Part 3(a)(i) of the <i>Guidance for Industry ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018)</i> , the need for a safety assessment of extractables and leachables, or inadequate assessment of extractables and leachables is classified as a major deficiency. Review of the submitted justification or toxicology data will require substantial expenditure of FDA resources.	

1 Memorandum:

This Pharmacology/Toxicology (Pharm/Tox) memorandum addresses a consult request from the Division of Liquid Based Products (DLBP) II in the Office of Pharmaceutical Quality (OPQ), regarding safety evaluation of leachables originating from the reconstituted suspension of the proposed risperidone long-acting injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial. The proposed drug product is the first generic of risperidone long-acting injection.

The reference listed drug (RLD) is Risperdal Consta® (NDA #021346), marketed by Janssen Pharmaceuticals Inc. and approved on 10/29/2003. Risperidone is an atypical antipsychotic indicated for the treatment of schizophrenia; and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder. Per the RLD label, risperidone long-acting injection is administered every two weeks by deep intramuscular deltoid or gluteal injection.¹ Previously, the Division of Clinical Review (DCR) and DPTR determined that the maximum daily dose (MDD) of risperidone long-acting injection is 50 mg/day.² The duration of use of risperidone long-acting injection is 1 – 10 years.³

Teva Pharmaceuticals USA Inc. conducted extractables studies on the rubber components of the proposed container closure system (CCS) and manufacturing components of the generic risperidone long-acting injection. The applicant submitted toxicological assessment reports to address the safety of extractables (b) (4). Further, the applicant conducted several leachables studies and submitted toxicological assessment reports to justify the safety of leachables from the proposed CCS. DLBP II consulted DPTR on 11/18/2021, to evaluate the submitted toxicological assessment reports to address the safety of extractables and leachables in the proposed drug product.⁴ After internal discussion with the Quality review team, DPTR was informed that the leachables study of the reconstituted suspension of the proposed risperidone long-acting injection (Study #1611_2021) is the most relevant study for safety evaluation of leachables in the proposed drug product.⁵ DLBP II submitted an updated consult request form, dated 01/18/2022.⁶

The applicant calculated an analytical evaluation threshold (AET) of (b) (4) using a safety concern threshold (SCT) of (b) (4). The applicant's SCT and MDD are adequate from a Pharm/Tox perspective. However, DPTR noted

¹ Risperdal Consta® label, Drugs@FDA;

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020272Orig1s083.020588Orig1s071.021444Orig1s057.021346Orig1s061bl.pdf#page=60, accessed on 01/21/2022.

² ANDA 214068, Panorama, A214068N000DCR-Consult Response-01_Risperidone_PLG excipient_final, dated 05/11/2020; <https://panorama.fda.gov/task/view?ID=5e1f48c9003f5e439de5ff2547ee38df>

³ Based on RLD labeling, risperidone long-acting injection is injected every two weeks (14 days). Therefore, per ICH M7(R1), the total number of dosing days in a patient's lifetime (70 years) is 1825 days (=365*70/14) or 5 years.

⁴ ANDA 214068, Panorama, A214068 OPQ-SafetyConsultForm.v3_FINAL, dated 11/18/2021;

<https://panorama.fda.gov/document/view?ID=618a96e8004c9c4fc117055f146fea87>

⁵ Email communication with Quality review team, dated 01/14/2022.

⁶ ANDA 214068, Panorama, A214068 OPQ-SafetyConsultForm.v3_Updated 1_18_2022, dated 01/18/2021;

<https://panorama.fda.gov/document/view?ID=61e70ca10010a762e73f28876ddcacb8>

⁷ ANDA 214068, docuBridge, Seq 0016, Module 3, Section 3.2.P.2; [\\CDSESUB1\evsprod\anda214068\0016\m3\32-body-data\32p-drug-prod\dp-powder\32p2-pharm-dev\leachable-entrapped.pdf](https://cdsesub1\evsprod\anda214068\0016\m3\32-body-data\32p-drug-prod\dp-powder\32p2-pharm-dev\leachable-entrapped.pdf), submitted on 05/27/2021.

that the applicant did not identify all leachables exceeding the AET with a CAS # and/or structure.⁸ Further discussion with the Quality review team confirmed that the applicant did not adequately characterize the leachables exceeding the AET and provided only “tentative identification”.⁹ The Quality review team intends to issue a deficiency asking the applicant to adequately identify all leachables exceeding the AET with CAS# and/or structure. At this point, from a Pharm/Tox perspective, a comprehensive safety evaluation of leachables in the generic risperidone long-acting injection cannot be performed due to lack of adequate identification and characterization of leachables.

Overall, the submitted leachables study is not adequate to qualify the safety of all leachables in the proposed drug product. DPTR provided internal recommendations for the Quality Review team in Section 2 and external recommendations for the applicant in Section 3 below.

2 Internal Recommendation:

The safety concern threshold (SCT) for leachables in risperidone long-acting injection is (b) (4). From a Pharm/Tox perspective, the SCT and the maximum daily dose (MDD) used by the applicant to calculate the analytical evaluation threshold (AET) of the leachables study are acceptable. However, DPTR noted that the applicant did not adequately identify all leachables exceeding the AET with a CAS # and/or structure. Hence, a comprehensive safety review could not be conducted and the submitted leachables study (Study #1611_2021) is not adequate to qualify the safety of all leachables in the proposed drug product.

DPTR defers to the Quality review team for requesting necessary Quality information from the applicant to reliably identify the leachables above the AET. We provided recommendations to the applicant for the safety evaluation of leachables in Section 3 below.

3 Comments to be conveyed by the RBPM/RPM to the DMF Holder/ANDA applicant as written:

The Division of Pharmacology/Toxicology Review has identified MAJOR Pharmacology/Toxicology deficiencies to be included in the Complete Response Letter.

- **For DMF consults, Pharm/Tox language will be conveyed as written. The DLAPI assessor may add CMC recommendations to the Pharm/Tox deficiency and provides courtesy notification to DPTR of the additions when finalizing the language to be sent to the DMF Holder.**
- **For ANDA consults, convey the comments as written to the ANDA applicant under the “PHARMACOLOGY/TOXICOLOGY” section of the Complete Response Letter. Please notify DPTR when the applicant responds to this deficiency.**

We reviewed the submitted leachable study (Study #1611_2021) and the toxicological assessment report, titled “Toxicological Review of Leachables from Risperidone LAI Finished Product), submitted on 05/27/2021 to address the safety of leachables originating from the reconstituted suspension of your proposed drug product. From a Pharmacology/Toxicology

⁸ ANDA 214068, docuBridge, Seq 0016, Module 3, Section 3.2.P.2; [\\CDSESUB1\evsprod\anda214068\0016\m3\32-body-data\32p-drug-prod\dp-powder\32p2-pharm-dev\tox-ass-entrapped-leach.pdf](#), submitted on 05/27/2021.

⁹ Email communication with Quality review team, dated 01/23/2022.

perspective, your submitted leachables study and the toxicological assessment report do not adequately address the safety of all potential leachables in your drug product.

Briefly, you did not adequately identify all leachables exceeding the analytical evaluation threshold (AET) with a CAS# and/structure. Without proper identification and characterization, a comprehensive safety review of leachables cannot be conducted. Hence, the proposed container closure system is not qualified for safety.

We refer you to any additional recommendations from the Drug Product Quality discipline with respect to your leachables study. We provide the following recommendations to address the safety of leachables in your proposed drug product:

- Identify and fully characterize all leachable compounds exceeding a maximum daily exposure (MDE) of (b) (4) with a CAS # and/or structure.
- Address the irritation/sensitization potential and general toxicity of leachable compounds with MDE (b) (4). Consider the context of use of your drug product, which is a long-acting injection administered intramuscularly. If you group compounds together and/or use surrogate compounds for safety assessment, provide a rationale for grouping and for the choice of surrogates.
- Address the mutagenicity of all leachable compounds with MDE (b) (4), using approaches described in ICH M7(R1) guidance. Mutagenic compounds should be limited to not-more-than (b) (4). Please provide complete, legible copies of references and published information used to justify the safety of your leachables.

The acceptability of your safety assessment will be a review issue upon submission.



Chanchal
Gupta

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Melanie
Mueller

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Robert
Dorsam

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 214068

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 214068-ORIG-1-AMEND-21
Product Name/Strengths	Risperidone Long Acting Injection/ 12.5mg, 25mg, 37.5mg, and 50mg
Applicant	Teva Pharmaceuticals USA Inc
Dosage Form /Route of Administration	Powder for Injection/intramuscular injection
Indication for Use	1) Treatment of schizophrenia. 2) Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
RLD	NDA 021346 Risperdal Consta® (risperidone) Long Acting Injection (12.5mg, 25mg, 37.5mg, and 50mg)
Submission Date	2/27/2023
Primary Reviewer	Jia Leo, Ph.D.
Recommendation	ADEQUATE

REVIEW SUMMARY

This amendment provides response to the Complete Response Letter (CRL) dated 3/25//2022. In the last review cycle, Biopharmaceutics is adequate. However, in this amendment, the Applicant provide additional information, adding an additional manufacturing (b) (4) to increase commercial manufacturing capacity.¹ To support the proposed change, the Applicant provided comparative in vitro dissolution profile data for the pre-change (b) (4) and the post-change (b) (4) drug products.²

The dissolution profiles of the pre-change drug product, including the pivotal BE batch, are similar to that of the post-change drug product under both accelerated (45°C) and real time (37°C) dissolution conditions (**Appendix 1**). The provided in vitro dissolution profile data support the proposed manufacturing change.

Conclusion and Recommendation: From a Biopharmaceutics perspective, ANDA 214068-ORIG-1-AMEND-21 for Risperidone Long-Acting Injection is ADEQUATE.

¹ [\\CDSESUB1\EVSPROD\anda214068\0021\m1\us\resp-fda-crl-25mar2022.pdf](#)

² [\\CDSESUB1\EVSPROD\anda214068\0021\m2\27-clin-sum\skid1-skid2-comp-disso.pdf](#)

Appendix 1: Supporting Data

Approved dissolution method and acceptance criteria

Apparatus	Medium/ Temperature	Volume (mL)	Acceptance Criteria
Cylinder bottle	HEPES buffer pH 7.4 /37°C (normal) and 45°C (accelerated) water bath	200	At 37 °C: NMT (b) (4) % in day 1 NMT (b) (4) % in day 21 At 45 °C: (b) (4) % in 120 hr (b) (4) % in 160 hr NLT (b) (4) % in 210 hr

Batches used in dissolution comparison for the pre-change (b) (4) and the post-change (b) (4) drug products

Product	SKID	Bulk	Strength	vial
(b) (4)				

*Pharmathen test product Lot 4700023B was used as bio-batch for the multiple-dose study

(b) (4)

Summary of f₂ values for pre-change (Sample 1) and post-change (Sample 2) drug products using the accelerated dissolution method (45°C)

Dissolution method water bath at 45°C ±0.3°C		
Sample 1	Sample 2	f ₂
LOT 4000381	LOT 4201234	51.3
Test Product 12.5mg LOT 4000381A	Test Product 12.5mg LOT 4201234A	62.5
Test Product 25mg* LOT 4700023B	Test Product 25mg LOT 4201234B	73.7
Test Product 25mg LOT 4000381B	Test Product 25mg LOT 4201234B	54.6
Test Product 37.5mg LOT 4000381C	Test Product 37.5mg LOT 4201234C	53.4
Test Product 50mg LOT 4000381D	Test Product 50mg LOT 4201234D	53.2

* BE Batch



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Leo

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BIOPHARMACEUTICS ANDA REVIEW	
Application No.	ANDA 214068-ORIG-1-AMEND-21
Product Name/Strengths	Risperidone Long Acting Injection/ 12.5mg, 25mg, 37.5mg, and 50mg
Applicant	Teva Pharmaceuticals USA Inc
Dosage Form /Route of Administration	Powder for Injection/intramuscular injection
Indication for Use	1) Treatment of schizophrenia. 2) Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
RLD	NDA 021346 Risperdal Consta® (risperidone) Long Acting Injection (12.5mg, 25mg, 37.5mg, and 50mg)
Submission Date	2/27/2023
Primary Reviewer	Jia Leo, Ph.D.
Recommendation	ADEQUATE

REVIEW SUMMARY

This amendment provides response to the Complete Response Letter (CRL) dated 3/25//2022. In the last review cycle, Biopharmaceutics is adequate. However, in this amendment, the Applicant provide additional information, adding an additional manufacturing (b) (4) to increase commercial manufacturing capacity.¹ To support the proposed change, the Applicant provided comparative in vitro dissolution profile data for the pre-change (b) (4) the post-change (b) (4) drug products.²

The dissolution profiles of the pre-change drug product, including the pivotal BE batch, are similar to that of the post-change drug product under both accelerated (45°C) and real time (37°C) dissolution conditions (**Appendix 1**). The provided in vitro dissolution profile data support the proposed manufacturing change.

Conclusion and Recommendation: From a Biopharmaceutics perspective, ANDA 214068-ORIG-1-AMEND-21 for Risperidone Long-Acting Injection is ADEQUATE.

¹ [\\CDSESUB1\EVSPROD\anda214068\0021\m1\us\resp-fda-crl-25mar2022.pdf](#)

² [\\CDSESUB1\EVSPROD\anda214068\0021\m2\27-clin-sum\skid1-skid2-comp-disso.pdf](#)

Appendix 1: Supporting Data

Approved dissolution method and acceptance criteria

Apparatus	Medium/ Temperature	Volume (mL)	Acceptance Criteria
Cylinder bottle	HEPES buffer pH 7.4 /37°C (normal) and 45°C (accelerated) water bath	200	At 37 °C: NMT (b) (4) % in day 1 NMT (b) (4) % in day 21 At 45 °C: (b) (4) % in 120 hr (b) (4) % in 160 hr NLT (b) (4) % in 210 hr

Batches used in dissolution comparison for the pre-change (b) (4) and the post-change (b) (4) drug products

Product	SKID	Bulk	Strength	vial
(b) (4)				

*Pharmathen test product Lot 4700023B was used as bio-batch for the multiple-dose study

(b) (4)

Summary of f₂ values for pre-change (Sample 1) and post-change (Sample 2) drug products using the accelerated dissolution method (45°C)

Dissolution method water bath at 45°C ±0.3°C		
Sample 1	Sample 2	f ₂
LOT 4000381	LOT 4201234	51.3
Test Product 12.5mg LOT 4000381A	Test Product 12.5mg LOT 4201234A	62.5
Test Product 25mg* LOT 4700023B	Test Product 25mg LOT 4201234B	73.7
Test Product 25mg LOT 4000381B	Test Product 25mg LOT 4201234B	54.6
Test Product 37.5mg LOT 4000381C	Test Product 37.5mg LOT 4201234C	53.4
Test Product 50mg LOT 4000381D	Test Product 50mg LOT 4201234D	53.2

* BE Batch

BIOPHARMACEUTICS ANDA REVIEW

Application No.	ANDA 214068-ORIG-1-AMEND-16
Product Name/Strengths	Risperidone Long Acting Injection/ 12.5mg, 25mg, 37.5mg, and 50mg
Applicant	Teva Pharmaceuticals USA Inc
Dosage Form /Route of Administration	Powder for Injection/intramuscular injection
Indication for Use	1) Treatment of schizophrenia. 2) Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
RLD	NDA 021346 Risperdal Consta® (risperidone) Long Acting Injection (12.5mg, 25mg, 37.5mg, and 50mg)
Submission Date	5/27/2021
Primary Reviewer	Jia Yin, Ph.D.
Recommendation	ADEQUATE

REVIEW SUMMARY

This review is focused on the Applicant's response to the Biopharmaceutics deficiencies in the Complete Response Letter (CRL) dated 10/14/2020. The deficiencies, the Applicant's responses, and the reviewer's assessment are in **Appendix 1**. Overall, the responses are adequate. The Applicant has addressed several concerns regarding the dissolution method. The proposed dissolution method is now acceptable. The provided dissolution data of the biobatch and exhibit batches¹ also support the proposed dissolution acceptance criteria.

Conclusion and Recommendation: From a Biopharmaceutics perspective, ANDA 214068-ORIG-1-AMEND-16 for Risperidone Long-Acting Injection is ADEQUATE. The Approved dissolution method and acceptance criteria are shown below:

Apparatus	Medium/ Temperature	Volume (mL)	Acceptance Criteria
Cylinder bottle	HEPES buffer pH 7.4 /37°C (normal) and 45°C (accelerated) water bath	200	At 37 °C: NMT 10% in day 1 NMT 10% in day 21

¹ \\CDSESUB1\evsprod\anda214068\0012\m2\27-clin-sum\comparative-dissolution-report.pdf

			At 45 °C: (b) (4) % in 120 hr (b) (4) % in 160 hr NLT (b) (4) % in 210 hr
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Appendix 1: Biopharmaceutics Deficiencies and the Applicant's Response

1. Provide the aqueous solubility data for the drug substance, risperidone, in your drug product over the physiological pH range (b) (4) at 37°C to support your claim regarding the solubility.

Applicant's Response:

The Applicant provided solubility data across the pH range (b) (4) at 37°C and 45°C (Table 1 and 2).

Table 1 Solubility at 37°C

Average concentration (n=3) of dissolved Risperidone (mg/mL)						
Time (hours)	(b) (4)					Hepes buffer pH 7.4 (b) (4)
3	(b) (4)					(b) (4)
24						
44						
90						
140						
190						
Saturation Solubility (mg/mL)	≥ 5.04	3.55	4.07	1.29	0.55	0.59

Table 2 Solubility at 45°C

Average concentration (n=3) of dissolved Risperidone (mg/mL)						
Time (hours)	(b) (4)					Hepes buffer pH 7.4 (b) (4)
3	(b) (4)					(b) (4)
24						
44						
90						
140						
190						
Saturation Solubility (mg/mL)	≥ 5.05	3.51	3.77	1.15	0.52	0.6

Reviewer's Assessment:

In the previous review cycle, the Applicant stated that the API (risperidone) is soluble at a concentration (b) (4) at both 37°C (normal) and 45°C (accelerated) conditions. However, no detailed solubility data were provided. In this response, the Applicant provided the requested solubility data. The response is adequate.

2. We acknowledge that you have adopted the dissolution method in the product specific guidance (PSG) for risperidone intramuscular injection for your proposed drug product. It is noted that for (b) (4) is proposed, while for the other strengths (b) (4) is proposed. Unless you have convincing or appropriate rationale and justification for using different medium volumes for different strengths, we request that optimize the dissolution method using the same medium volume for all strengths of your product.

Applicant's Response:

The Applicant revised the dissolution medium volume for the 12.5 mg strength from (b) (4) and compared the dissolution profiles for the 12.5 mg strength using both (b) (4) medium volumes (Figure 1 and 2).

Figure 1 Dissolution comparison for 12.5 mg (b) (4) medium volumes and at 45°C

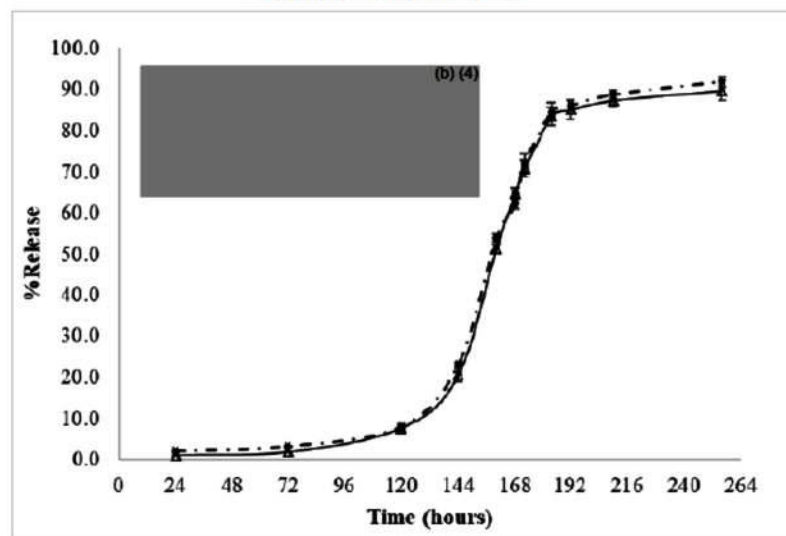
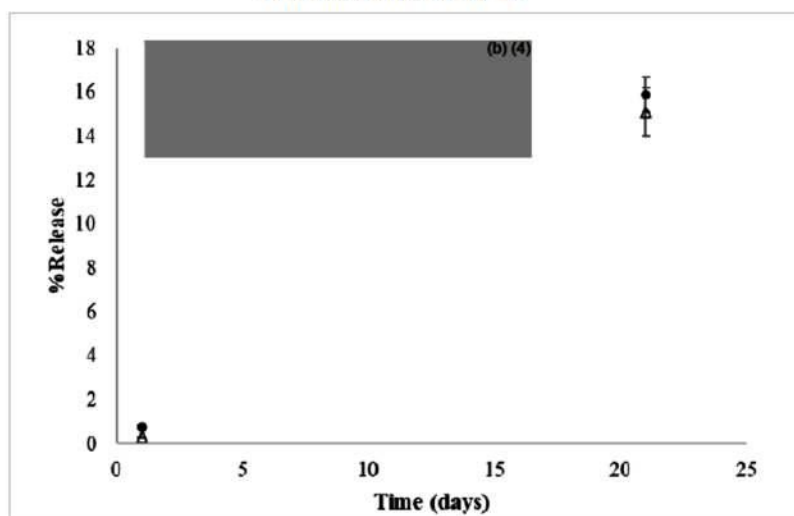


Figure 2 Dissolution comparison for 12.5 mg strength in [REDACTED] (b) (4)
volumes and at 37°C



Reviewer's Assessment:

The response is adequate.

3. We acknowledge that you have evaluated the discriminating ability of your proposed dissolution method. However, the changes of the tested critical process parameters (CPPs) are beyond what the Agency typically recommended range, i.e., $\pm 20\%$ of target value, without appropriate justification. Re-evaluate the discriminating ability of your proposed dissolution method against critical material attributes (CMAs) and CPPs that affect dissolution of your product. Submit the following information and data to demonstrate the discriminating ability of the dissolution method:
 - a) A list of CMAs and CPPs affecting the dissolution of your product.
 - b) Percentage change of CMAs and CPPs of the tested aberrant batches.
 - c) Complete in vitro dissolution data (individual, mean, SD, RSD) and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference/target drug products.
 - d) If available, data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference/target drug product.

Note that, if different dissolution medium volume is used for different strengths of your product, discriminating ability of the dissolution method needs to be demonstrated for each dissolution medium volume.

Applicant's Response:

The Applicant re-evaluated the discriminating ability of the dissolution method against the CMA and CPPs shown in **Table 3**. Total 10 aberrant batches were manufactured, and dissolution profile of the aberrant batches were compared with that of the target batch (**Table 4**). Details for each aberrant batch can be found at <\\CDSESUB1\evsprod\anda214068\0016\m1\us\response-doc.pdf>.

Table 3 CMA and CPPs and the range of their variations for demonstration of discriminating ability of the dissolution method



(b) (4)

Table 4 f2 values of the aberrant batches (trial formulation) vs. the target batch (optimal lab trial formulation)

Comparison	f2 value
Formulation trial 1 vs optimum lab trial formulation	76.4
Formulation trial 2 vs optimum lab trial formulation	63.1
Formulation trial 3 vs optimum lab trial formulation	42.9
Formulation trial 4 vs optimum lab trial formulation	64.5
Formulation trial 5 vs optimum lab trial formulation	49.2
Formulation trial 6 vs optimum lab trial formulation	47.7
Formulation trial 7 vs optimum lab trial formulation	27.8
Formulation trial 8 vs optimum lab trial formulation	22.9
Formulation trial 9 vs optimum lab trial formulation	16.1
Formulation trial 10 vs optimum lab trial formulation	55.6

Reviewer's Assessment:

Based on the provided data, the discriminating ability of the dissolution method has been demonstrated. The response is adequate.

- In your Table 34 of Pharmaceutical Development Report, one of the tested dissolution medium pH is (b) (4). In Table 35, Table 36, Figure 26, and Figure 27 of the same document, the pH value is (b) (4). Clarify your tested dissolution medium pH and update the information in your Pharmaceutical Development Report.

Applicant's Response:

The Applicant clarified that the dissolution medium pH is (b) (4) and the pH value in Table 34 of the Pharmaceutical Development report is updated.

Reviewer's Assessment:

The response is adequate.



Jia
Yin

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BIOPHARMACEUTICS ANDA REVIEW

Application No.	ANDA 214068-ORIG-1
Product Name/Strengths	Risperidone Long Acting Injection/ 12.5mg, 25mg, 37.5mg, and 50mg
Applicant	Teva Pharmaceuticals USA Inc
Dosage Form /Route of Administration	Powder for Injection/intramuscular injection
Indication for Use	1) Treatment of schizophrenia. 2) Monotherapy or adjunctive therapy to lithium or valproate for the maintenance treatment of Bipolar I Disorder
RLD	NDA 021346 Risperdal Consta® (risperidone) Long Acting Injection (12.5mg, 25mg, 37.5mg, and 50mg)
Submission Date	12/16/2019
Review Date	5/23/2020, 7/30/2020
Primary Reviewer	Jia Yin, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.
Recommendation	Inadequate - Minor

REVIEW SUMMARY

The reference listed drug (RLD) for the proposed drug product is Risperdal Consta® (risperidone) Long Acting Injection under NDA 021346 held by Janssen Pharmaceuticals Inc. The proposed formulation is deemed by Office of Generic Drug (OGD) to be qualitatively and quantitatively same as the RLD.¹

The proposed drug product is provided as a dose pack, consisting of a vial containing the risperidone powder (b) (4)

(b) (4), a pre-filled syringe containing 2 mL of diluent for extended-release injectable suspension of risperidone, a vial adapter, and two Terumo SurGuard® 3 Needles for intramuscular (IM) injection. The risperidone powder needs to be suspended in the diluent prior to IM injection. After injection, (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

¹ <\\cdsesub1\evsprod\anda214068\0001\m2\23-qos\drug-prod-powder.pdf>

(b) (4)

Biopharmaceutics review is focused on the in vitro dissolution specification (dissolution method and acceptance criteria) of risperidone powder.

The Applicant adopted the dissolution method in the product specific guidance (PSG) for risperidone IM injection and investigated the discriminating ability of the method against several process parameters (b) (4)

However, different medium volumes (b) (4) were proposed for different strengths and the change of the process parameters during the evaluation of the discriminating ability of the dissolution method is beyond the Agency typically recommended range (i.e., $\pm 20\%$ of target value). The Biopharmaceutics deficiencies will be conveyed to the Applicant in Complete Response Letter (CRL).

The assessment of the proposed dissolution acceptance criteria is pending the decision on the dissolution method.

Conclusion and Recommendation: From a Biopharmaceutics perspective, ANDA 214068 for Risperidone Long Acting Injection is INADEQUATE due to unacceptable dissolution method.

REVIEWER'S ASSESSMENT

a) Solubility

According to the Applicant, the API (risperidone) is soluble at a concentration greater than 2.5 mg/mL in tested media (b) (4) at both 37°C (normal) and 45°C (accelerated) conditions. However, no detailed solubility data were provided. The Applicant will be requested to provide solubility data for the drug substance over the (b) (4).

b) Proposed Dissolution Method

Apparatus	Medium/ Temperature	Volume (mL)	Sampling time
(b) (4)			

During the product development, the Applicant developed a dissolution method for risperidone powder (b) (4). After the product specific guidance (PSG) for risperidone IM injection was updated to include a recommendation for in vitro dissolution method, the Applicant updated the dissolution method (b) (4).

(b) (4)

Recommended dissolution method in PSG for risperidone IM injection

Type of study: In vitro drug release
 Strength: 25 mg/vial
 Medium: Dissolution medium (pH 7.4) prepared as indicated below
 Volume: 400 mL (200 mL for each temperature)
 Apparatus: Cylinder bottle
 Temperature: 37 °C and 45 °C (water bath)
 Sampling Times: Day 1 and Day 21 for 37 °C
 Multiple time points from Days 0 to 8 for 45 °C. Two sampling time points, that bracket T_{50%} (which is defined as the time of 50% drug release), are to be linearly interpolated to determine T_{50%}.

* pH 7.4 medium is prepared in HEPES buffer

The Applicant further evaluated different dissolution media (Table 1) in both (b) (4) (b) (4). The results at (b) (4) (Table 2 and Figure 1) and at (b) (4) (Table 3 and Figure 2) are shown below. According to the Applicant, the release profiles obtained in (b) (4)

2 Pages have been withheld in full as b4 immediately following this page

(b) (4)

Reviewer's assessment

(b) (4)

The provided data support the selection of pH 7.4 medium. However, it is noted that (b) (4) are proposed for (b) (4)

(b) (4) The Applicant will be requested to provide justification for dissolution medium volume. It is also noted that during the evaluation of the discriminating ability of the proposed dissolution method, the changes of CPPs are beyond the typically recommended range, i.e., $\pm 20\%$ of target value, without appropriate justification. The Applicant will be requested to re-evaluate the discriminating ability of the proposed dissolution method.

c) Proposed Dissolution Acceptance Criterion

(b) (4)

The assessment of the proposed dissolution acceptance criteria is pending the decision on the proposed dissolution method.

BIOPHARMACEUTICS DEFICIENCIES

1. Provide the aqueous solubility data for the drug substance, risperidone, in your drug product over the (b) (4) to support your claim regarding the solubility.

2. (b) (4)
(b) (4)
(b) (4)
(b) (4) is proposed.
Unless you have convincing or appropriate rationale and justification for using different medium volumes for different strengths, we request that optimize the dissolution method using the same medium volume for all strengths of your product.

3. We acknowledge that you have evaluated the discriminating ability of your proposed dissolution method. However, the changes of the tested critical process parameters (CPPs) are beyond what the Agency typically recommended range, i.e., $\pm 20\%$ of target value, without appropriate justification. Re-evaluate the discriminating ability of your proposed dissolution method against critical material attributes (CMAs) and CPPs that affect dissolution of your product. Submit the following information and data to demonstrate the discriminating ability of the dissolution method:
 - a) A list of CMAs and CPPs affecting the dissolution of your product.
 - b) Percentage change of CMAs and CPPs of the tested aberrant batches.
 - c) Complete in vitro dissolution data (individual, mean, SD, RSD) and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference/target drug products.
 - d) If available, data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference/target drug product.

Note that, if different dissolution medium volume is used for different strengths of your product, discriminating ability of the dissolution method needs to be demonstrated for each dissolution medium volume.

4. In your Table 34 of Pharmaceutical Development Report, one of the tested dissolution (b) (4). In Table 35, Table 36, Figure 26, and Figure 27 of the same document, the (b) (4). Clarify your tested dissolution medium pH and update the information in your Pharmaceutical Development Report.



Ta-Chen
Wu

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Jia
Yin

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DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	214068	
Drug Product Name	Risperidone Long-Acting Injection	
Strength(s)	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	
Applicant Name	Teva Pharmaceuticals USA Inc.	
Applicant Address	Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054	
US Contact Name and US Mailing Address	Anil Sachdeva Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054 anil.sachdeva@tevapharm.com	
US Contact Telephone Number	(b) (6)	
US Contact Fax Number	973-658-0057	
Original Submission Date(s)	December 16, 2019	
Submission Date(s) of Amendment(s) Under Review	July 20, 2020 (Supporting Document #12)	
Primary Assessor	Zakaria Wahba, Ph.D.	
Secondary Assessor	Svetlana Cherstniakova, Ph.D.	
Tertiary Assessor	Wendy Cai, Ph.D.	
Study Number(s)	CAC15003	PHA-RIP.I-01.15-208/147
Study Type(s)	Fasting, Steady State (Pivotal)	Fasting, single dose (Pilot)
Strength(s)	25 mg/vial	25 mg/vial
Clinical Site	<u>Clinical Sites for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 04- State Psychiatric Hospital – Tsarev brod, Tsarev Brod, Bulgaria (BG04) 05- Center for Mental Health – Sofia District, Sofia, Bulgaria (BG05) 06- Center for Mental Health – Vratsa EOOD, Vratsa, Bulgaria (BG06)	

	07- State Psychiatric Hospital – Lovech, Lovech, Bulgaria (BG07) 08- State Psychiatric Hospital "Sveti Ivan Rilski", Novi Iskar, Bulgaria (BG08) 09- Center for Mental Health – Plovdiv EOOD, Plovdiv, Bulgaria (BG09) 10- MHAT - Levski EOOD, Levski, Bulgaria (BG10) 11- Instytut Psychiatrii i Neurologii, Warsaw, Poland (PL01) 12- Zespół Poradni Zdrowia Psychicznego, Toruń, Poland (PL02) 13- Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland (PL03) 14- Centrum Badań Klinicznych, Krakow, Poland (PL04) 15- Milickie Centrum Medyczne, sp. z o.o., Milicz, Poland (PL05) 16- Rodzinne Centrum Medyczne LUBIMED, Lublin, Poland (PL06) 17- Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ, Krakow, Poland (PL07) 18- Podlaskie Centrum Psychogeriatric, Bialystok, Poland (PL08) 19- IMSP Clinical Psychiatric Hospital, Chisinau, Moldova (MD01) 20- IMSP Psychiatry Hospital Balti, Balti, Moldova (MD02) 21- State University of Medicine and Pharmacy, Moldova (MD03) 22- PMSI Psychiatry Hospital Balti, MD3110, Moldova (MD04) 23- Hospital of Psychiatry and Phthisiopulmonology, Orhei, Moldova (MD05) <u>Clinical Sites for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Amman, Jordan
Clinical Site Address	<u>Clinical Sites address for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 4- 3 "Sveti Georgy Sofiyski" Str, 1000 Sofia, Bulgaria (BS04) 05- 309 "Slivnitsa" Blvd., Sofia Bulgaria (BG05) 06- Vratsa EOOD, 1 "Belasitsa" Str., 3000 Vratsa Bulgaria (BG06) 07- Lovech, 1 "Aleksandar Batenberg" str., Lovech 5500, Bulgaria (BG07) 08- Sveti Ivan Rilski, 140 Hristo Botev Str., Novi Iskar 1282, Bulgaria, (BG08) 09- Plovdiv EOOD, 68 Peshetrsko shosse Blvd., 4002 Plovdiv, Bulgaria (BG09) 10- Levski EOOD, 5 Nikola Vaptsarov, 5900 Levski, Bulgaria (BG10) 11- ul. Jana III Sobieskiego 9, 02-957 Warszawa, Poland (PL01) 12- ul. A. Mickiewicza 24/26, 87-100 Toruń Poland (PL02) 13- ul. Dębinki 7 80-952 Gdańsk, Poland (PL03) 14- Life Science Parkul. Bobrzyńskiego 14 30 - 348 Kraków, Poland (PL04) 15- Grzybowa 1, 56-300 Milicz, Poland (PL05) 16- ul. Woronieckiego 1120-492 Lublin, Poland (PL06) 17- ul. Babińskiego 39, 30-393 Kraków, Poland (PL07) 18- ul. Swobodna 38/9, 15-756 Białystok, Poland (PL08) 19- Department no. 4, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD01) 20- Department no. 3, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD02) 21- 3, Costiujeni str., Chisinau, MD2011, Moldova (MD03) 22- 114, Gagarin str., Balti, MD3110, Moldova (MD04) 23- 2 Dubasari str., Orhei, MD 3500, Moldova (MD05) <u>Clinical Site for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Opposite Al-Jubaiha Circle, Amman, Jordan, Jordan
Analytical Site	(b) (4)

Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)	<u>Post October 1, 2014 ANDAs</u> ☐ To Be Determined by OSIS ☒ Pending ¹ ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☒ Granted ☐ Tentatively granted ☐ Not granted ☐ N/A	
QC Dissolution	☒ Pending ² ☐ Adequate ☐ Inadequate	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☐ No ☒ N/A	
Deficiency Classification	☐ Major ☐ Minor ☒ N/A (Review is Adequate)	
Major Deficiency Theme	NA	
Justification for Major Designation	NA	
Overall Review Result	☒ Adequate ☐ Inadequate	

¹ For details see: GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020;

<https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

² The dissolution testing for establishment of the regulatory method and specifications for the test product for quality control (QC) purpose was reviewed separately in a biopharmaceutics review with an “Inadequate – Minor” outcome.

Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: August 2016 RLD Number: NDA 021346 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 12	Steady State	25 mg/vial	☒ Adequate ☐ Inadequate
1, 12	In Vitro Drug Release Test	25 mg/vial	☒ Adequate ☐ Inadequate
1, 12	Waiver/Deem Bioequivalent	12.5, 37.5 and 50 mg/vial	☒ Adequate ☐ Inadequate

Review of a Response to Discipline Review Letter (DRL)

1 EXECUTIVE SUMMARY

This is a bioequivalence amendment (Supporting Document #12) assessment of Teva Pharmaceuticals USA Inc.'s response to a Discipline Review Letter (DRL) dated 06/15/2020 for its Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial.³

Per the original bioequivalence (BE) assessment⁴, the applicant conducted a pivotal steady-state BE study (#CAC15003) comparing Teva Pharmaceuticals USA Inc.'s Risperidone Long-Acting Intramuscular Injection, 25 mg/vial, to the corresponding reference standard (RS) product, Janssen Pharmaceuticals Inc.'s Risperdal Consta[®] (risperidone) Intramuscular Injection, 25 mg/vial. The pivotal BE study was found inadequate due to deficiencies related to pre-study method validation, missing information for study design, resubmission of concentration and pharmacokinetic (PK) datasets, and missing supportive data for steady-state attainment of individual subjects. In addition, in vitro drug release test was inadequate due to deficiency related to missing T_{50%} analysis data.⁵

In the current amendment (07/20/2020), the applicant provided adequate responses to the identified deficiencies (for details refer to section 4.3 of this assessment report).

A total of seventy-seven (77) patients were dosed at 14 clinical sites in 3 countries (Bulgaria, Moldova and Poland) for the pivotal BE study (#CAC15003).⁶ To assess the BE of this steady state BE study (#CAC15003), the assessor performed following statistical and BE analyses using the resubmitted datasets: (i) with inclusion of data from all 77 patients who completed study according to the protocol (N= 77), (ii) with exclusion of data from 8 patients who did not demonstrate steady-state attainment based on the linear regression analysis (N= 69); and (iii) with exclusion of 3 patients (b) (6) who did not demonstrate steady-state attainment based on the regression analysis and having a greater than 20% difference in pre-dose trough levels between Day 42 and Day 28 (N= 74).

Since patients were dosed at 14 clinical sites in 3 countries, TRT*GRP (country) interaction term was initially included in the SAS model for the BE analysis. There was no significant TRT*GRP interaction ($p > 0.1$) for AUC_{tau} and C_{max,ss} of risperidone in all 3 analyses (N = 77, 69 or 74 patients). Therefore, TRT*GRP term was dropped from subsequent analysis. The BE criteria are all met for LnAUC_{tau} and LnC_{max,ss} in the 3 BE analyses with data from 77, 69, or 74 patients. The results calculated by the current assessor (for N = 74) are summarized in

³ DARRTS: ANDA 214068, dated 04/01/2020, M1.11 Response to DRL; [\cdsesub1\evsprod\anda214068\0012\m1\us\drl-response-to-fda.pdf](#)

⁴ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

⁵ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

⁶ For details, please see GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

the tables below (refer to section 4.3 of this review for all analyses in response to Deficiency #6).

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=74 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)							
Fasting Bioequivalence Study (Study No. CAC15003)							
Parameter (units)	Test	N	RLD	N	Ratio (T/R)	90% C.I.	
Ln(AUC_Tau) [ng*h/mL]	1625.56	74	1843.33	74	0.88	84.15	92.42
Ln(Cmax) (SS) [ng/mL]	8.71	74	9.91	74	0.88	80.85	95.40

On 05/13/2020, the Division of Bioequivalence III (DBIII) sent a consult request to the Division of Clinical Review (DCR)⁷ regarding two serious adverse (SAEs) events for patients (b) (6) (low hemoglobin and anemia) and patient (b) (6) (pneumonia), with the test product treatment during the pivotal BE study. On 8/24/2020, the DCR⁸ responded to the DBIII's consult request with the following conclusion: *"The SAE of anemia in Subject (b) (6) and pneumonia in Subject (b) (6) were unlikely related to the administration of the test product. The occurrence of these adverse events does not indicate a safety or quality concern for the test product compared to the reference listed drug (RLD)".*

The formulation of test product is qualitatively (Q1) and quantitatively (Q2) the same as the RLD for all strengths, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial and is proportionally similar across all strengths. The test product formulation is adequate.

In addition to the in vivo BE study, the in vitro drug release study on the 25 mg/vial strength was conducted per the current product specific guidance (PSG) for this drug.⁹ The % cumulative drug release for the test and reference products is comparable at Day 1 and Day 21 at 37 °C, and at Day 8 at 45 °C. The 90% confidence interval (CI) of the test/reference ratio of T_{50%} at 45 °C is within the acceptable range (80.00-125.00%). The results are provided in the table below (refer to section 4.3 of this review in response to Deficiency #7)

Risperidone Long-Acting Injection Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)							
Fasting Bioequivalence Study (Study No. CAC15003)							
Parameter	Test	N	RLD	N	Ratio (T/R)	90% C.I.	
T50% (hours)	158.02	12	161.05	12	0.9812	0.9782 (97.82%)	0.9842 (98.42%)

⁷ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB_ConultRequest01-DCR04272020.doc, dated 05/13/2020; <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f78f6bcf470202aflac3>

⁸ GDRP: ANDA 214068, Application Life Cycle, file: A214068_DCR-Review_Risperidone Injection_SAEs.docx, dated 08/24/2020; <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f7b6eb473ee6794cddb9>

⁹ [https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf)

The dissolution testing for establishment of the regulatory method and specifications for the test product for quality control (QC) purpose was reviewed separately in a biopharmaceutics review with an “Inadequate-Minor” outcome.¹⁰

The dissolution data are adequate with respect to supporting waiver request(s) under 21 CFR 320.24(b)(6) for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths. The DBIII grants the waiver requests for in vivo BE study requirements for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths based on criteria set forth in 21 CFR § 320.24(b)(6).

OSIS Outcome: Routine inspections of the clinical sites [(i) State Psychiatric Hospital Pazardzhik, Bulgaria, (ii) MHAT "Dr. Ivan Seliminski" JSC, Bulgaria, and (iii) PMSI Clinical Psychiatric Hospital, Republic of Moldova] for the current ANDA (#214068) are **pending**.¹¹ The study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the assessor. The OSIS inspection status of the current ANDA is pending. Upon completion of the BE Site Inspection tasks by OSIS, the BE review team will evaluate the inspection outcome (per EIR or Decline to Inspect Memo).

The application is **adequate**.

¹⁰ GDRP; ANDA-214068-ORIG-1; Biopharmaceutics review; file: ANDA 214068 biopharm review.docx ; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6feca8242a10f0805801>

¹¹ No change from the original assessment (for details, see section 3.6 of the original assessment); GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

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3 BACKGROUND INFORMATION

- In the original submission (12/16/2019), the applicant submitted results of a pivotal steady-state fasting BE study (#CAC15003) comparing a test product, Teva Pharmaceuticals USA Inc.'s Risperidone Long-Acting Injection, 25 mg/vial, to the corresponding reference standard (RS) product, Janssen Pharmaceuticals Inc.'s Risperdal Consta® (risperidone) Intramuscular Injection, 25 mg/vial. The BE study was designed as a randomized, multiple-dose, multi-center, open-label, two-way crossover study in schizophrenic patients who are already receiving a stable regimen of 12.5, 25, 37.5 or 50 mg Risperdal Consta® biweekly via the intramuscular gluteal injections, at least four bi-weekly maintenance doses.¹²
- The applicant conducted the pivotal steady-state BE study, which is in line with the recommendations in the current PSG for this drug (recommended in Aug 2016).¹³ Deficiency was found with the concentration and PK datasets for the pivotal steady-state BE study and thus the applicant was asked to resubmit datasets in the DRL dated 06/15/2020. The BE analysis was not performed by the assessor in the original BE review. In addition, the applicant was asked to provide data to demonstrate steady-state attainment for individual subjects.
- Two serious adverse events (SAEs) were reported for patients (b) (6) (decreased haemoglobin and anemia) and (b) (6) (pneumonia) after administration of test product and one SAE was observed after administration of the reference product for patient (b) (6) (bilateral adnexitis) in the pivotal steady-state BE study (#CAC15003). A consult request was sent to DCR on 5/13/2020 to evaluate if the SAEs observed in patients (b) (6) indicate any safety concerns for the test product.¹⁴
- The formulation of test drug product contains the same active and inactive ingredients in the same concentration as the reference listed drug (RLD) product. Therefore, it is deemed as Q1 and Q2 the same as the RLD for all strengths, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial. The test drug product formulation is adequate.
- The in vitro drug release study on the 25 mg/vial strength was conducted per the current PSG.¹⁵ However, the applicant did not provide the data for T_{50%} at 45 °C and the 90% CI of the test/reference ratio of T_{50%}. Thus, the in vitro drug release study was inadequate. The applicant was asked to submit the in vitro drug release data in an electronic file and requested analysis.

¹² GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6c2e43210dc8b5cdddc3>

¹³

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

¹⁴ <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f78f6bcf470202af1ac3>

¹⁵

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

- The dissolution data were adequate with respect to supporting the waiver requests for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths. However, the waiver requests for in vivo BE study requirements for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths was not granted due to unacceptable in vivo steady-state BE study and in vitro drug release test on the 25 mg/ vial strength.

4 SUBMISSION SUMMARY

4.1 Drug Product Information and PK/PD Information

The drug product information and PK/PD information are provided in the original BE assessment, completed on 06/08/2020.¹⁶

4.2 Contents of Submission

Study Types	Yes/No?	How many?
BE Studies	No	--
Solubility	No	--
Permeability	No	--
In vitro dissolution	No	--
Waiver requests	No	--
BCS Waivers	No	--
Failed Studies	No	--
Amendments	No	1

4.3 Review of Responses to DRL dated June 15, 2020¹⁷

Deficiency #1:

Based on your submitted bioequivalence (BE) Summary Table 10 Study Information (Module 2.7) for the pivotal BE study No. CAC15003, the total sample storage duration is 625 days. Per your bioanalytical report, study samples were initially stored at clinical sites and then transferred to the bioanalytical sites, and storage duration was up to 414 days for sample aliquote-1 and up to 476 days for sample aliquote-2 at clinical sites (i.e., Subject (b) (6)). However, you only provided separate long-term storage stability data for 358 days at -70 °C and a total of 425 days at 2 different temperatures (417 days at -30 °C and 8 days at 5 °C or 351 days at -30 °C and then 74 days at -70 °C). It is also noted that during shipment of sample aliquot-2, the temperature was up to 22.2 °C for some subject samples. Please clarify the sample storage duration and temperature at clinical site and analytical site, as well as sample shipment time and temperature for each subject, and provide the additional long-term storage stability data to cover the study sample storage duration and condition.

¹⁶ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6c2e43210dc8b5cdddc3>

¹⁷ DARRTS: ANDA 214068, dated 07/20/2020, Cover Letter; <\\cdsesub1\evsprod\anda214068\0012\m1\us\cover-letter.pdf>

Applicant's Response to Deficiency #1:

We acknowledge the agency's comment and wish to clarify that the total sample storage duration (i.e. 625 days) was derived by considering the first day of sample collection of the first subject (i.e. (b) (6) of subject (b) (6)) to the last day of retrieval of samples from the deep freezer for analysis of the last ISR run (i.e. (b) (6)). However, when the sample storage duration was calculated for each subject, none of the subjects experienced 625 days of storage from the day of first sample collection to the last day of analysis because the samples were analyzed as and when they were received from the clinical sites. As an example, for subject (b) (6) the duration of long-term storage is 406 days (first day of sample collection: (b) (6) to last day of retrieval of samples from deep freezer for analysis of ISR run: (b) (6)).

This study was conducted at multiple clinical sites and dosing was performed on different days. After collection of samples from the subjects, they were stored at -20°C or lower at each clinical site and a local Bulgarian site management organization (SMO), Milray JSC. Subsequently these samples were transferred to the bioanalytical site for analysis in multiple shipments. Please note that the SMO, Milray JSC, was referred to as a local CRO in the bioanalytical report. Upon receipt, these samples were stored at -70°C at the bioanalytical site till analysis. Considering a longer than average study duration and an anticipated longer storage period, analysis was conducted in multiple stages to reduce the long-term stability duration.

The details of first day of sample collection and last day of retrieval of samples from deep freezer for analysis of ISR run for each subject are presented in Table 1. ***(For details and convenience of the reviewing process, the applicant's Table 1: Storage duration of study samples for study # CAC15003, is provided in the Attachments section 4.7).***

In this study, samples of subject (b) (6) have experienced the maximum duration of storage as compared to other subjects, wherein Aliquot-1 samples of subject (b) (6) were stored for 424 days till completion of analysis (first day of sample collection: (b) (6) to last day of retrieval of samples from deep freezer for analysis of ISR run: (b) (6)). These aliquot-1 samples of subject (b) (6) were stored at the clinical site for 414 days (from (b) (6) to (b) (6)) and then transferred to the bioanalytical site. The analysis of these samples including ISR was completed till (b) (6).

Aliquot-2 samples of subject (b) (6) were stored at the clinical site for 476 days (from (b) (6)) and then transferred to the bioanalytical site. Aliquot-2 samples of subject # 0015 were not used for analysis. Therefore, the maximum sample storage duration for this study was considered as 424 days based on aliquot-1 samples of subject (b) (6).

During conduct of analysis, subjects (b) (6) and subjects (b) (6) were analyzed using aliquot-2 and subjects (b) (6) were analyzed using aliquot-1. No samples for subjects (b) (6) were analyzed as these subjects did not complete both the study periods.

The long-term stability of risperidone in K₂EDTA plasma was performed on 3 occasions as mentioned below and reported in the method validation reports:

1. Long term stability for 358 days at -70°C.
2. Long term stability for 425 days, wherein the stability samples were stored at -30°C for 417 days and at 5°C for 8 days.
3. Long term stability for 425 days, wherein the stability samples were stored at -30°C for 351 days and at -70°C for 74 days.

When subject samples were stored at the clinical site, multiple temperature excursions were encountered, wherein the maximum temperature reached up to 1.7°C and the total duration of the temperature excursion was 154 hours for aliquot-2 samples and the maximum temperature reached up to 2.1 °C and the total duration of the excursion was 30 hours for aliquot-1 samples. To justify the maximum storage duration (i.e. 424 days) and temperature excursions (i.e. 1.7°C and 2.1°C) observed during sample storage at clinical site, long term stability was evaluated for 425 days wherein the stability samples were first stored at -30°C (acceptance range -20°C to -35°C) for 417 days and then transferred to 5°C storage for 8 days. This stability mimics the actual sample storage conditions and covers the entire storage duration of all analyzed subjects of this study.

We would like to clarify that even though we performed three long term stabilities, the long-term stability for 425 days (at -30°C for 417 days and at 5°C for 8 days) is applicable for this study and other two long term stabilities are additional and are not applicable for subject sample analysis of this study.

We would like to clarify that during transit period of aliquot-2 samples, the maximum temperature reached up to -25.9°C which was recorded by data logger ID FDJ2200GC0 (refer section 8.7.2 of the bioanalytical report, Module 5.3.1.4). In section 8.7.2 of the bioanalytical report, the reported temperature of 22.2°C was recorded by the data logger (ID FDJ2201370) immediately after placement of data logger inside the sample shipment container at the local SMO in Bulgaria. A note has been mentioned under section 8.7.2 of the bioanalytical report that *“Though the actual temperature range during transit period is ranging from -87.5°C to 22.2°C, the temperature 22.2°C is not actual temperature. This temperature is reached by data logger immediately after placement. After that data logger temperature reached at acceptable temperature range (-60°C to -80°C), further there was no excursion.”*

The plasma samples from the clinical sites at Bulgaria were transferred to a local SMO for interim storage till transfer to the bioanalytical site. For transfer of samples from the local SMO in Bulgaria to the bioanalytical site at India, aliquot-2 samples were retrieved from the deep freezer at the local SMO at 13:00 hrs (local time Bulgaria) on (b) (6). These samples were packed in an insulated container with sufficient dry ice and the data logger (ID FDJ2201370) was placed into the sample container to monitor the temperature during the entire transit period. The data logger was switched on at 13:11 hrs (local time Bulgaria) on (b) (6).

After delivery of this shipment at the bioanalytical site in India on (b) (6), during the receiving process of these samples, it was observed that the samples were in acceptable frozen condition. The data logger temperature was noted to have reached up to 22.2°C. Thus, a supposed temperature excursion was observed for a few minutes at the beginning of the temperature logger recording. However, this minor supposed temperature deviation is not a concern, since room-temperature benchtop stability with an acceptance limit of 24°C ± 5°C was established for up to 15 hours during method validation. This information can be located in method validation report # VR-318-16-03 section 5.5 (page 80, 81 of 540) and section 10.0 table 8 (page 92 of 540) (in Bioanalytical Study Validation Report in Module 5.3.1.4, eCTD Seq. 0001). It is also noted that the samples were immediately placed into the shipping container with sufficient dry ice upon pulling them from the freezer at 13:00 hrs. This was confirmed by the SMO in the attached signed Biological Sample Shipment Record and signed Note to File (refer to *Attachments # 01 and 02, respectively*). It's theorized that adequate time to equilibrate the temperature logger in the shipping container prior to its recording was not given and is therefore, not a true temperature deviation. Furthermore, the temperature logger quickly reached below -60°C after 24 minutes and was maintained till receipt of the samples at the bioanalytical site in India and the room-temperature stability data covers any supposed temperature increase up to 22.2°C.

The details of sample storage durations and temperatures at the clinical sites (including interim storage at local SMO in Bulgaria) for aliquot-1 and aliquot-2 are presented in sections 8.6.1 and 8.6.2 respectively, of the Bioanalytical Study Report (in Module 5.3.1.4 of eCTD Seq. 0001).

The details of sample storage durations and temperatures at the bioanalytical site for aliquot-1 and aliquot-2 are presented in section 8.8.1 and 8.8.2 respectively, of the Bioanalytical Study Report (in Module 5.3.1.4 of eCTD Seq. 0001).

The dates of the sample shipments, receipt at the bioanalytical site, and temperatures during shipment for aliquot-1 and aliquot-2 are presented in sections 8.7.1 and 8.7.2, respectively, of the Bioanalytical Study Report (in Module 5.3.1.4 of eCTD Seq. 0001).

We would like to assure that the long-term stability performed for 425 days (at -30°C for 417 days and at 5°C for 8 days) covers the study sample storage duration and condition for all analyzed subjects of study # CAC15003.

Assessor's Comments on Applicant's Response to Deficiency #1:

The applicant indicated that the total sample storage duration (i.e. 625 days) was derived by considering the first day of sample collection of the first subject (i.e. (b) (6) of subject # (b) (6)) to the last day of retrieval of samples from the deep freezer for analysis of the last ISR run (i.e. (b) (6)). However, when the sample storage duration was calculated for each subject, none of the subjects experienced 625 days of storage because the samples were analyzed as and when they were received from the clinical sites.

The details of first day of sample collection and last day of retrieval of samples from deep freezer for analysis for each individual subject was provided in the applicant's Table 1: Storage

duration of study samples for study # CAC15003 (For details, please see the table in the Attachments section 4.7).

The applicant also indicated that the long-term stability of risperidone in K₂EDTA plasma was performed on 3 occasions as mentioned below and reported in the method validation reports: (i). Long term stability for 358 days at -70°C, (ii) Long term stability for 425 days, wherein the stability samples were stored at -30°C for 417 days and at 5°C for 8 days, and (iii) Long term stability for 425 days, wherein the stability samples were stored at -30°C for 351 days and at -70°C for 74 days.

In this response, the applicant stated that the long-term stability performed for 425 days (at -30°C for 417 days and at 5°C for 8 days) covers the study sample storage duration and condition for all analyzed subjects of study # CAC15003.

The applicant's response to deficiency #1 is adequate.

Deficiency #2:

Per your clinical study report (No. CAC15003), the bioanalytical lab was moved to a new location between 04/26 – 05/20/2019 during the conduct of study. Based on your bioanalytical report (Protocol #CAC15003; issued date: 11 December 2019), the study sample analysis was conducted initially at Watson Pharma Pvt. Ltd., Unit V, International Technology Center (CBD Belapur Railway Station Complex Navi Mumbai – 400614, India), and later at Watson Pharma Pvt. Ltd. Seawoods Grand Central (Tower 2, Level-11, Wing-E, Plot No R-1, Sector 40, Nerul, Navi Mumbai –400706). Please clarify if additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site and provide the required method validation information per FDA guidance for Bioanalytical Method Validation (May 2018).

Applicant's Response to Deficiency #2:

We acknowledge the agency's comment and wish to clarify that the study sample analysis was conducted at two sites of (b) (4). (an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc) as mentioned in Table 2 below:

Table 2: Study sample analysis was conducted at two sites of Watson Pharma Pvt. Ltd

	Old Bioanalytical Site	New Bioanalytical Site
Site Name	(b) (4)	
Site address		
Analysis Duration		

We would like to clarify that the additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site as per FDA guidance for Bioanalytical Method Validation (May 2018) and in-house SOPs. The parameters to be evaluated for the change in bioanalytical site were included in the partial validation protocol # VP-318-16-03 (refer pg. 33/540 of the Bioanalytical Study Validation Report Module 5.3.1.4)

and the results of validation are included in the validation report # VR-318-16-03 (refer pg. 49/540 of the Bioanalytical Study Validation Report Module 5.3.1.4; also refer to Addendum 01 (pg. 315/540), Addendum 02 (pg. 513/540) for the validation report # VR-318-16-03). Addendum 03 to the validation report VR-318-16-03 (refer to Attachment # 03), is now included in the submission.

Assessor's Comments on Applicant's Response to Deficiency #2:

The applicant stated that study sample analysis was conducted at two sites of [REDACTED] (b) (4) [REDACTED] (an indirect wholly-owned subsidiary of Teva Pharmaceuticals USA, Inc).

- First study sample analysis was conducted at [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED].
- Second study sample analysis conducted at [REDACTED] (b) (4) [REDACTED] [REDACTED] [REDACTED].

The applicant also indicated that partial method validation (protocol # VP-318-16-03) was performed prior to the sample analysis at the new bioanalytical site. The results of partial method validation (protocol # VP-318-16-03) parameters that were performed prior to the sample analysis at the new bioanalytical site are acceptable and meet the acceptance criteria specified in method validation protocol ((# VP-318-16-03). *(For details and convenience of the reviewing process, the applicant's partial method validation no VP-318-16-03 for Deficiency 2, is provided in the Attachments section 4.7).*

The applicant's response to deficiency #2 is adequate.

Deficiency #3:

Per your clinical study report, it is unclear about the length of confinement for patients at the clinical sites during the course of study. Please provide this information.

Applicant's Response to Deficiency #3:

There was no overnight confinement for this study and as such, no confinement period was specified in the study protocol. The exact procedures to be followed for entry visit, drug administration, PK-sampling and final examination visit were described in sections 9.1 to 9.7 of the study protocol (refer pg. 90/403 of the Protocol and Protocol Amendments in Module 5.3.1.2) and sections 9.5.1.2.1, 9.5.1.2.2, 9.5.1.2.3 (refer pg. 55/102) and 9.5.4.1 (pg. 59/102) of the final study report. All patient visits were ambulatory. The patients were allowed to leave the site after the planned activities for the corresponding visits were completed. Please refer to the excerpt below from section 9.1 of the study protocol:

Both treatment periods together will last approximately 4 months for each patient. During this time the subjects will report to the clinic on the days of drug administration and blood sampling as ambulatory patients.

On the days of drug administration (days 0, 14, 28 and 42 of each study period) the patients will be requested to come to the clinic in the morning after an overnight fast and remain there for at least two hours. The patients will also return to the clinic as ambulatory patients on the days of blood sampling (including sampling collection for the 4h and 8h)¹⁸.

Assessor's Comments on Applicant's Response to Deficiency #3:

The applicant indicated that there was no overnight confinement nor confinement period specified in the study protocol. On the days of drug administration (days 0, 14, 28 and 42 of each study period) the patients were requested to come to the clinic in the morning after an overnight fast and the patients were allowed to leave the site after the planned activities for the corresponding visits were completed. The patients also instructed to return to the clinic as ambulatory patients on the days of blood sampling.

The applicant's response to deficiency #3 is adequate.

Deficiency #4:

Your pivotal BE study was conducted at 14 clinical sites. You did not include group as a variable in the submitted dataset. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose Number, Time (hours), Concentration. Please also resubmit the pharmacokinetic (PK) dataset including the following variable: Subject, Period, Sequence, Group, Treatment, Dose Number, and all relevant PK parameters (Cmax, AUCtau, Cavg, Cmin, Fluctuation, and Tmax).

Applicant's Response to Deficiency #4:

The legacy datasets, pk.xpt and conc.xpt have been updated to include group as a variable as specified in the FDA request. Each site refers to one group. All other variables specified in FDA's request are also included in the respective dataset. The corresponding define document has also been updated.

Assessor's Comments on Applicant's Response to Deficiency #4:

The applicant submitted the data for pk.xpt and conc.xpt with group variable as specified in the FDA request. It should be pointed out that submitted data was used to calculate the 90% CI for PK parameters of the study (provided below in response to deficiency #6).

The applicant's response to deficiency #4 is adequate.

Deficiency #5:

Per product specific guidance for Risperidone Long-Acting Injectable, an intensive sampling is recommended for the 3rd dosing interval in period 2. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose

¹⁸ Per the applicant study protocol (ANDA 214068, dated 12/16/2019, M5.3 section 16.1.1 Protocol); <\\CDSESUB1\evsprod\anda214068\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cac15003\protocol.pdf>

Number, Time (hours), Concentration for the 3rd dosing interval in period 2. Please also provide PK parameters such as C_{min} and C_{max} for this dosing interval.

Applicant's Response to Deficiency #5:

The concentration data for the 3rd dosing interval in period 2 are contained in the conc.xpt file in the CONC column and can be separated out by using the Filter tab conditions PERIOD=2 together with DOSENUM=3.

Please see below a summary of C_{max} (Peak) and C_{min} (Trough) values for the 3rd dosing interval in period 2. These values have also been included in the pk.xpt dataset within the PLABEL column, they are referred to as C_{max}(P2D3) and C_{min}(P2D3).

The applicant provided the information in Table 3: Peak and Trough levels of risperidone (ng/mL) in the third dosing interval in the second period (***For convenience of the reviewing process, the applicant's Table 3: Peak and Trough levels of risperidone (ng/mL) in the third dosing interval in the second period, is provided in the Attachments section 4.7).***

Assessor's Comments on Applicant's Response to Deficiency #5:

As requested by DBIII, the applicant submitted the data for the 3rd dosing interval in period 2 in an excel file (please see the attachment section 4.7, Sampling for the 3rd dosing interval in period 2 table). The submitted data was used to calculate the 90% CI for PK parameters of the 3rd dosing interval in period 2 of study (provided below in response to deficiency #6). The applicant also provided data on Peak and Trough levels of risperidone (ng/mL) for the third dosing interval in the second period (attachment in section 4.7).

The applicant's response to deficiency #5 is adequate.

Deficiency #6:

Per the FDA guidance for Industry: Bioequivalence studies with pharmacokinetic endpoint for drugs submitted under an ANDA (Issued December 2013), it is recommended that for steady-state study, applicant carry out appropriate dosage administration and sampling to document the attainment of steady-state. You collected multiple samples after 1st, 2nd, and 3rd injections. Please provide supporting document/data to demonstrate that individual patients have reached steady-state prior to conducting the BE analysis. Please also submit the dataset and SAS program for your analysis.

Applicant's Response to Deficiency #6:

According to the statistical analysis plan (SAP), we have shown population based steady state. See Section 9 (pg. 376/631) in the Documentation of Statistical Methods and Interim Analysis Plans in Module 5.3.1.2, Appendix 16.1.9.1 (pg. 17/631). Because mean steady state could be concluded, no further testing of individual steady state was required as per section 9.5 (pg. 379/631) of the SAP in Documentation of Statistical Methods and Interim Analysis Plans in Module 5.3.1.2, Appendix 16.1.9.2 (pg. 366/631).

The analysis of individual steady state can be performed using the analysis dataset ADPC (adpc.xpt) located in module 5's ADAM datasets folder in the original ANDA. A linear regression is determined through the (pre-dose) concentration values on days 0, 14, 28 and 42 using SAS (Version 9.4 on Windows 10).¹⁹

The subjects (Random Numbers) for which individual steady state was not shown are:

(b) (6), (b) (4)

For sensitivity purpose, evaluation of bioequivalence was then performed with those subjects that did not meet individual steady state removed. Please see the full statistical analysis attached (CAC 15003_Results_without_SS_failures) with a summary of the results below. As shown, bioequivalence between the two drug products is still met.

(b) (6)

Assessor's Comments on Applicant's Response to Deficiency #6:

Per original BE review, 77 patients were dosed at 14 clinical sites in 3 countries (Bulgaria, Moldova and Poland) for the pivotal steady-state BE study (#CAC15003).²⁰

1. The assessor conducted following three BE analyses²¹ to assess the bioequivalence of the current steady state BE study using the resubmitted datasets:

- 1) The assessor conducted statistical and BE analysis on the 77 dosed patients who completed study according to the protocol (N= 77; see table below). Since patients were dosed at 14 clinical sites in 3 countries, TRT*GRP (country) interaction term was initially included in the SAS model for the BE analysis. There was no significant TRT*GRP interaction for

¹⁹ The applicant submitted its SAS program code, for convenience of the reviewing process, the applicant's SAS program code is provided in the Attachments section 4.7.

²⁰ Details of the dosed subjects are provide in the original DB-review for this ANDA; please refer to: GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB-Review01-12162019.docx, dated 06/08/2020; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6c2e43210dc8b5cdddc3>

²¹ The statistical analyses for this ANDA were conducted by Dev Patel, Pharm. D., the OB/DBIII consultant for statistical analysis.

AUCtau (p= 0.404) and Cmax,ss (p= 0.469) of risperidone. Therefore, TRT*GRP term was dropped from subsequent analysis. The BE criteria are met for LnAUCtau and LnCmax,ss in the BE analysis with data from 77 patients (see table below).

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=77 Least Squares Geometric Means, Ratio of Means Fasting Bioequivalence Study (Study No. CAC15003)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC(Tau) [ng*h/mL]	2174.96	126.18	570.55	22558.71	2502.51	113.87	577.29	21161.06	0.87
Cavg (SS) [ng/mL]	6.47	126.18	1.70	67.14	7.45	113.87	1.72	62.98	0.87
Cmax(SS) [ng/mL]	11.68	114.63	3.31	100.78	12.96	95.19	3.39	83.92	0.90
Cmin(SS) [ng/mL]	3.00	121.45	0.00	27.24	3.94	156.37	0.00	48.82	0.76
Fluctuation%	138.91	44.87	49.21	441.78	144.31	66.94	44.14	712.11	0.96
*Tmax(SS) [h]	72.00	-	4.00	336.00	48.00	-	0.00	336.00	1.50

* Tmax values are presented as median, range

Assessor's Comments:

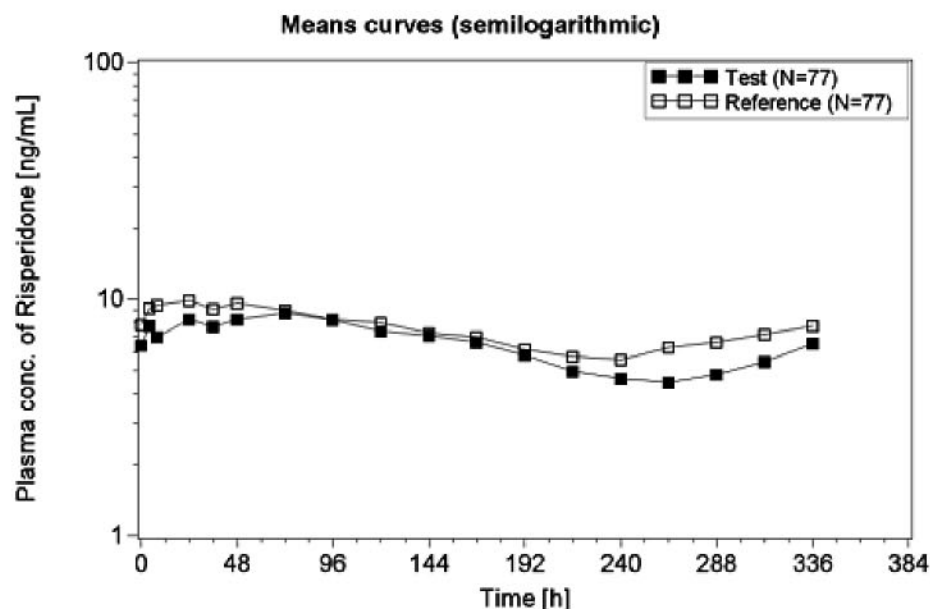
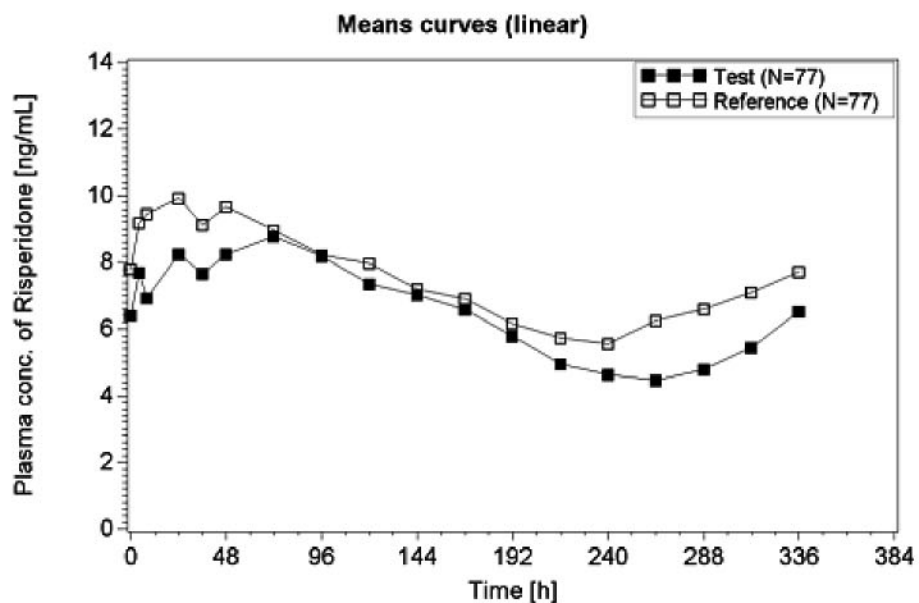
It is noted that for Subject (b) (6), the Cmax was observed at 0 hour for the reference product in Period 1 and 4 hours for the test product in Period 2 (see figures below). The assessor checked that the difference in plasma concentrations between time 0 (b) (4) and 4 hours post dose (b) (4) is minimal (b) (4) for the reference product. A fluctuation in plasma concentrations of risperidone was also observed for both test and reference products, especially in the early sampling time points. Thus, Subject (b) (6) was included in the BE analysis since the impact on Cmax results was minimal due to this observation.

(b) (6), (b) (4)

The median (range) Tmax values are 72.00 hours (range: (4.00 – 336.00 hours) for the test product and 48.00 hours (0.00 – 336.00 hours) for the reference product, with a T/R ratio of median Tmax as 1.5 and overlapping individual Tmax range. The Tmax information is not provided in the RLD labeling; however, the RLD labeling states the followings: “*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.*”²²

The assessor considers the observed difference in median Tmax between the test and reference products is acceptable for the following reasons: 1) Based on the mean plasma concentration profiles, the observed peak region is flat and broad (see figures below); 2) The individual Tmax values vary significantly with a wide and overlapping range for test and reference products (see table above); 3) The drug is a long-acting injectable given to patients on chronic bases, every 2 weeks; and 4) Thus, the observed difference in median Tmax (Day 3 and Day 2, respectively: the 2 sequential sampling time points) for the test and reference products should not have any significant impact on the therapeutic outcome.

²² Drugs@FDA, key word “Risperidone”, assessed date: 04/14/2020;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021346s063lbl.pdf



Risperidone Long-Acting Injection					
Dose: 1 x 25 mg Risperidone, n=77					
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals					
Fasting Bioequivalence Study (Study No. CAC15003)					
Parameter	Test	Reference	Ratio (T/R)	CI_90_Lower	CI_90_Upper
Ln(AUC_Tau) [ng*h/mL]	1612.15	1837.40	0.88	83.77	91.90
Ln(Cmax) (SS) [ng/mL]	8.62	9.91	0.87	80.28	94.28

- 2) In the current amendment, the applicant provided the results of liner regression using pre-dose concentrations on Days 0, 14, 28 and 42 for individual subjects to demonstrate steady-state attainment, which showed that 8 subjects did not achieve the steady-state.

The assessor performed a linear regression analysis using the applicant's resubmitted dataset of pre-dose concentrations on Days 0, 14, 28 and 42 for individual patients, to verify whether patients reached steady-state prior to the 4th injection in each period. Based on the regression results, p-values of 8 patients are statistically significant (p-value < 0.05), suggesting that steady-state has not been reached (see table below).

RANNO*	per	Dependent	Parameter	Estimate	StdErr	tValue	Probt
1	1	lconc	day	0.058610	0.01262962	4.64	0.0434
1	2	lconc	day	0.008859	0.00184945	4.79	0.0409
11	1	lconc	day	0.019505	0.00417161	4.68	0.0428
12	1	lconc	day	-0.007810	0.00017776	-43.94	0.0005
32	1	lconc	day	0.036658	0.00792307	4.63	0.0437
38	2	lconc	day	0.017775	0.00401569	4.43	0.0474
76	2	lconc	day	-0.040915	0.00753447	-5.43	0.0323
83	1	lconc	day	-0.004749	0.00044682	-10.63	0.0087
89	2	lconc	day	0.015206	0.00193720	7.85	0.0158

*RANNO = subject number

Note: The outcome of the assessor's regression analysis (Table above) matches the applicant's results provided in the DRL response.

The assessor also plotted the data for 4 pre-dose concentrations to verify the steady-state of individual patients (figures presented below).

Stick plot for test product (pre-dose concentration for days 0, 14, 28 and 42)

Figure represents: Days 0, 14, 28 and 42 (x-axis) vs. pre-dose concentrations in ng/mL (y-axis)



Stick plot for reference product (pre-dose concentration for days 0, 14, 28 and 42)

Figure represents: Days 0, 14, 28 and 42 (x-axis) vs. pre-dose concentrations in ng/mL (y-axis)



The assessor performed statistical and BE analysis with exclusion of data from 8 subjects (b) (6) who did not demonstrate steady-state attainment based on the linear regression analysis of pre-dose concentrations. A total of 69 subjects (77 dosed – 8 excluded= 69) were included in the statistical and BE analysis. Similarly, there was no significant TRT*GRP (country) interaction for AUCtau (p= 0.354) and Cmax,ss (p= 0.828) of risperidone and thus TRT*GRP term was dropped from subsequent analysis. The BE criteria are met for LnAUCtau and LnCmax,ss in the BE analysis with data from 69 patients (see table below).

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=69 Least Squares Geometric Means, Ratio of Means Fasting Bioequivalence Study (Study No. CAC15003)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC(Tau) [ng*h/mL]	2212.97	128.19	570.55	22558.71	2536.36	115.28	577.29	21161.06	0.87
Cavg (SS) [ng/mL]	6.59	128.19	1.70	67.14	7.55	115.28	1.72	62.98	0.87
Cmax(SS) [ng/mL]	11.78	113.87	3.31	100.78	13.24	96.58	3.39	83.92	0.89
Cmin(SS) [ng/mL]	3.02	124.97	0.00	27.24	3.98	158.59	0.00	48.82	0.77

Fluctuation%	140.56	44.44	49.21	441.78	145.18	69.47	44.14	712.11	0.97
*Tmax(SS) [h]	72.00	-	4.00	336.00	48.00	-	0.00	336.00	1.50

* Tmax values are presented as median, range

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=69 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. CAC15003)					
Parameter	Test	Reference	Ratio (T/R)	CI 90 Lower	CI 90 Upper
Ln(AUC Tau) [ng*h/mL]	1631.95	1858.46	0.88	83.61	92.22
Ln(Cmax) (SS) [ng/mL]	8.76	10.04	0.87	80.24	94.97

Note: The assessor's results are similar to the applicant's results that submitted in the current DRL response (see below).

(b) (4)

- 3) Among the 8 patients (b) (6) identified in the linear regression analysis, the assessor further evaluated their pre-dose concentrations. Up reviewing 8 patients' pre-dose concentrations, although there are slight slopes observed in the 4 pre-dose concentrations, the difference in pre-dose trough levels between Day 42 and Day 28 is within 20% for Subjects (b) (6) (see table below). Therefore, the assessor considers that steady-state has been attained for these 5 subjects prior to the 4th injection, with every 14 days dosing and a terminal half-life of 3-6 days per RLD labeling.

Sub#	Per	Day 0	Day 14	Day 28	Day 42	Ratio day42/day28
1	1	0.495	2.057	4.353	5.942	1.37
1	2	4.457	5.628	5.873	6.644	1.13
11	1	3.208	4.768	6.774	7.091	1.05
12	1	3.558	3.168	2.87	2.554	0.89
32	1	1.401	1.889	4.975	5.613	1.13
38	2	3.389	4.325	6.648	6.731	1.01
76	2	11.033	8.914	3.243	2.29	0.71
83	1	15.832	14.43	13.781	12.881	0.93
89	2	3.834	4.685	5.367	7.45	1.39

The assessor performed statistical and BE analysis with exclusion of 3 patients (b) (6) who did not demonstrate steady-state attainment based on the regression analysis and having a greater than 20% difference in pre-dose trough levels between Day 42 and Day 28. A total of 74 subjects (77 dosed – 3 excluded= 74) were included in the analysis. Similarly, there was no significant TRT*GRP (country) interaction for AUCtau (p= 0.356) and Cmax,ss (p= 0.481) of risperidone and thus TRT*GRP term was dropped from subsequent

analysis. The BE criteria are met for LnAUCtau and LnCmax,ss in the BE analysis with data from 74 patients (see table below).

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=74 Least Squares Geometric Means, Ratio of Means Fasting Bioequivalence Study (Study No. CAC15003)									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC(Tau) [ng*h/mL]	2208.17	126.54	570.55	22558.71	2531.07	114.63	577.29	21161.06	0.87
Cavg (SS) [ng/mL]	6.57	126.54	1.70	67.14	7.53	114.63	1.72	62.98	0.87
Cmax(SS) [ng/mL]	11.88	114.67	3.31	100.78	13.07	96.12	3.39	83.92	0.91
Cmin(SS) [ng/mL]	3.03	122.45	0.00	27.24	4.00	156.58	0.00	48.82	0.76
Fluctuation%	139.64	45.05	49.21	441.78	143.73	68.24	44.14	712.11	0.97
*Tmax(SS) [h]	72.00	-	4.00	336.00	48.00	-	0.00	336.00	1.50

* Tmax values are presented as median, range

Risperidone Long-Acting Injection Dose: 1 x 25 mg Risperidone, n=74 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. CAC15003)					
Dependent	Test	Reference	Ratio (T/R)	CI 90 Lower	CI 90 Upper
Ln(AUC Tau) [ng*h/mL]	1625.56	1843.33	0.88	84.15	92.42
Ln(Cmax) (SS) [ng/mL]	8.71	9.91	0.88	80.85	95.40

2. The assessor conducted following statistical analyses for the 3rd and 4th injections:

Per current PSG, intensive sampling should be performed during the 3rd dosing interval (days 28-42) to accurately capture changes in trough and peak levels. The assessor performed the statistical analysis comparing the Cmax and Cmin for the 3rd injection to those for the 4th injection in Period 2. The results show that peak and trough levels after the 3rd injection are comparable to the respective peak and trough levels after the 4th injection. This information can be used as supporting data to confirm that there is no significant transient difference in Cmin.

Dose 3 Test (Period 2) vs Dose 4 Test (Period 2)

Parameter	Dose3Test	Dose4Test	Dose 3T/Dose 4T	CI 90 Lower	CI 90 Upper
Cmax(SS) [ng/mL]	8.10	8.45	0.96	84.86	108.16
Cmin(SS) [ng/mL]	2.06	2.23	0.92	82.43	103.75

Dose 3 Ref (Period 2) vs Dose 4 Ref (Period 2)

Parameter	Dose3Reference	Dose4Reference	Dose 3R/Dose 4R	CI 90 Lower	CI 90 Upper
Cmax(SS) [ng/mL]	9.52	9.95	0.96	84.26	108.49
Cmin(SS) [ng/mL]	2.70	2.80	0.96	84.75	109.60

The assessor also performed a statistical analysis for AUC and Cmax using the applicant's resubmitted dataset for the 3rd injection in Period 2 (see table below).

Dependent	TestGeoLSM	RefGeoLSM	Ratio (T/R)
Ln(AUC_TAU)	1657.69	1718.10	0.96
Ln(Cmax)	8.29	9.43	0.88
Ln(Cmin)	2.06	2.68	0.77

Note: N=74 (37 test and 37 reference)

Based on above results, the steady state BE study (#CAC15003) is **adequate**.

The applicant's response to deficiency #6 is adequate.

Deficiency #7:

For the in vitro release test, you did not submit the data for T50% and the 90% confidence interval of the test/reference ratio of T50%, as recommended in the product specific guidance for Risperidone Long-Acting Injectable. Please provide the requested data and also submit dataset and SAS program for your analysis. Additionally, please submit all data for the in vitro release test in Excel format.

Applicant's Response to Deficiency #7:

As per the Agency's request, in vitro release test data is presented in Excel format (and excel converted to pdf), as well as data for T50% (which is defined as the time of 50% drug release) and for the 90% confidence interval (CI) of the test/reference ratio of T50% according to the calculation of the statistical SAS program. The dissolution data was acquired by applying the dissolution method parameters and the release calculations included in Module 3.2.P.5.1 (dp-spec-exhibit-batches).

According to the product specific guidance (PSG) for Risperidone Long-Acting Injectable, the below listed dissolution parameters are measured:

- Cumulative drug release at Days 1 and 21 at 37 °C,
- Cumulative drug release at Day 8 at 45 °C, and T50% at 45 °C and are presented in Table 4 (below).

Table 4: Cumulative drug release at Days 1 and 21 at 37 °C, cumulative drug release at Day 8 at 45 °C and T50% for all tested RLD & test products

	Risperal Consta® 25mg LOT 83365P2	Risperal Consta® 12.5mg LOT 91889P1	Risperal Consta® 37.5mg LOT 87385P1	Risperal Consta® 50mg LOT 92828P1	Test product 37.5mg 4800013C	Test product 25mg 4700023B	Test product 50mg 4800014D	Test product 12.5mg 4800014A
%Release D1	(b) (4)							
%Release D21								
%Release D8								
T50%								

As noted above, the PSG also requires test/reference ratio of T50% with 90% CI to be within 80-125% for the 25 mg strength. T50% and CI 90% of 25 mg strength (Risperdal Consta® Lot

83365P2 and Test product Lot 4700023B) were calculated by means of SAS program as shown in Table 5.

Table 5: T50% and CI 90% data of Risperdal Consta® Lot 83365P2 and Test product Lot 4700023B according to SAS program

Risperdal Consta® 25mg LOT 83365P2					
Time (h)	Average %Release	SD	%RSD	min	max
24	1.0	(b) (4)	2.6	(b) (4)	
72	3.8		5.1		
120	7.0		2.9		
144	22.0		0.5		
160	47.5		4.5		
168	64.6		3.6		
172	79.0		0.5		
184	86.9		2.0		
192	90.5		0.5		
210	90.8		1.9		
256	94.9		1.1		
Test product 25mg LOT 4700023B					
Time (h)	Average %Release	SD	%RSD	min	max
24	2.0	(b) (4)	7.6	(b) (4)	
72	4.0		3.5		
120	9.3		3.2		
144	27.7		4.5		
160	53.1		0.4		
168	70.1		3.5		
172	81.3		2.4		
184	89.1		1.3		
192	90.5		1.6		
210	93.2		0.7		
256	95.3		0.6		
T/R Ratio 90% CI: 0.981 (0.978, 0.984)					

As shown in Table 5, the calculated 90% CI of the test/reference ratio of T50% was equal to 98.1% with a range of $\pm 0.03\%$, which is well within the specification range of 80-125%. SAS program data sets (xsRisperidone.sas, t50.xpt, xsrisperidone.pdf) are included in Module 5.3.1.3.

Additionally, all dissolution profiles of RLD and the test product are presented in excel format (and excel converted to pdf). The excel workbook includes eight excel sheets, where each one refers to a specific sample lot. The below data is included in Module 5.3.1.3.

- Attachment 1 – (b) (4)
- Attachment 2 – (b) (4)

The dissolution release was also calculated for each sampling point leading to the total % release depicted in the respective graph. Furthermore, summary tables including % release individual values, as well as average, SD, %RSD, min and max values and are provided in a separate excel workbook also included in Module 5.3.1.3

- Attachment 3 – (b) (4)

It is important to note that individual and average % release values for test product Lot 4800013C, 4800014A and 4800014D included in the excel format files slightly deviate (after the decimal) from the already submitted values in the below listed documents due to corrective actions that were applied in the % release calculation of water bath 45°C, as per the deviation report DIR: DIR-2020-30-0185 available on site. As noted in the deviation report, during review, errors including typographical errors were noticed in the calculations presented in the input cells of the excel files of the release profiles for the above-mentioned lots. While further investigation is ongoing as part of the deviation, the erroneous values were recalculated, and all the updated values are well within the proposed specifications and similar values of the similarity factor f2. The documents were updated to reflect correct % release values. Please note, these value changes have no impact on the overall release profile of the product.

- Comparative Dissolution Report (comparative-dissolution-report) included in Module 2.7
- Essential Similarity Report – Test and RLD (essential-similarity-report) included in Module 3.2.P.2.

Summary of Biopharmaceutics Studies and Associated Analytical Methods (sum-biopharm-pivotal): Table 5.2: Summary of In Vitro Dissolution Studies- (b) (4)

Assessor's Comments on Applicant's Response to Deficiency #7:

As requested, the applicant submitted the supporting data as specified in the above FDA deficiency #7. The assessor calculated the 90% CI of the test/reference ratio of T_{50%} and the outcome is within the acceptable range (80.00-125.00%). The results are provided in the table below.

Risperidone Long-Acting Injection							
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)							
Fasting Bioequivalence Study (Study No. CAC15003)							
Parameter (in-vitro testing)	Test	N	RLD	N	Ratio (T/R)	90% C.I. (low and upper bound)	
T50% (hours)	158.02	12	161.05	12	0.9812	0.9782 (97.82%)	0.9842 (98.42%)

The assessor's calculation for 90% CI of the test/reference ratio of T_{50%} for in-vitro data in agreement with the applicant's results.

Comment on the Dissolution Data:

- Per original BE review, the applicant provided comparative dissolution data for the test and RLD products of the 4 strengths (12.5 mg, 25 mg, 37.5 mg and 50 mg/vial) of the drug product. The calculated f₂ similarity values for the 12.5 mg, 37.5 mg and 50 mg/vial strengths of test product comparing to 25 mg/vial strength test product were all greater than 50. The % cumulative drug release for the test and reference products was comparable at Days 1 and 21 at 37 °C and at Day 8 at 45 °C.
- In the current amendment, the applicant provided summary tables and datasets of dissolution data for cumulative drug release at 37 °C and 45 °C and calculated T_{50%} values at 45 °C for all 4 strengths of test and reference products. In addition, the applicant submitted statistical analysis including SAS code for T_{50%} at 45 °C for the 25 mg/vial strength.
- The assessor calculated T_{50%} at 45 °C for the 25 mg/vial strength using applicant submitted datasets and performed BE analysis. The mean T_{50%} was 158.02 hours and 161.06 hours for the test and reference products, respectively. The 90% CI for the test/reference ratio of T_{50%} calculated by assessor is within 80.00 – 125.00%, which agrees with applicant's results.
- The submitted dissolution data are adequate with respect to supporting the waiver requests for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths. The DBIII grants the waiver requests for in vivo BE study requirements for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths based on criteria set forth in 21 CFR § 320.24(b)(6).
- The dissolution testing for establishment of the regulatory method and specifications for the test product for quality control (QC) purpose was reviewed separately in a biopharmaceutics review with "Inadequate-Minor" outcome.²³

The applicant's response to deficiency #7 is adequate.

²³ GDRP; ANDA-214068-ORIG-1; Biopharmaceutics review; file: ANDA 214068 biopharm review.docx ; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6feca8242a10f0805801>

Deficiency #8:

It is noticed that your dissolution method validation (Report No. CC-2019-30-0190; issued on 11/28//2019 and report addendum No. CC-2019-10-1170; issued on 12/10/2019) was performed after the comparative dissolution testing (Report No:CC-2019-10-1170; issued 11/27/2019). Please provide explanation for this discrepancy.

Applicant's Response to Deficiency #8:

We acknowledge Agency's comment and would like to clarify that the noticed discrepancies refer to issuance dates of report's revision from version 001 to version 002 (due to editorial and formatting changes), with no impact to the actual validation activity or the dissolution studies included in the comparative report. All validation reports and relevant activities were completed by 08/07/2019 (dd/mm/yyyy). The comparative dissolution report was issued subsequently, with date of issuance 27/11/2019 (dd/mm/yyyy).

It should also be noted that the report numbers mentioned in the question refer to relevant Change Control numbers and not to the report number. The details on Validation report and comparative dissolution report number, version number, relevant Change control (CC) number and date of issuance of reports are summarized in following table.

Table 6: Summary of the Reports issued

Report Name, Number And Version (Current Report)	Date Of Issuance (DD/MM/YYYY)	Change Control (CC) (Requested Date DD/MM/YYYY)	Comments
(b) (4)			

Report Name, Number And Version (Current Report)	Date Of Issuance (DD/MM/YYYY)	Change Control (CC) (Requested Date DD/MM/YYYY)	Comments
(b) (4)			

Assessor's Comments on Applicant's Response to Deficiency #8:

The applicant provided clarification to the above deficiency. The applicant clarified that all validation reports and relevant activities were completed by July 08, 2019, prior to the completion of comparative dissolution report issued on November 27, 2019.

The applicant's response to deficiency #8 is adequate.

4.4 Clinical Consultation Review

On 05/13/2020, the Division of Bioequivalence III (DBIII) sent a consult request to the Division of Clinical Review (DCR)²⁴ regarding the serious adverse events for 2 subjects administered test product in pivotal steady-state fasting BE study (#CAC15003), on the following two questions:

- 1) Do the two serious adverse (SAEs) events for patients (b) (6) (low hemoglobin) and patient (b) (6) (pneumonia), with the test product treatment during the pivotal BE study indicate any safety concerns for the test product? In addition, please evaluate if the SAEs observed in patients (b) (6) were related to the drug product.
- 2) Is there any additional information that DBIII needs to communicate to the applicant concerning these SAEs?

On 8/24/2020, the DCR²⁵ responded to the DBIII' consult request with the following conclusion: DCR concludes that the serious adverse event (SAE) of anemia in Subject (b) (6) and pneumonia in Subject (b) (6) were unlikely related to the administration of the test product. Anemia and pneumonia are listed as adverse reactions for the RLD (Risperdal Consta®). The

²⁴ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DB_ConultRequest01-DCR04272020.doc, dated 05/13/2020; <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f78f6bcf470202af1ac3>

²⁵ GDRP: ANDA 214068, Application Life Cycle, file: A214068_DCR-Review_Risperidone Injection_SAEs.docx, dated 08/24/2020; <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f7b6eb473ee6794cbdb9>

occurrence of these adverse events does not indicate a safety or quality concern for the test product compared to the RLD, and no additional information is needed from the Applicant.

4.5 Deficiency Comments

None

4.6 Comments for Other OGD Disciplines

Discipline	Comment
N/A	N/A

4.7 Attachments

List of the 77 dosed patients	 List of the 77 dosed patients.docx
<u>For Deficiency #1</u> Table 1: Storage duration of study samples for study # CAC15003	 For Deficiency 1 -Table 1 Storage dur
<u>For Deficiency #2</u> Partial method validation no VP-318-16-03	 For Deficiency 2 -Partial method valic
<u>Deficiency #5</u> Table 3 Peak and Trough levels of risperidone in the third dosing interval in the second period.docx	 Deficiency 5 Table 3 Peak and Trough lev
<u>Deficiency #6</u> The applicant submitted SAS program code	 For Deficiency 6 - program code SAS.d
Data Analysis (Phoenix used for all 3 analyses used in this study)	 214068 new data_072020.xlsx  Dose 4 PK parameters 77 sub.x  214068 - Pre dose data.xlsx  214068 - Pre dose data v2.xlsx  data 77 subjects.xlsx

	 Two-way Crossover.phxproj  214068-SteadyState 77sub.sas  SAS output 77 sub.pdf
linear regression analysis	 Check steady state.sas  ADPC.sas7bdat  failures.sas7bdat  Regression_allsub.x lsx
Sampling for the 3rd dosing interval in period 2.	 Two-way Crossover.phxproj  214068 Dose 3 Period 2 PK data.xls
Emails -results and communications	 ANDA 214068 - Dose 4 - 77 subjects  ANDA 214068 - Dose 4 - 77 subjects  ANDA 214068 - Dose 2 period 2 ana  ANDA 214068 - Dose 3 Test_Period
In Vitro Dissolution	 214068-Dissolution data for T50.xlsx  Dissolution T50.sas

BIOEQUIVALENCE COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA:	214068
APPLICANT:	Teva Pharmaceuticals USA Inc.
DRUG PRODUCT:	Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial

The Division of Bioequivalence III (DBIII) has completed its review of your submission acknowledged on the cover sheet and has no further questions at this time.

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.8 Outcome Page

ANDA No. 213982

Completed Assignment for 214068 ID: 43037

Reviewer: Wahba, Zakaria

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial (Amendment)

Items:

ID	Letter Date	Productivity Category	Sub Category	Score	Subtotal
43037	7/20/2020	BIO	ANDA Amendment [1]	1	1
43037	7/20/2020	Parallel	Major Amendment (original or supplement) [1.5]	1.5	1.5
43037	7/20/2020	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
				Total:	3.5

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	214068	
Drug Product Name	Risperidone Long-Acting Injection	
Strength(s)	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	
Applicant Name	Teva Pharmaceuticals USA Inc.	
Applicant Address	Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054	
US Contact Name and US Mailing Address	Anil Sachdeva Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054 anil.sachdeva@tevapharm.com	
US Contact Telephone Number	(b) (6)	
US Contact Fax Number	973-658-0057	
Original Submission Date(s)	December 16, 2019	
Submission Date(s) of Amendment(s) Under Review	July 20, 2020 (Supporting Document #12)	
Primary Assessor	Zakaria Wahba, Ph.D.	
Secondary Assessor	Svetlana Cherstniakova, Ph.D.	
Tertiary Assessor	Wendy Cai, Ph.D.	
Study Number(s)	CAC15003	PHA-RIP.I-01.15-208/147
Study Type(s)	Fasting, Steady State (Pivotal)	Fasting, single dose (Pilot)
Strength(s)	25 mg/vial	25 mg/vial
Clinical Site	<u>Clinical Sites for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 04- State Psychiatric Hospital – Tsarev brod, Tsarev Brod, Bulgaria (BG04) 05- Center for Mental Health – Sofia District, Sofia, Bulgaria (BG05) 06- Center for Mental Health – Vratsa EOOD, Vratsa, Bulgaria (BG06) 07- State Psychiatric Hospital – Lovech, Lovech, Bulgaria (BG07) 08- State Psychiatric Hospital "Sveti Ivan Rilski", Novi Iskar, Bulgaria (BG08) 09- Center for Mental Health – Plovdiv EOOD, Plovdiv, Bulgaria (BG09)	

	10- MHAT - Levski EOOD, Levsk, Bulgaria (BG10) 11- Instytut Psychiatrii i Neurologii, Warsaw, Poland (PL01) 12- Zespół Poradni Zdrowia Psychicznego, Toruń, Poland (PL02) 13- Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland (PL03) 14- Centrum Badań Klinicznych, , Krakow, Poland (PL04) 15- Milickie Centrum Medyczne, sp. z o.o., Milicz, Poland (PL05) 16- Rodzinne Centrum Medyczne LUBIMED, Lublin, Poland (PL06) 17- Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ, Krakow, Poland (PL07) 18- Podlaskie Centrum Psychogeriatric, Białystok, , Poland (PL08) 19- IMSP Clinical Psychiatric Hospital, Chisinau, Moldova (MD01) 20- IMSP Psychiatry Hospital Balti, Balti, Moldova (MD02) 21- State University of Medicine and Pharmacy, Moldova (MD03) 22- PMSI Psychiatry Hospital Balti, MD3110, Moldova (MD04) 23- Hospital of Psychiatry and Phthisiopulmonology, Orhei, Moldova (MD05) <u>Clinical Sites for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Amman, Jordan
Clinical Site Address	<u>Clinical Sites address for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 4- 3 "Sveti Georgy Sofiyski" Str, 1000 Sofia, Bulgaria (BS04) 05- 309 "Slivnitsa" Blvd., Sofia Bulgaria (BG05) 06- Vratsa EOOD, 1 "Belasitsa" Str., 3000 Vratsa Bulgaria (BG06) 07- Lovech, 1 "Aleksandar Batenberg" str., Lovech 5500, Bulgaria (BG07) 08- Sveti Ivan Rilski, 140 Hristo Botev Str., Novi Iskar 1282, Bulgaria, (BG08) 09- Plovdiv EOOD, 68 Peshetrsko shosse Blvd., 4002 Plovdiv, Bulgaria (BG09) 10- Levski EOOD, 5 Nikola Vaptsarov, 5900 Levski, Bulgaria (BG10) 11- ul. Jana III Sobieskiego 9, 02-957 Warszawa, Poland (PL01) 12- ul. A. Mickiewicza 24/26, 87-100 Toruń Poland (PL02) 13- ul. Dębinki 7 80-952 Gdańsk, Poland (PL03) 14- Life Science Parkul. Bobrzyńskiego 14 30 - 348 Kraków, Poland (PL04) 15- Grzybowa 1, 56-300 Milicz, Poland (PL05) 16- ul. Woronieckiego 1120-492 Lublin, Poland (PL06) 17- ul. Babińskiego 39, 30-393 Kraków, Poland (PL07) 18- ul. Swobodna 38/9, 15-756 Białystok, Poland (PL08) 19- Department no. 4, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD01) 20- Department no. 3, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD02) 21- 3, Costiujeni str., Chisinau, MD2011, Moldova (MD03) 22- 114, Gagarin str., Balti, MD3110, Moldova (MD04) 23- 2 Dubasari str., Orhei, MD 3500, Moldova (MD05) <u>Clinical Site for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Opposite Al-Jubaiha Circle, Amman, Jordan, Jordan
Analytical Site	(b) (4)

² GDRP: Biopharmaceutics Review;
<https://panorama.fda.gov/task/view?ID=6408e63e002f8438cc655849a0e7a906>

Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1, 12	Steady State	25 mg/vial	☒ Adequate ☐ Inadequate
1, 12	In Vitro Drug Release Test	25 mg/vial	☒ Adequate ☐ Inadequate
1, 12	Waiver/Deem Bioequivalent	12.5, 37.5 and 50 mg/vial	☒ Adequate ☐ Inadequate

Addendum for the Assessment Report of Bioequivalence Review

This is an addendum to a previous assessment of bioequivalence Review (a Response to Discipline Review Letter (DRL)).³ During completion of the bioequivalence assessment, the inspection status of this ANDA was pending. The purpose of this addendum is to update the status of the inspection of Office of Study Integrity and Surveillance (OSIS), and to change the inspection status in the table above from “Pending to **Complete**”.

OSIS’ summary report indicated “Remote Record Review (RRR) of multiple clinical sites in support of ANDA (b) (4) and ANDA 214068”. Based on OSIS review of the Remote Record Review findings, OSIS concluded that the data from the audited studies are reliable.⁴

For the Analytical sites: OSIS determined that an inspection is not warranted at this time for the analytical sites. The rationale for this decision is due to the following: OSIS inspected the sites in September 2019, which falls within the surveillance interval. The inspection was conducted under the following submissions: ANDAs (b) (4). The final classification for the inspection was No Action Indicated (NAI).⁵ **Therefore, the inspection for the clinical and analytical sites are COMPLTE.**

All other sections of the previous review remain same.

³ GDRP: Bioequivalence Review, ANDA 214068, file: A214068N000DB-Review02-DRLResponse07202020.pdf; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6c2e43210dc8b5cdddc3>

⁴ Per GDRP:

<https://panorama.fda.gov/task/view?ID=5e05237f007da01a125c1dc91090efbd>

<https://panorama.fda.gov/task/view?ID=5e052eb9007ff539378e45c5c5cb0218>

<https://panorama.fda.gov/task/view?ID=5e05236a007d929dd61f67ac0b1b7296>

⁵ <https://panorama.fda.gov/task/view?ID=5df8e06c009a6b439c42884ac5927bb7>

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	214068	
Drug Product Name	Risperidone Long-Acting Injection	
Strength(s)	12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial	
Applicant Name	Teva Pharmaceuticals USA Inc.	
Applicant Address	Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054	
US Contact Name and US Mailing Address	Anil Sachdeva Teva Pharmaceuticals USA Inc. 400 Interpace Parkway Parsippany, NJ 07054 anil.sachdeva@tevapharm.com	
US Contact Telephone Number	(b) (6)	
US Contact Fax Number	973-658-0057	
Original Submission Date(s)	December 16, 2019	
Submission Date(s) of Amendment(s) Under Review	-	
Primary Assessor	Zakaria Wahba, Ph.D.	
Secondary Assessor	Svetlana Cherstniakova, Ph.D.	
Tertiary Assessor	Wendy Cai, Ph.D.	
Study Number(s)	CAC15003	PHA-RIP.I-01.15-208/147
Study Type(s)	Fasting, Steady State (Pivotal)	Fasting, single dose (Pilot)
Strength(s)	25 mg/vial	25 mg/vial
Clinical Site	<u>Clinical Sites for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 04- State Psychiatric Hospital – Tsarev brod, Tsarev Brod, Bulgaria (BG04) 05- Center for Mental Health – Sofia District, Sofia, Bulgaria (BG05) 06- Center for Mental Health – Vratsa EOOD, Vratsa, Bulgaria (BG06)	

	07- State Psychiatric Hospital – Lovech, Lovech, Bulgaria (BG07) 08- State Psychiatric Hospital "Sveti Ivan Rilski", Novi Iskar, Bulgaria (BG08) 09- Center for Mental Health – Plovdiv EOOD, Plovdiv, Bulgaria (BG09) 10- MHAT - Levski EOOD, Levsk, Bulgaria (BG10) 11- Instytut Psychiatrii i Neurologii, Warsaw, Poland (PL01) 12- Zespół Poradni Zdrowia Psychicznego, Toruń, Poland (PL02) 13- Uniwersyteckie Centrum Kliniczne, Gdańsk, Poland (PL03) 14- Centrum Badań Klinicznych, , Krakow, Poland (PL04) 15- Milickie Centrum Medyczne, sp. z o.o., Milicz, Poland (PL05) 16- Rodzinne Centrum Medyczne LUBIMED, Lublin, Poland (PL06) 17- Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ, Krakow, Poland (PL07) 18- Podlaskie Centrum Psychogeriatric, Bialystok, , Poland (PL08) 19- IMSP Clinical Psychiatric Hospital, Chisinau, Moldova (MD01) 20- IMSP Psychiatry Hospital Balti, Balti, Moldova (MD02) 21- State University of Medicine and Pharmacy, Moldova (MD03) 22- PMSI Psychiatry Hospital Balti, MD3110, Moldova (MD04) 23- Hospital of Psychiatry and Phthisiopulmonology, Orhei, Moldova (MD05) <u>Clinical Sites for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Amman, Jordan
Clinical Site Address	<u>Clinical Sites address for the Pivotal BE study (CAC15003)</u> 01- State Psychiatric Hospital Pazardzhik Bulgaria (BG01) 02- MHAT "Dr. Ivan Seliminski" JSC, Bulgaria (BG02) 03- Military Medical Academy, Sofia, Bulgaria (BG03) 4- 3 "Sveti Georgy Sofiyski" Str, 1000 Sofia, Bulgaria (BS04) 05- 309 "Slivnitsa" Blvd., Sofia Bulgaria (BG05) 06- Vratsa EOOD, 1 "Belasitsa" Str., 3000 Vratsa Bulgaria (BG06) 07- Lovech, 1 "Aleksandar Batenberg" str., Lovech 5500, Bulgaria (BG07) 08- Sveti Ivan Rilski, 140 Hristo Botev Str., Novi Iskar 1282, Bulgaria, (BG08) 09- Plovdiv EOOD, 68 Peshetrsko shosse Blvd., 4002 Plovdiv, Bulgaria (BG09) 10- Levski EOOD, 5 Nikola Vaptsarov, 5900 Levski, Bulgaria (BG10) 11- ul. Jana III Sobieskiego 9, 02-957 Warszawa, Poland (PL01) 12- ul. A. Mickiewicza 24/26, 87-100 Toruń Poland (PL02) 13- ul. Dębinki 7 80-952 Gdańsk, Poland (PL03) 14- Life Science Parkul. Bobrzyńskiego 14 30 - 348 Kraków, Poland (PL04) 15- Grzybowa 1, 56-300 Milicz, Poland (PL05) 16- ul. Woronieckiego 1120-492 Lublin, Poland (PL06) 17- ul. Babińskiego 39, 30-393 Kraków, Poland (PL07) 18- ul. Swobodna 38/9, 15-756 Białystok, Poland (PL08) 19- Department no. 4, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD01) 20- Department no. 3, 3, Costiujeni str., Chisinau, MD2011, Moldova (MD02) 21- 3, Costiujeni str., Chisinau, MD2011, Moldova (MD03) 22- 114, Gagarin str., Balti, MD3110, Moldova (MD04) 23- 2 Dubasari str., Orhei, MD 3500, Moldova (MD05) <u>Clinical Site for the Pilot BE study (PHA-RIP.I-01.15-208/147)</u> Triumpharma, Opposite Al-Jubaiha Circle, Amman, Jordan, Jordan
Analytical Site	(b) (4)

	(b) (4)	
Analytical Site Address		
Office of Study Integrity and Surveillance (OSIS) status	<u>Backlog, Year 1 and Year 2 ANDAs</u> ☐ Pending ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) ¹	<u>Post October 1, 2014 ANDAs</u> ☒ To Be Determined by OSIS ☐ Pending for Cause Inspection ☐ Complete ☐ N/A (Waiver/Deem Bioequivalent) Error! Bookmark not defined.
Waiver/Deem Bioequivalent	☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A	
QC Dissolution	☒ Pending ☐ Adequate ☐ Inadequate	
Formulation	☒ Adequate ☐ Inadequate	
Will Response to CR Result in a Reformulation?	☐ Possibly ☒ No ☐ N/A	
Deficiency Classification	☐ Major ☒ Minor/DRL ☐ N/A (Review is Adequate)	
Major Deficiency Theme	NA	
Justification for Major Designation	NA	
Overall Review Result	☐ Adequate ☒ Inadequate	
Product Specific Guidance (PSG) Referenced in Review	☒ Recommended/Latest Revision Date: August 2016	

¹ Requests submitted under 21 CFR 320.22(d)(2) or 320.24(b)(6).

	RLD Number: NDA 021346 ☐ N/A (no PSG available at time of review)		
Revised/New Draft Guidance Generated as Part of Current Review	☐ YES ☒ NO		
Bioequivalence study tracking/supporting document #	Study/test type	Strength	Review Result
1	Steady State	25 mg	☐ Adequate ☒ Inadequate
1	In Vitro Study	25 mg	☐ Adequate ☒ Inadequate
1	Waiver/Deem Bioequivalent	12.5, 37.5 and 50 mg	☐ Adequate ☒ Inadequate
1	Pilot	1 x 25 mg	For information purposes

1 EXECUTIVE SUMMARY

This application contains the results of a pivotal steady-state fasting bioequivalence (BE) study (#CAC15003) comparing a test product, Teva Pharmaceuticals USA Inc.'s Risperidone Long-Acting Injection, 25 mg/vial, to the corresponding reference standard (RS) product, Janssen Pharmaceuticals Inc.'s Risperdal Consta® (risperidone) Intramuscular Injection, 25 mg/vial. The BE study was designed as a randomized, multiple-dose, multi-center, open-label, two-way crossover study in schizophrenic patients who are already receiving a stable regimen of 12.5, 25, 37.5 or 50 mg Risperdal Consta® biweekly via the intramuscular gluteal injections, at least four bi-weekly maintenance doses. The applicant conducted the pivotal steady-state BE study, which is in line with the recommendations in the current product specific guidance (PSG) for this drug (Recommended in Aug 2016).²

Seventy-seven (77) patients were dosed at 14 clinical sites in 3 countries, Bulgaria, Moldova and Poland for the pivotal BE study (#CAC15003). The applicant's steady-state BE study is **inadequate** due to multiple deficiencies related to pre-study method validation, resubmission of concentration and pharmacokinetic (PK) datasets, and pre-dose evaluation of steady-state achievement. Therefore, the assessor will conduct the PK and statistical analysis after applicant resubmit the datasets.

Two serious adverse events (SAEs) were reported after administration of test product and one SAE was observed after administration of the reference product in the pivotal steady-state BE study (#CAC15003). The evaluation of 2 SAEs observed for patients with the test treatment is pending the Division of Clinical Review (DCR)'s response to consult request sent on 5/13/2020.³

The applicant also submitted a pilot single dose, two-way, parallel BE study (#PHA-RIP.I-01.15-208/147) in healthy adults under fasting conditions. The adverse event reported from the pilot fasting BE study did not raise any safety concern that would adversely affect the pivotal BE studies.

The formulation of test drug product contains the same active and inactive ingredients in the same concentration as the reference listed drug (RLD) product. Therefore, it is deemed as qualitatively (Q1) and quantitatively (Q2) the same as the approved RLD for all strengths, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial. The test drug product formulation is adequate.

²

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

³ <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f78f6bcf470202af1ac3>

In addition to the in vivo BE study, the in vitro drug release study on the 25 mg/vial strength was conducted per the current PSG.⁴ The % cumulative drug release for the test and reference products is comparable at Day 1 and Day 21 at 37 °C, and at Day 8 at 45 °C. However, the applicant did not provide the data for T_{50%} at 45 °C and the 90% confidence interval of the test/reference ratio of T_{50%}. The in vitro drug release study is **inadequate** due to the above deficiencies. The applicant will be asked to submit the in vitro drug release data in an electronic file and requested analysis.

The dissolution testing for establishment of the regulatory method and specifications for the test product for quality control (QC) purpose was reviewed separately in a biopharmaceutics review with an adequate outcome.⁵ The submitted dissolution data are adequate with respect to supporting the waiver requests for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths. However, at this time the Division of Bioequivalence III (DBIII) cannot grant the waiver requests for in vivo BE study requirements for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths.

OSIS Outcome: The OSIS status of this ANDA is **pending** (see section 3.6 of this review report for details).

The application is **inadequate**.

⁴

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

⁵ GDRP; ANDA-214068-ORIG-1; Biopharmaceutics review; file: ANDA 214068 biopharm review.docx, Last update: 05/24/2020 by Jian Yin; <https://panorama.fda.gov/task/view?ID=5df8e06d009a6feca8242a10f0805801>

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3 SUBMISSION SUMMARY

3.1 Drug Product Information⁶

Test Drug Product and Strength(s)	Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
Reference Standard (RS) and Strength(s)	Risperdal Consta (risperidone) Intramuscular Injection, RS: 25 mg/vial
RS Holder; NDA/ANDA Number; Approval Date	Janssen Pharmaceuticals Inc., NDA 021346, 10/29/2003
Reference Listed Drug (RLD) and Strength(s)	Risperdal Consta (risperidone) Intramuscular Injection, RLDs (all strengths): 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial
RLD Holder; NDA/ANDA Number; Approval Date	Janssen Pharmaceuticals Inc., NDA 021346, Approved date: 10/29/2003 (for 25 mg/vial, 37.5 mg/vial, and 50 mg/vial) Approved date: 04/12/2007 (for 12.5 mg/vial)

3.2 PK/PD Information⁷

Most recent RLD label (provide embedded document) Please check if an NG/G/J tube study is needed.	 Labeling 021346 Risperdal Consta s0 Action date: 02/05/2020 (Suppl-63); Last accessed: 04/14/2020 No NG/G/J tube study is needed.
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.
Boxed warning	WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS <i>See full prescribing information for complete boxed warning.</i>

⁶ Per Orange Book, key word “Risperidone”, assessed date: 04/14/2020;
https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021346#19640

⁷ Drugs@FDA, key word “Risperidone”, assessed date: 04/14/2020;
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021346s063lbl.pdf

	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.
Bioavailability	The labeling does not provide specifics on Risperidone bioavailability. Deltoid and gluteal intramuscular injections at the same doses are bioequivalent and, therefore, interchangeable.
Food Effect	N/A, intramuscular injection.
Tmax	The label does not provide information.
Metabolism	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 is polymorphic in the population and can be inhibited by a variety of psychotropic and other drugs. 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.
Excretion	Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces.
Half-life	The apparent half-life of risperidone plus 9-hydroxyrisperidone following RISPERDAL CONSTA® administration is 3 to 6 days and is associated with a mono-exponential decline in plasma concentrations. This half-life of 3-6 days is related to the erosion of the microspheres and subsequent absorption of risperidone.
Maximum Daily Dose	The maximum dose should not exceed 50 mg RISPERDAL CONSTA® every 2 weeks.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	 PSG - Risperidone_intram Recommended Feb 2010; Revised Aug 2013, May 2015, Aug 2016, Last accessed date: 04/14/2020
---	---

Summary of OGD or DB History	Approved ANDAs ⁸ :	None
	Pending ANDAs ⁹ :	None
	Controls:	Yes (cc 1524801 from tis applicant, inquire about Q1 & Q2)
	Protocols ¹⁰ :	None for this drug
	Pending Citizen Petitions and other legal and regulatory issues: ¹¹ If yes, please comment.	☒ Yes ☐ No A Citizen Petition submitted to the FDA on February 10, 2011 (Docket No. FDA-2011-P-0086).

Assessor's Note: Petitioner believes the proposed methodology in the Draft Guidance on Risperidone does not adequately evaluate safety and efficacy issues surrounding the release of risperidone and may pose a potential public health risk; and the importance of adequate bioequivalence measures for RISPERDAL CONSTA® as a reference drug is highlighted by the real-world situation of LY03004, an intramuscular risperidone injectable product being developed by Luye Pharma Group Ltd.

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data			
Analyte	Risperidone			
Internal standard (IS)	Risperidone D ₄			
Method description	LC-MS/MS, Solid Phase extraction technique			
Limit of quantitation(ng/mL)	0.1101			
Average recovery of drug (%)	using peak area ratio, % Overall Recovery = 74.37% (range 73.00% – 75.35%, with %CV=1.64) using peak area response, % Overall Recovery = 80.01% (range 78.82% - 81.04%, with %CV=1.40)			
Average recovery of IS (%)	using peak area ratio, % recovery = 83.08% using peak area response, % recovery = 89.81%			
Standard curve concentrations (ng/mL)	0.1101 to 73.5857			
QC concentrations (ng/mL)	LLOQ QC	0.1138	MQC	36.7420
	LQC	0.3105	HQC	58.2179
	AQC	4.3987	DIQC	121.6108
			*DIQC4T	227.493

⁸ Per Orange Book, key word “Risperidone Injection”, assessed date: 04/14/2020.

https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021346#19640

⁹ DARRTS search: key word “Risperidone”, assessed date: 04/14/2020

¹⁰ Document search key word “Risperdal Consta”; <http://ogd.fda.gov/ODoc/rfs/Search> ; and

<http://ogd.fda.gov/seltrack/ProtocolGrid.ASP>

¹¹ OGD Policy Alert List, updated: 04/13/2020; <http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx>

QC Intraday precision range (%)	0.71 to 7.09
QC Intraday accuracy range (%)	92.19 to 104.29
QC Inter day precision range (%)	2.36 to 5.32
QC Interday accuracy range (%)	93.30 to 102.47
Bench-top stability (hrs)	At least 15 hours at room temperature
Stock stability (days)	Refrigerated Stock Solution and Stock Dilution Stability of Analyte and IS: At least 118 days at -10°C. Stock Solution Stability and Stock Dilution Stability of Analyte and IS: At least 17 hrs at room temperature.
Processed stability (hrs)	Autosampler Stability: 215 hours at 5°C in Autosampler tray Wet extract Stability: At least 193 h at 5°C in cooling cabinet
Freeze-thaw stability (cycles)	a. 5 cycles (below -50 °C) b. 4 cycle (FT-1 and FT-2 at -30°C) and (FT-3 and FT-4 at -70°C)
Long-term storage stability (days)	At least 358 days at -70°C. A total of 425 days, 417 days at -30 °C and 8 days at 5°C. A total of 425 days, 351 days at -30 °C and then 74 days at -70 °C. 202 days at -10 °C.
Dilution integrity	Concentration (121.6108 ng/mL) diluted 2-fold (%CV=2.29%) and 4-fold (%CV=3.39%)
Selectivity	No Interference noted in 10 matrix batches screened (Concentration of LLOQ – 0.1101 ng/mL)

* Dilution Integrity Quality Control Sample 4 times

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No SOP No.: (b) (4) "bioanalytical method validation" (effective date:)
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? If not, was cross validation study conducted?	☒ Yes ☐ No K ₂ EDTA (human plasma)
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☐ Yes ☒ No (see comments below)
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation: Inadequate

- Per bioanalytical method validation report, the method was validated for the measurement of risperidone in presence of risperidone major active metabolite, 9-hydroxyrisperidone (paliperidone).¹²

¹² Under study # PHA-RIP.I-01.15-208/147 for the pilot single dose BE study.

- No significant interference was observed from Risperidone D4, Paliperidone, Caffeine, Nicotine and OTC drugs (Paracetamol, Ibuprofen, Diclofenac and Ranitidine) at retention time and mass transition of risperidone. Similarly, no significant interference was observed from Risperidone, Paliperidone, Caffeine, Nicotine and OTC drugs (Paracetamol, Ibuprofen, Diclofenac and Ranitidine) at retention time and mass transition of Risperidone D4.
- It is noted that the % average recovery for risperidone is slightly lower than the % recovery of IS (risperidone: (b) (4) % vs IS: (b) (4) %). However, the % recovery of risperidone is consistent across the QC concentrations. The %CV is (b) (4) % at all QC concentrations. Both precision and accuracy of the method has been demonstrated in the method validation and sample analysis. Therefore, the difference in absolute % recovery between risperidone and its isotopic IS is considered acceptable.
- The applicant provided separate long-term storage stability data for 358 days at -70 °C and a total of 425 days at 2 different temperatures (417 days at -30 °C and 8 days at 5 °C or 351 days at -30 °C and then 74 days at -70 °C). Per applicant's bioanalytical report, study samples were initially stored at clinical sites and then transferred to the bioanalytical sites, and storage duration was up to 414 days for sample aliquote-1 and up to 476 days for sample aliquote-2 at clinical sites (i.e., Subject (b) (6)). Based on BE Summary Table 10 (Module 2.7), the total sample storage duration is 625 days. It is also noted that during shipment of sample aliquote-2, the temperature was up to 22.2 °C for some subject samples. The applicant will be asked to clarify the sample storage duration and temperature at clinical site and analytical site, as well as sample shipment time and temperature for each subject, and provide the additional long-term storage stability data to cover the study sample storage duration and condition.
- The bioanalytical lab was moved to a new location between 04/26 – 05/20/2019, per clinical study report. The applicant will be asked if additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site.

3.5 In Vivo Studies

Summary of Multiple-Dose Steady-State Bioequivalence Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD)						Study Report Location
					Cmax(SS) (ng/mL)	Tmax* (hr)	AUC(Tau) (ng-h/mL)	Cmin(SS) (ng/mL)	Cavg(SS) (ng/L)	% fluctuation	
CAC15003	Randomized, multiple-dose, multi-national, multi-center, open-label, two-way crossover pharmacokinetic study to assess the bioequivalence of Risperidone Long-Acting Injection, 12.5, 25, 37.5 and 50 mg, manufactured by Pharmathen International S.A. for Actavis Group PTC ehf (TEST) compared to RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION,	randomized, multiple-dose, multi-national, multi-center, open-label, two-period crossover study in schizophrenic patients	Risperidone Long-Acting Injection, 25 mg per vial 25 mg powder and solvent for prolonged-release suspension for intramuscular injection 25 mg risperidone [powder lot # 4700023B; diluent lot # 4700037] RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION, 25 mg per vial 25 mg powder and solvent for prolonged-release suspension for intramuscular injection 25 mg risperidone lot # 83365P2]	77 (48 M/ 29 F) schizophrenic patients completed Mean Age: 43.9 years (21 – 63 years)	8.619 ± 13.393 (114.6%)	72.000 (0.000-359.667)	1612.765 ± 2744.279 (126.1%)	4.520 ± 8.293 (127.3%)	4.800 ± 8.167 (126.1%)	127.10 ± 61.76 (44.5%)	Module 5.3.1.2; report-body.pdf page 77
					9.912 ± 12.333 (95.2%)	48.0 (0.000 - 337.000)	1830.670 ± 2846.692 (114.1%)	5.247 ± 9.023 (115.9%)	5.448 ± 8.472 (114.1%)	126.78 ± 96.85 (67.0 %)	

	12.5, 25, 37.5 and 50 mg, Janssen Pharmaceutica ls, Inc., USA (REFERENCE) , in patients																		
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Note: *For all parameters mean $\pm$ SD (%CV) values are reported except T_{max} for which median (min-max) values are reported

Summary of Pilot - Single dose Bioequivalence Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range)	Mean Parameters (+/-SD) (% CV)								Study Report Location
					C _{max} (ng/mL)	AUC ₀₋₄ (ng*hr/mL)	AUC ₀₋₈₈₈ (ng*hr/mL)	AUC _{0-888-1521.18} (ng*hr/mL)	AUC _{0-∞} (ng*hr/mL)	#T _{max} (hr)	T _{half} (hr)	K _{el} (1/hr)	
PHA-RIP-I-01.15-208/147	To compare the pharmacokinetic profile of Risperidone LAI 25 mg Powder and solvent for prolonged-release suspension for injection (Test Product/ Pharmathen, Greece) and Risperdal Consta 25 mg Powder and solvent for prolonged-release suspension for injection (Reference Product/ Janssen Pharmaceuticals Inc.) in healthy, adult subjects under fasting conditions in terms of rate and extent of absorption.	Open label, laboratory-blind randomized, single dose, two- way, parallel design performed under fasting conditions	A (Test): Risperidone LAI 25 mg Powder and solvent for prolonged-release (Pharmathen S.A., Greece) . Batch #: RLAI1402)	48 subjects (male) healthy subjects 30 years (19-48) (24 subjects received A, 24 subjects received B)	4.341 ± 3.5642 (82.10%)	1311.365 ± 1111.2577 (84.74%)	826.972 ± 678.1722 (82.01%)	503.812 ± 620.7815 (123.22%)	1356.159 ± 1126.6463 (83.08%)	840.67 (337.37-1106.43)	78.52 ± 40.745 (51.89%)	0.0105 ± 0.00389 (37.08%)	Module 5.3.1.2 Page #s 09, 25, & 303 of PHA-RIP.I-01.15-208-147-study-summary-report.pdf
			B (Reference): Risperdal Consta 25 mg Powder and solvent for prolonged-release suspension for injection (Janssen Pharmaceuticals Inc.) Batch #: 411682		2.538 ± 1.4093 (55.53%)	833.277 ± 401.4794 (48.18%)	471.436 ± 264.3696 (56.08%)	374.130 ± 266.3048 (71.18%)	875.595 ± 410.3939 (46.87%)	888.87 (47.65-1108.60)	98.34 ± 59.172 (60.17%)	0.0092 ± 0.00422 (46.03%)	

#For Tmax: Median (min – max)

Summary of Pilot - Single dose Bioequivalence Study (9-OH Risperidone Results)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age: mean (Range))	Mean Parameters (+/-SD) (%CV)							Study Report Location	
					C _{max} (ng/mL)	AUC ₀₋₄ (ng*hr/mL)	AUC ₀₋₈₈₈ (ng*hr/mL)	AUC _{0-888-1521.18} (ng*hr/mL)	AUC _{0-∞} (ng*hr/mL)	#T _{max} (hr)	T _{half} (hr)		K _{el} (1/hr)
PHA-RIP-I-01.15-208/147	To compare the pharmacokinetic profile of Risperidone LAI 25 mg Powder and solvent for prolonged-release suspension for injection (Test Product/ Pharmathen, Greece) and Risperdal Consta 25 mg Powder and solvent for prolonged-release suspension for injection (Reference Product/ Janssen Pharmaceuticals Inc.) in healthy, adult subjects under fasting conditions in terms of rate and extent of absorption.	Open label, laboratory-blind randomized, single dose, two- way, parallel design performed under fasting conditions	A (Test) : Risperidone LAI 25 mg Powder and solvent for prolonged-release (Pharmathen S.A., Greece) . Batch #: RLAI1402)	48 subjects (male) healthy subjects 30 years (19-48) (24 subjects received A, 24 subjects received B)	8.532 ± 4.8057 (56.33%)	3014.557 ± 1303.5809 (43.24%)	1636.862 ± 885.10 (54.07%)	1280.121 ± 507.4203 (39.64%)	2864.691 ± 970.6828 (33.88%)	889.07 (767.60-1346.57)	97.28 ± 27.153 (27.91%)	0.0076 ± 0.00202 (26.45%)	Module 5.3.1.2 Page #s 10, 25, & 304 of PHA-RIP-I-01.15-208-147-study-summary-report.pdf
			B (Reference) : Risperdal Consta 25 mg Powder and solvent for prolonged-release suspension for injection (Janssen Pharmaceuticals Inc.) Batch #: 411682		9.531 ± 3.7523 (39.37%)	3248.221 ± 803.3676 (24.73%)	1627.458 ± 659.9324 (40.55%)	1628.003 ± 668.4187 (41.06%)	3325.552 ± 805.7381 (24.23%)	892.56 (96.80-1108.60)	113.58 ± 50.998 (44.90%)	0.0068 ± 0.00192 (28.03%)	

#For Tmax: Median (min – max)

3.6 OSIS Status

OSIS's Outcome on the Analytical and Clinical Sites of this Application.¹³

For the Analytical Sites:				
The final classification for the inspection was No Action Indicated (NAI).				
#	Site	Facility Name	Facility Address	Comment/ outcome
1	Analytical			
2	Analytical			
For the Clinical Sites:				
OSIS recommends that a clinical inspection will not be needed at all following clinical sites <u>except</u> BG01, BG02 and MD01 (see below) – for additional information see an email communication with OSIS’s PM (provided in the attachment section).				
1	BG01	State Psychiatric Hospital Pazardzhik	28 Bolnichna Str., 4400 Pazardzhik Bulgaria	Inspection Pending
2	BG02	MHAT "Dr. Ivan Seliminski" JSC	1 "Hristo Botev"Str., 8800 Sliven, Bulgaria	Inspection Pending
3	BG03	Military Medical Academy	3 Sveti Georgy Sofiyski Street, 1000 Sofia, Bulgaria	Decline to Inspect Memo
4	BG04	State Psychiatric Hospital – Tsarev brod	30 Hristo Botev Street, 9747 Tsarev Brod, Bulgaria	Decline to Inspect Memo
5	BG05	Center for Mental Health – Sofia District	309 Slivnitsa Boulevard, 1000 Sofia, Bulgaria	Decline to Inspect Memo
6	BG06	Center for Mental Health – Vratsa EOOD	1 Belasitsa Street, 3000 Vratsa, Bulgaria	Decline to Inspect Memo
7	BG07	State Psychiatric Hospital – Lovech	1 Aleksander Batenberg Street, 5500 Lovech, Bulgaria	Decline to Inspect Memo
8	BG08	State Psychiatric Hospital "Sveti Ivan Rilski"	140 Hristo Botev Street, 1282 Novi Iskar, Bulgaria	Decline to Inspect Memo
9	BG09	Center for Mental Health – Plovdiv EOOD	68 Peshtersko Shose Boulevard, 4002 Plovdiv, Bulgaria	Decline to Inspect Memo
10	BG10	MHAT - Levski EOOD	5 Nikola Vaptsarov Street, 5900 Levski,Bulgaria	Decline to Inspect Memo
11	PL01	Instytut Psychiatrii i Neurologii	ul. Jana III Sobieskiego 9, 02-957 Warsaw, Poland	Decline to Inspect Memo

¹³ GDRP: ANDA 214068-ORIG-1, Application Life Cycle,
<https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

12	PL02	Zespół Poradni Zdrowia Psychicznego	ul. Adama Mickiewicza 24/26, 87-100 Toruń, Poland	Decline to Inspect Memo
13	PL03	Uniwersyteckie Centrum Kliniczne.	Klinika Chorób Psychiczych i Zaburzeń Nerwicznych, ul. Dębinki 7, 80-952 Gdańsk, Poland	Decline to Inspect Memo
14	PL04	Centrum Badań Klinicznych, Jagiellońskie Centrum Innowacji	Life Science Park, ul. Michała Bobrzyńskiego 14, 30-348 Krakow, Poland	Decline to Inspect Memo
15	PL05	Milickie Centrum Medyczne, sp. z o.o.	ul. Grzybowa 1, 56-300 Milicz, Poland	Decline to Inspect Memo
16	PL06	Rodzinne Centrum Medyczne LUBIMED	ul. Jacka Woronieckiego 11, 20-492 Lublin, Poland	Decline to Inspect Memo
17	PL07	Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ	ul. Józefa Babińskiego 29, 30-393 Krakow, Poland	Decline to Inspect Memo
18	PL08	Podlaskie Centrum Psychogeriatry	ul. Swobodna 38/9, 15-756 Białystok, Poland	Decline to Inspect Memo
19	MD01	IMSP Clinical Psychiatric Hospital	Department of Psychiatry, Narcology, and Medical Psychology, 3 Costiujeni Street, Chisinau, MD2011, Republic of Moldova	Inspection Pending
20	MD02	PMSI Clinical Psychiatric Hospital	Department no. 3, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova	Decline to Inspect Memo
21	MD03	Department of Psychiatry, Narcology and Medical Psychology, State University of Medicine and Pharmacy “Nicolae Testemitanu”, located in the PMSI Clinical Psychiatric Hospital	, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova	Decline to Inspect Memo
22	MD04	IMSP Psychiatry Hospital Balti	114 Gagarin Street, Balti, MD 3110, Republic of Moldova	Decline to Inspect Memo
23	MD05	Hospital of Psychiatry and Phthisiopulmonology	2 Dubasari Street, Orhei, MD 3500, Republic of Moldova	Decline to Inspect Memo

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Multiple-Dose Steady-State Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	CAC15003			
Study Title	Randomized, multiple-dose, multi-national, multi-center, open-label, two-way crossover pharmacokinetic study to assess the bioequivalence of Risperidone Long-Acting Injection, 12.5, 25, 37.5 and 50 mg, manufactured by Pharmathen International S.A. for Actavis Group PTC (TEST) compared to RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION, 12.5, 25, 37.5 and 50 mg, Janssen Pharmaceuticals, Inc., USA (REFERENCE), in patients			
Study Type	☒ In Vivo BE	☐ In Vitro BE	☐ Permeability	☐ Other (Specify)
Clinical Site BG01 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital Pazardzhik 28 Bolnichna Str., 4400 Pazardzhik, Bulgaria Phone: +359-34-44-88-12 Fax: +359-34-44-33-87			
Principal Clinical Investigator BG01 (Name, Email)	Dora Atanasova, MD, PhD Email: dora_pazardjik@abv.bg			
Clinical Site BG02 (Name, Address, Phone #, Fax #)	MHAT "Dr. Ivan Seliminski" JSC 1 "Hristo Botev" Str., 8800 Sliven, Bulgaria Phone: +359-887-80-1 5-45 Fax: +359-44-62-32-71			
Principal Clinical Investigator BG02 (Name, Email)	Dr. Rozalina Petrova Email: dr.rozalina.petrova@gmail.com			
Clinical Site BG03 (Name, Address, Phone #, Fax #)	Military Medical Academy 3 "Sveti Georgy Sofiyski" Str, 1000 Sofia Bulgaria Phone: +359-887-40-82-42 Fax: +359-2-444-12-70			
Principal Clinical Investigator BG03 (Name, Email)	Assoc. Prof. Dr. Tony Donchev Email: tonyd@abv.bg			
Clinical Site BG04 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital Tsarev brod 30 "Hristo Botev" Str., 9747 Tsarev brod, Bulgaria Phone: +359-53-1 5-20-22 Fax: +359-53-1 5-20-23			
Principal Clinical Investigator BG04 (Name, Email)	Dr. Neli Todorova Email: nelly_nik@abv.bg			
Clinical Site BG05 (Name, Address, Phone #, Fax #)	Center for Mental Health - Sofia district 309 "Slivnitsa" Blvd., Sofia, Bulgaria Phone: +359-887-50-82-04 Fax: +359-2-831-90-98			
Principal Clinical Investigator BG05	Dr. Emil Grashnov Email: dr.emo@mail.bg			

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(Name, Email)	
Clinical Site BG06 (Name, Address, Phone #, Fax #)	Center for Mental Health - Vratsa EOOD 1 "Belasitsa" Str., 3000 Vratsa, Bulgaria Phone: +359-92-66-50-75 Fax: +359-92-66-32-07
Principal Clinical Investigator BG06 (Name, Email)	Dr. Nadya Ivanova Email: nadia_odpzs@abv.bg
Clinical Site BG07 (Name, Address, Phone #, Fax #)	"State Psychiatric Hospital – Lovech" 1 "Aleksandar Batenberg" str., Lovech 5500, Bulgaria Phone: +359-68-60-35-90 Fax: +359-68-60-35-93
Principal Clinical Investigator BG07 (Name, Email)	Dr. Mitko Mitev Email: mitev1960@abv.bg
Clinical Site BG08 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital "Sveti Ivan Rilski" 140 Hristo Botev Str., Novi Iskar 1282, Bulgaria Phone: +359-2-936-04-40 Fax: +359-2-991-42-75
Principal Clinical Investigator BG08 (Name, Email)	Dr. Tsveteslava Galabova Email: cveteslava.galabova@abv.bg
Clinical Site BG09 (Name, Address, Phone #, Fax #)	Center for Mental Health - Plovdiv EOOD 68 Peshetrsko shosse Blvd., 4002 Plovdiv, Bulgaria Phone: +359-894-655-078 Fax: +359-32-643-241
Principal Clinical Investigator BG09 (Name, Email)	Dr. Milena Trendafilova-Andonova Email: m.trendafilova@abv.bg
Clinical Site BG10 (Name, Address, Phone #, Fax #)	MHAT - Levski EOOD 5 Nikola Vaptsarov, 5900 Levski, Bulgaria Phone: +359-888-464-676 Fax: +359-64-807-440
Principal Clinical Investigator BG10 (Name, Email)	Dr. Plamen Atanasov Gueorguiev Email: apex_medic@mail.bg
Clinical Site PL01 (Name, Address, Phone #, Fax #)	Instytut Psychiatrii i Neurologii ul. Jana III Sobieskiego 9, 02-957 Warszawa, Poland Phone: +4882242 4087 Fax: +4882242 4087
Principal Clinical Investigator PL01 (Name, Email)	Prof. Marek Jarema, MD, PhD jarema@ipin.edu.pl
Clinical Site PL02 (Name, Address, Phone #, Fax #)	Zespół Poradni Zdrowia Psychicznego ul. A. Mickiewicza 24/26, 87-100 Toruń, Poland Phone: +566580843 Fax: +485661 26303
Principal Clinical Investigator PL02 (Name, Email)	Ewa Kordyjak-Starczewska, MD, PhD Email: ewastarczewska@gmail.com
Clinical Site PL03 (Name, Address, Phone #, Fax #)	Uniwersyteckie Centrum Kliniczne. Klinika Chorób Psychiczych i Zaburzeń Nerwicznych, ul. Dębinki 7, 80-952 Gdańsk, Poland Tel: +48 583492650 Fax: +48 583492748

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Principal Clinical Investigator PL03 (Name, Email)	Wiesław Cubala, MD, PhD Email: cubala@gumed.edu.pl
Clinical Site PL04 (Name, Address, Phone #, Fax #)	Centrum Badań Klinicznych, Jagiellońskie Centrum Innowacji Life Science Park, ul. Bobrzyńskiego 14, 30 - 348 Kraków, Poland Phone: +48 602 600 399 Fax: 48 (12) 3402435
Principal Clinical Investigator PL04 (Name, Email)	Rafał Jaeschke, MD, PhD Email: rafal.jaeschke@gmail.com
Clinical Site PL05 (Name, Address, Phone #, Fax #)	Milickie Centrum Medyczne Sp. z o.o. Wielospecjalistyczny Szpital w Miliczu, ul. Grzybowa 1, 56-300 Milicz, Poland Phone: +4871 38467 78 Fax: +48 71 384 06 52
Principal Clinical Investigator PL05 (Name, Email)	Krzysztof Klementowski, MD Email: k.klementowski@mcm-milicz.pl
Clinical Site PL06 (Name, Address, Phone #, Fax #)	Rodzinne Centrum Medyczne LUBIMED ul. Woronieckiego 11, 20-492 Lublin, Poland Phone: +48 81 504 93 96 Fax: +48 81 504 93 B9
Principal Clinical Investigator PL06 (Name, Email)	Grzegorz Opielak, MD Email: biuro@lubimed.pl
Clinical Site PL07 (Name, Address, Phone #, Fax #)	Szpital Specjalistyczny im. Dr. J. Babińskiego SP ZOZ ul. Babińskiego 39, 30-393 Kraków, Poland Phone: +48 12 65 24 280 Fax: +48 1265 24 283
Principal Clinical Investigator PL07 (Name, Email)	Krzysztof Walczewski, MD, PhD Email: Krzysztof.walczewski@babibski.pl
Clinical Site PL08 (Name, Address, Phone #, Fax #)	Podlaskie Centrum Psychogeriatrici ul. Swobodna 38/9, 15-756 Białystok, Poland Phone: +48 85 661 02 98 Fax: +48 667 98 04 48
Principal Clinical Investigator PL08 (Name, Email)	Jacek Dobryniewski, MD, PhD Email: jacekdobryniewski@gmail.com
Clinical Site MD01 (Name, Address, Phone #, Fax #)	PMSI Clinical Psychiatric Hospital, Department no. 4 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova Phone: +373 79888854 Fax: +373 22 761 569
Principal Clinical Investigator MD01 (Name, Email)	Grigore Garaz, MD Email: garazgrigore@gmail.com
Clinical Site MD02 (Name, Address, Phone #, Fax #)	PMSI Clinical Psychiatric Hospital, Department no. 3 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova Phone: +373 79429943 Fax: +373 22 761569
Principal Clinical Investigator MD02 (Name, Email)	Vladimir Sterpu, MD Email: dr.sterpu@mail.ru
Clinical Site MD03	Department of Psychiatry, Narcology and Medical Psychology State University of Medicine and Pharmacy "Nicolae Testemitanu", located in

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(Name, Address, Phone #, Fax #)	the PMSI Clinical Psychiatric Hospital, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova Phone: +37367133770 Fax: not available
Principal Clinical Investigator MD03 (Name, Email)	Igor Nastas, MD, PhD Email: igornastas@yahoo.com
Clinical Site MD04 (Name, Address, Phone #, Fax #)	PMSI Psychiatry Hospital Balti 114, Gagarin str., Balti, MD3110, Republic of Moldova Phone: +37379032023 Fax: not available
Principal Clinical Investigator MD04 (Name, Email)	Lilia Ignatiuc Email: lillya_t@yandex.ru
Clinical Site MD05 (Name, Address, Phone #, Fax #)	HOSPITAL OF PSYCHIATRY AND FTIZIOPNEUMOLOGY 2 Dubasari str., Orhei, MD 3500, Republic of Moldova Phone: +37368513 650 Fax: Not available
Principal Clinical Investigator MD05 (Name, Email)	Lilia Calestru Email: liliacalestru1111@yahoo.com
Dosing Dates	Dosing Period: 10/26/2017 to 04/04/2019
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Principal Analytical Investigator (Name, Email)	
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g. -20°C to -80°C)	a) 625 days [from the date of first sample collection (26 October 2017) till date of retrieval of last sample for analysis (12 July 2019)] b) At -20°C, at clinical sites At -70°C (-60°C to -80°C), at bioanalytical facility

Clinical sites: Total 23 sites in Bulgaria, Poland and Moldova were enrolled in this study for clinical trial. Out of 23 clinical sites, patients from 14 clinical sites were used for this BE study (refer to Section 4.4.1 for details).

4.1.1.1.2 Product (Bio-batch) Information

Product	Test products	Reference product
Treatment ID	A	B
Product Name	Risperidone Long Acting Injection, 25 mg/vial	Risperdal Consta (risperidone) Long-Acting Injection, 25 mg/vial
Manufacturer	(b) (4)	(b) (4)
Batch No./Lot No.	KIT: 4700023B-P Powder in vial: 4700023B Diluent: 4700037	Powder in vial: 83365P2 Diluent: GIS58 (8336552)
Manufacturing Date	Powder in vials: May/2017 Diluent: 05/2017	NA
Expiration Date	NA	Apr/2019
Strength	25 mg/vial	25 mg/vial
Dosage Form	Injection	Injection
Bio-batch Size	(b) (4)	N/A
Production Batch Size	(b) (4)	NA
Assay	102.6%	101.5%
Content Uniformity (mean,%CV)	% mean: 101.6 %CV: 0.5	NA
Dose Administered	1 x 25 mg	1 x 25 mg
Route of Administration	IM	IM

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
Is same bio-batch used in the dissolution and all BE studies? If No, please comment.	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? If No, please comment.	☐ Yes ☐ No ☒ N/A
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 104 Dosed: 98 Completed: 80* Samples Analyzed: ** Statistically Analyzed: ** *A total number of 98 subjects were randomized and treated with study medication at least once and 18 subjects (b) (6) dropped out without replacement. **Eighty subjects completed both study periods and 77 of them completed according to the protocol without major protocol deviations. The samples of all study completers were analyzed, and 77 patients were subjected to statistical evaluation.
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	Steady-state BE study was conducted at 14 different clinical sites; each site included small number of patients, see information below for number of patients at each clinical site
Washout Period	There was no wash-out period between the two study periods.
Randomization	☒ Yes ☐ No (see table below)
Duration of treatment:	Each patient has received randomly four deep intramuscular gluteal injections every 2 weeks (14 days) of 25 mg risperidone (either 25 mg/2 ml of the test product or 25 mg/2 ml of the reference drug) in each of the two study periods. Patients have received the same dosage strength in both periods. (Note: Administration of study medication are on Days 0, 14, 28 and 42 of each period).
Blood Sampling Times	In the first study period, 0 h (pre-dose) and 4h, 8h, 1d and 3d after the first injection, 0 h (pre-dose) and 8h, 1d and 3d after the second and the third injections, and pre-dose (0h) and 4h, 8h, 24h, 36h, 2d, 3d, 4d, 5d, 6d, 7d, 8d, 9d, 10d, 11d, 12d, 13d and 14 days after the fourth administration. In the second study period, the same samples as in the first period and additional samples 2d, 4d, 5d, 6d, 7d, 8d, 9d, 10d, 11d, 12d and 13d after the third administration were taken.
IRB Approval	☒ Yes ☐ No (Bulgaria: approved 05/18/2016; Poland: approved 06/09/2016; and Moldova: approved 09/11/2018) \\cdsesub1\evsprod\anda214068\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cac15003\iec-irb-list.pdf

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Informed Consent	☒ Yes ☐ No (Bulgaria: approved 05/18/2016; Poland: approved 06/09/2016; and Moldova: approved 09/11/2018) \\cdsesub1\evsprod\anda214068\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\cac15003\iec-irb-list.pdf
Length of Fasting	Days of drug administration and length of fasting: The subjects had to fast from food and beverages other than water from the evening of the day before the days 0, 14, 28 and 42 of each study period until 2 hours after drug administration. Water was provided ad libitum.
Length of Confinement	Per study protocol, on the drug administration days a meal may be served after the 2:00 hr confinement and the patients may remain in the hospital or be discharged at the investigator's discretion (see comments below).
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A IM injection
Safety Monitoring	☒ Yes ☐ No

Note: Total number of patients is 98.

Eighteen (18) patients (b) (6) dropped out.

*Patients (b) (6) excluded from statistical analysis due to missing 3 or 4 consecutive blood samples.

The applicant included 77 patients [98 – (18-3) =77] in its statistical analysis.

Patients used for the pivotal BE study conducted in 14 Clinical Sites (from three countries, Bulgaria, Moldova and Poland).

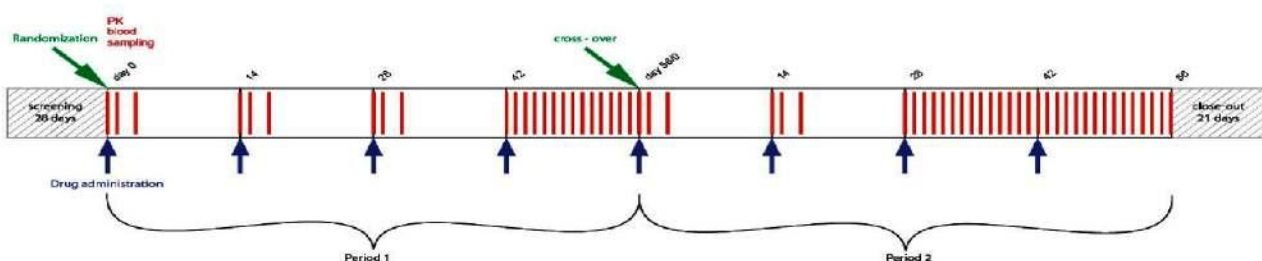
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[illegible]

# of clinical sites	Clinical Site	Total number of patients dosed at each site
1	BG01	16
2	BG02	12

3	BG04	7
4	BG05	6
5	BG06	6
6	BG07	6
7	BG08	8
8	BG09	7
9	BG10	6
10	MD01	10
11	MD02	4
12	MD03	3
13	MD04	5
14	PL03	2

2.1 Overview of Study Timeline



Comments on Study Design: Inadequate

- The applicant conducted the pivotal steady-state BE study in line with the recommendations in the current product specific guidance (PSG) for this drug (Recommended Feb 2010; Revised Aug 2013, May 2015, Aug 2016).¹⁴ Per RLD labeling, steady-state plasma concentrations are reached after 4 injections and are maintained for 4 to 6 weeks after the last injection.
- Patients with schizophrenia who were already receiving a stable regimen of 12.5, 25, 37.5 and 50 mg risperidone extended release suspension biweekly via the intramuscular route (at least four bi-weekly maintenance doses) were enrolled in this study.
- Per RLD labeling, deltoid and gluteal intramuscular injections at the same doses are bioequivalent and interchangeable. Therefore, the administration of the test and reference products via gluteal intramuscular injections was chosen. The study medication was administered in the morning (on empty stomach) between 7 am and 9

¹⁴

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

am by means of deep intramuscular gluteal injection of 25 mg risperidone of the test or of the reference drug.

- Per applicant's clinical study report, in study period I, blood samples were collected at 0 (predose) and 8h, 1d and 3d after the 1st (on Day 0), 2nd (on Day 14), and 3rd (on Day 28) administration of test or reference products and an additional sample was collected at 4h after the 1st administration, while a full pharmacokinetic (PK) profile was collected after 4th (on Day 42) administration of test or reference products. In study period II, blood samples were collected, with the same sampling schedule after the 1st, 2nd, and 4th as in the period I. Additional blood samples were collected between Days 28-42 after the 3rd administration of test or reference products in study period II, which is consistent with the recommendation in the current PSG in order to accurately capture changes in trough and peak drug levels.
- It is unclear about the length of confinement for patients at the clinical sites during the course of study. The applicant will be asked to provide this information.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. CAC15003		Treatment Groups	
		Test Product N =77	Reference Product N =77
Age (years)	Mean ± SD	43.9 ± 10.7	43.9 ± 10.7
	Min, Max	21, 63	21, 63
Age Groups	< 18	0 (0.0)	0 (0.0)
	18 – 40	27 (35.1)	27 (35.1)
	40 – 64	50 (64.9)	50 (64.9)
	65 – 75	0 (0.0)	0 (0.0)
	> 75	0 (0.0)	0 (0.0)
Sex	Male	48	48
	Female	29	29
Race	American Indian or Alaska Native	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)
	Black or African American	0 (0.0)	0 (0.0)
	Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)
	White	77 (100.0)	77 (100.0)
BMI (kg/m ²)	Mean ± SD	25.4 ± 4.0	25.4 ± 4.0
	Min, Max	18.7, 34.3	18.7, 34.3
Other Factors		N/A	N/A

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No
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4.1.1.2.2 Dropout Information

Study No.: CAC15003				
Subject No	Reason for dropout/replacement	Period	Replaced?	Replaced with
(b) (6)	On patient's request, Test (b) (6), after the 4 th dose)	1	No	N/A
	On patient's request, Test (b) (6), after the 4 th dose)	2	No	N/A
	On patient's request, Reference (b) (6) after the 4 th dose)	2	No	N/A
	Withdraw consent, Test (b) (6), after the 4 th dose)	1	No	N/A
	On patient's request, Reference (b) (6), after the 4 th dose)	2	No	N/A
	On patient's request, Reference (b) (6) after the 1 st dose)	1	No	N/A
	On patient's request, Reference (b) (6) after the 1 st dose)	1	No	N/A
	Non-compliance, Reference (b) (6) after the 4 th dose)	1	No	N/A
	On patient's request, Test (b) (6) after the 4 th dose)	1	No	N/A
	On patient's request, Reference (b) (6) after the 3 rd dose)	1	No	N/A
	Adverse Event (Chronic Obstructive Pulmonary Disease), Test (b) (6) after the 1 st dose)	1	No	N/A
	Patient did not show up for Day 42 Period 1, Reference (b) (6) after the 3 rd dose)	1	No	N/A
	Contact to patient lost, Reference (b) (6) after the 4 th dose)	2	No	N/A
	On patient's request, Test (b) (6) after the 1 st dose)	1	No	N/A
	On patient's request, Reference (b) (6) after the 1 st dose)	1	No	N/A
	Non-compliance, Reference (b) (6), after the 2 nd dose)	1	No	N/A
	On patient's request, Test (b) (6), after the 3 rd dose)	1	No	N/A
	Non-compliance, Reference (b) (6) after the 2 nd dose)	1	No	N/A
Are dropouts appropriate? If no, please comment.			☒ Yes ☐ No	

4.1.1.2.3 Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasted Bioequivalence Study	
	Study No. CAC15003	
	Test N (%)	Reference N (%)
Gastrointestinal disorders	1 (1.3)	2 (2.5)
Nausea	0 (0.0)	2 (2.5)
Salivary hypersecretion	1 (1.3)	0 (0.0)
General disorder and administration conditions	6 (7.5)	2 (2.5)
Asthenia	2 (2.5)	2 (2.5)
Fatigue	4 (5.0)	0 (0.0)
Hepatobiliary disorders	1 (1.3)	0 (0.0)
Hepatitis toxic	1 (1.3)	0 (0.0)
Infections and infestations	2 (2.5)	2 (2.5)
Bacterial infection	0 (0.0)	1 (1.3)

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Bronchitis	0 (0.0)	1 (1.3)
Viral infection	2 (2.5)	0 (0.0)
Investigations	4 (5.0)	0 (0.0)
Hemoglobin decreased	1 (1.3)	0 (0.0)
Weight increased	3 (3.8)	0 (0.0)
Nervous system disorders	14 (17.5)	5 (6.3)
Dizziness	6 (7.5)	0 (0.0)
Headache	1 (1.3)	0 (0.0)
Stupor	1 (1.3)	2 (2.5)
Tremor	5 (6.3)	4 (5.0)
Psychiatric disorders	20 (25.0)	17 (21.3)
Affective disorder	1 (1.3)	2 (2.5)
Aggression	0 (0.0)	1 (1.3)
Anxiety	4 (5.0)	3 (3.8)
Delirium	0 (0.0)	1 (1.3)
Fear	0 (0.0)	3 (3.8)
Hallucination	0 (0.0)	1 (1.3)
Insomnia	12 (15.0)	5 (6.3)
Nervousness	0 (0.0)	1 (1.3)
Restlessness	1 (1.3)	0 (0.0)
Sleep disorder	2 (2.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.3)	0 (0.0)
Chronic obstructive pulmonary disease	1 (1.3)	0 (0.0)
Surgical and medical procedures	1 (1.3)	0 (0.0)
Dental operation	1 (1.3)	0 (0.0)
Vascular disorders	1 (1.3)	1 (1.3)
Hypotension	1 (1.3)	1 (1.3)
Total	51 (63.8)	29 (36.3)

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
None					

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☐ Yes ☒ No (see comments below)
Are there any serious adverse events or death?	☒ Yes ☐ No (see comments below)
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☒ Yes ☐ No (pending DCR consult response)

4.1.1.2.4 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
Time Schedule Violated		(b) (6)
Exclusion Criteria Met (Exclusion Criterion No. 17)		
Treatment Schedule Violated (wrong treatment sequence applied, T-R instead of R-T)		
Missing blood sample(s)		
Sample was taken but could not be analyzed due to faulty sample handling on site.		
Subject violated the study restrictions concerning the 2 h after drug administration		

Assessor's comments on protocol deviations: The above protocol deviations were assessed minor except for subject (b) (6) which was dropped out due to non-compliance (reference treatment). Protocol deviations regarding blood sampling, such as delays from scheduled sampling times and missing blood samples were assessed as defined in the study protocol.

None of the minor protocol deviations had any implication on the calculation of PK parameters. Actual blood sampling times were used for the purpose of calculating PK parameters.

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results: Inadequate

- Fifty-one (51) adverse events (AEs) were reported from 25 subjects following administration of test product and 29 AEs were reported from 10 subjects after administration of reference product during the study. Overall, a higher incidence of AEs was observed for the test product than for the reference product. Majority of AEs were mild to moderate in severity.
- Two serious adverse events (SAEs) were reported after administration of test product and one SAE was observed after administration of the reference product. Patient (b) (6) had decreased haemoglobin after test product treatment (last dose given on (b) (6)) and was hospitalized from (b) (6) due to mild anemia (see table below). Patient (b) (6) had chronic obstructive pulmonary disease after test product treatment (last

dose given on (b) (6) and was hospitalized from (b) (6). Patient (b) (6) reported stupor, delirium, hallucination and affective disorder after administration of reference product (last dose given on (b) (6)) and was hospitalized from (b) (6). One SAE (bilateral adnexitis) was reported for patient (b) (6) prior to the administration of test or reference products in the study. All SAEs were resolved per clinical study report.

Rnd. Report *No. No.	No. Observed AE/reaction	Seriousness due to	Severity/ Intensity	Outcome	>>>>Duration of AE<<<< Onset End
(b) (6) 1	1 MILD ANEMIA	Requires or Prolongs Hospitalization	MODERATE	RECOVERED/RESOLVED	(b) (6)
1	1 BILATERAL ADNEXITIS	Requires or Prolongs Hospitalization	MODERATE	RECOVERED/RESOLVED	(b) (6)
1	1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	Requires or Prolongs Hospitalization	MODERATE	RECOVERED/RESOLVED	(b) (6)
1	1 HALLUCINATION *	Requires or Prolongs Hospitalization	SEVERE	RECOVERED/RESOLVED	(b) (6)
	2 STUPOR *	Requires or Prolongs Hospitalization	SEVERE	RECOVERED/RESOLVED	(b) (6)
	3 DELIRIOUS *	Requires or Prolongs Hospitalization	SEVERE	RECOVERED/RESOLVED	(b) (6)
	4 AFFECTIVE COMPONENT *	Requires or Prolongs Hospitalization	SEVERE	RECOVERED/RESOLVED	(b) (6)

*:The reported term is "HALLUCINATORY - DELIRIOUS STUPOR WITH AFFECTIVE COMPONENT" and was coded as 4 PTs (Preferred Terms): Stupor, Delirium, Hallucination, Affective disorder.

- A consult request was sent to the Division of Clinical Review (DCR) on 5/13/2020 for the evaluation of 2 SAEs observed for patients (b) (6) with the test treatments after an e-mail communication with the DCR¹⁵. Currently, it is pending the response from DCR.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)	(b) (4)	Repeat Analysis
(b) (4)	(b) (4)	Repeat Analysis
(b) (4)	(b) (4)	Reporting of Bioanalytical Results
(b) (4)	(b) (4)	Reporting of Bioanalytical Results
(b) (4)	(b) (4)	Incurred Sample Reanalysis
(b) (4)	(b) (4)	Incurred Sample Reanalysis
(b) (4)	(b) (4)	Bioanalytical Method Validation
(b) (4)	(b) (4)	Bioanalytical Method Validation
(b) (4)	(b) (4)	High Performance Liquid Chromatography Mass Spectrometric Method for the Measurement of Risperidone In presence of Paliperidone in Human Plasma Using Risperidone D4 As an Internal Standard
(b) (4)	(b) (4)	Bioanalytical Protocol for Measurement of Risperidone in Presence of Paliperidone in Human Plasma Using LC-MS/MS Method

¹⁵ <https://panorama.fda.gov/task/view?ID=5ea6e61e0005f78f6bcf470202af1ac3>

BA-006-12	17 April 2017	Chromatography Acceptance Criteria
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All necessary SOPs submitted?	☒ Yes ☐ No
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4.1.1.3.2 Sample Analysis Calibration and Quality Control

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses- Using bulk spike-1

Bioequivalence Study No. Study No. CAC15003 Risperidone								
Parameter	Standard Curve Samples							
	A	B	C	D	E	F	G	H
Concentration (ng/mL)	0.113	0.216	3.698	7.292	18.231	36.718	58.287	72.923
Inter day Precision (CV%)	1.63	2.96	2.27	2.12	1.64	1.56	2.17	3.64
Inter day Accuracy (%Actual)	98.76	102.22	102.39	103.15	103.31	95.36	98.19	96.67
Linearity	0.9974 to 0.9998 (range of r values)							
Linearity Range (ng/mL)	0.113 to 72.923							
Sensitivity/LOQ (ng/mL)	0.113							

Bioequivalence Study No. CAC15003 Risperidone				
Parameter	Quality Control Samples			
	LQC	AQC	MQC	HQC
Concentration (ng/mL)	0.312	2.235	36.385	57.177
Inter day Precision (CV %)	4.13	2.86	2.5	2.9
Inter day Accuracy (%Actual)	93.62	100.95	100.5	98.25

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses- Using bulk spike-2

Bioequivalence Study No. Study No. CAC15003 Risperidone								
Parameter	Standard Curve Samples							
	A	B	C	D	E	F	G	H
Concentration (ng/mL)	0.112	0.215	3.680	7.257	18.142	36.284	58.004	72.568
Inter day Precision (CV%)	1.44	2.65	1.85	1.76	1.51	1.80	1.85	2.09
Inter day Accuracy (%Actual)	99.82	100.33	101.02	101.50	100.76	99.26	100.50	96.88
Linearity	0.9987 to 1.0000 (range of r values)							
Linearity Range (ng/mL)	0.112 to 72.568							
Sensitivity/LOQ (ng/mL)	0.112							

Bioequivalence Study No. CAC15003 Risperidone					
Parameter	Quality Control Samples				
	LQC	AQC	MQC	HQC	DIQC4T

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Concentration (ng/mL)	0.307	2.201	36.854	57.329	227.493
Inter day Precision (CV %)	4.61	2.77	2.13	2.61	10.92
Inter day Accuracy (%Actual)	92.77	95.12	95.49	94.26	101.39

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☒ Yes ☐ No (See assessor's comments below)
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

4.1.1.3.3 Reanalysis of Study Samples

Study No. CAC15003 Risperidone								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	00.00	00.00	0	0	00.00	00.00
Code VA	11	17	0.19	0.29	11	17	0.19	0.29
Code IAV	13	09	0.22	0.15	13	09	0.22	0.15
Code IA	01	00	0.02	0.00	01	00	0.02	0.00
Code UC	00	02	0.00	0.03	00	02	0.00	0.03
Code RB	208	200	3.52	3.39	208	200	3.52	3.39
Total	233	228	3.94	3.86	233	228	3.94	3.86

Code VA= Value above upper limit of quantification

Code IAV = Internal standard area variation

Code IA= Incomplete Analysis

Code UC= Unacceptable chromatography

Code RB= Rejected bioanalytical batch

T=Test Product, R=Reference Product

Total number of samples analyzed for Risperidone: 5907

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No (see assessor's comments below)
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A

Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A
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Comments on Bioanalytical Results: Inadequate

- Total 7.8% of samples were reanalyzed including the rejected runs.
- There were 6 rejected samples runs (57 samples for #070219-S0015, 72 samples for # 051218-S0050, 68 samples for # 110219-S0059, 68 samples for # 110219-S0060, 72 samples for # 120219-S0065 and 72 samples for # 130219-S0068) out of 109 runs in the BE study:
 - Runs #110219-S0059, and 110219-S0060, 120219-S0065, 130219-S0068 due to that QCs failed to meet acceptance criteria.
 - Run #051218-S0050 due to that calibration standards failed to meet accuracy acceptance criteria.
 - Run #070219-S0015 due to significant interference observed in blank+IS sample.

These samples were reanalyzed under Code RB. The applicant reported the numerical values for the repeated samples. The repeat analyses of the samples were verified by the assessor and were found consistent with the applicant's pre-established SOP (b) (4)

- Additionally, 53 samples were repeated under following reasons:
 - 28 samples for the reasons of "Value above upper limit of quantification (Code VA)".
 - 22 samples for "Internal standard area variation (Code IAV)", one sample for "Incomplete Analysis (Code IA)".
 - 2 samples for "Unacceptable chromatography (Code UC)".

The applicant reported the numerical values for the repeated samples. The repeat analyses of the samples were verified by the assessor and were found consistent with the applicant's pre-established SOP (b) (4).

- The applicant conducted incurred sample reanalysis (ISR) for 436 samples out of 5907 total analyzed samples (represents 7.38%). In the ISR, 373 out of 436 samples (represents 85.55%) were found to be within $\pm 20\%$ of their original value, which coincides with the acceptance criteria of the current bioanalytical guidance.¹⁶ It is also noted that among those samples exceeding $\pm 20\%$ of their original values, close to 50% of the samples had difference between original and repeat values $< 30\%$. The applicant's ISR analysis is acceptable and the method is reproducible.
- Bioanalytical lab was moved to a new location between 04/26 – 05/20/2019 per clinical study report. Per Bioanalytical Report (Protocol #CAC15003, issued date: 11 December 2019), the study sample analysis was conducted initially at (b) (4)

¹⁶ Guidance for Industry: Bioanalytical Method Validation (Draft Guidance), September 2013, Revision 1.

(b) (4) and later at (b) (4)

The applicant will be asked if additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site (refer to Section 3.4).

- The bioanalytical results are inadequate due to deficiency related to pre-study method validation.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters

The assessor will perform the final PK analysis after applicant re-submit the datasets.

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Risperidone Long-Acting Injection						
Dose (25 mg Risperidone), n=77						
Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study No. CAC15003)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC(Tau) [ng*h/mL]	1614.062	77	1832.619	77	88.07%	84.09% - 92.23%
Cmax(SS) [ng/mL]	8.619	77	9.912	77	87.00%	80.28% - 94.28%

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Assessor Calculated

Note: See deficiencies in the letter to the applicant for requesting complete datasets (plasma concentrations and PK) for doses #1, #2, #3, and #4. The assessor will perform the final PK and statistical analysis after applicant re-submit the datasets.

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	AUC0-τ: 0.188368 Cmax ss: 0.275319
Is there a Tmax difference between Test and Reference? If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	☐ Yes ☐ No (will calculate in the final analysis)
Were the subjects dosed in groups? If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?	☒ Yes ☐ No (see comments below)
Are there measurable drug concentrations at 0 hr? If yes, please comment (and take necessary action, if needed).	☒ Yes ☐ No ☐ NA (Multiple-dose steady-state BE Study)
Are there first measurable drug concentration as Cmax?	☐ Yes ☒ No

If yes, please comment.	
Are there Cmax at the first time point? If yes, is the study (sample) design adequate?	☐ Yes ☒ No

Group Analysis Consideration (If Applicable); if not, please delete this section

Is the drug product highly variable drug? If yes, please check the current DB policy to evaluate group effect: \\cdsnas\ogds11\firm\snz\ppd\controls\98-392a.doc	☐ Yes ☒ No
If no, is the group*treatment interaction term statistically significant at alpha=0.1 (i.e., $p < 0.1$)? If $p \geq 0.1$, no need to consider group effect.	☐ Yes ☐ No ☒ N/A Please see accessor's comments
If yes, did you use the statistical model with group effect included?	☐ Yes ☐ No ☒ N/A
If yes, specify which PK parameter(s).	☐ Yes ☐ No ☒ N/A
If yes (i.e. group*treatment term is significant), was each group analyzed separately?	☐ Yes ☐ No ☒ N/A
If each group was analyzed, did any individual group meet BE criteria?	☐ Yes ☐ No ☒ N/A
If none of individual group meets the BE criteria, did you have other justifications for accepting the data? If yes, please provide justifications.	☐ Yes ☐ No ☒ N/A

Comments on PK results: Inadequate

- The pivotal BE study was conducted at 14 clinical sites in 3 countries, Bulgaria, Moldova and Poland (see table below). The applicant did not include group*treatment interaction term in the statistical analysis due to small number of subjects included in each group.

# of sites involved	Site #	Number of Patients dosed at each site	Number of Patients that completed study at each site
1	BG01 (Bulgaria)	16	15
2	BG02 (Bulgaria)	12	12
3	BG04 (Bulgaria)	7	6
4	BG05 (Bulgaria)	6	5
5	BG06 (Bulgaria)	6	4
6	BG07 (Bulgaria)	6	4
7	BG08 (Bulgaria)	8	6
8	BG09 (Bulgaria)	7	5
9	BG10 (Bulgaria)	6	5
10	MD01 (Moldova)	10	6
11	MD02 (Moldova)	4	3
12	MD03 (Moldova)	3	1
13	MD04 (Moldova)	5	5
14	PL03 (Poland)	2	0

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		Total = 98	Total = 77*
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Note:

Total number of patients is 98.

Patients dropped-out: 18 subjects

Patients (b) (6) excluded from statistical analysis due to missing 3 or 4 consecutive blood samples

*The applicant included 77 patients in its statistical analysis [i.e., 98 - (18+3)] = **77 subjects**)

- The applicant did not include the group variable in the submitted dataset and will be asked to re-submit data with group variable. The applicant will perform the final PK and statistical analysis with the resubmitted dataset.
- Per clinical study report, pre-dose sampling was performed in order to establish proof of steady-state. However, the applicant did not conduct an analysis to see whether the patients have achieved steady-state. It is recommended that the applicant carry out appropriate dosing and sampling to document attainment of steady-state per FDA guidance for industry.¹⁷ Therefore, the applicant will be asked to perform an analysis to determine if subjects have achieved steady-state. In addition, the applicant submitted datasets for the 1st, 2nd, and 3rd injections can't be converted to appropriate format for assessor to perform the analysis and verify if steady-state has been achieved for individual patients. The applicant will be asked to re-submit the dataset.

4.1.1.5 Overall Comment

Was the steady state bioequivalence study acceptable? Not acceptable due to deficiencies listed in the deficiency letter.

¹⁷ FDA Guidance for Industry. Bioequivalence studies with PK endpoint for drugs submitted under an ANDA. Available at: <https://www.fda.gov/media/87219/download>; Issued December 2013.

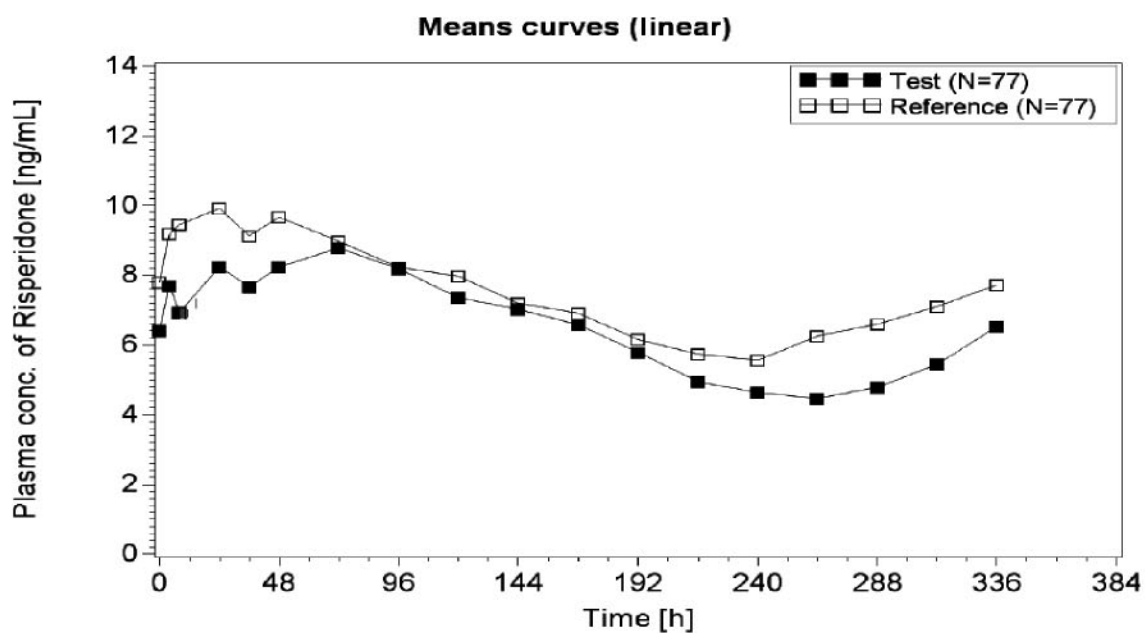
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Mean Plasma Concentrations, Steady State Bioequivalence Study (n=77)

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	6.47	8.70	7.31	8.88	0.89
4	7.83	10.81	8.24	10.11	0.95
8	6.46	5.95	8.04	11.21	0.80
24	7.41	7.11	8.80	10.13	0.84
36	7.66	6.85	9.13	9.18	0.84
48	7.33	6.17	9.45	9.78	0.78
72	7.89	8.59	8.64	9.76	0.91
96	8.18	10.28	8.22	8.22	1.00
120	5.75	4.54	7.71	9.13	0.75
144	7.03	11.80	7.19	8.78	0.98
168	6.58	12.35	6.92	10.58	0.95
192	4.15	4.23	6.13	9.95	0.68
216	4.93	8.85	5.39	9.16	0.91
240	3.41	3.16	4.76	7.19	0.72
264	3.21	3.14	5.82	9.03	0.55
288	4.17	6.37	5.24	6.28	0.80
312	4.77	6.82	7.10	9.10	0.67
336	6.52	8.29	7.72	9.07	0.84

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Figure 1. Mean Plasma Concentrations, Steady State Bioequivalence Study



Please note that the following summary tables for pilot study are provide here as information purpose only. The assessor did not perform statistical analysis for the applicant's pilot study.

4.1.2 Pilot Single Dose Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	PHA-RIP.I-01.15-208/147
Study Title	A Randomized, Two-way, Parallel , Open label, Laboratory-Blind, Pilot , Single dose Comparative Bioavailability Study Between Risperidone LAI 25 mg Powder and solvent for prolonged-release suspension for injection (Test Product/ Pharmathen, Greece) and Risperdal Consta 25 mg Powder and solvent for prolonged-release suspension for injection (Reference Product/ Janssen Pharmaceuticals Inc.) In Healthy Adults Under Fasting Conditions.
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (specify)
Clinical Site	Triumpharma Opposite Al-Jubaiha Circle, Amman, Jordan Tel. No.: 00962-6-5350582 Fax. No.: 00962-6-5350583 P.O. Box: 2233, Amman, 11941, Jordan
Dosing Dates	Study Initiation Date: 25 January 2015 Study Completion Date: 30 March 2015
Principal Clinical Investigator	Prof. Mustafa Shennak, M.D Tel: +962796662555 E-mail: PI@triumpharma.com
Analytical Site	(b) (4)
Analytical Dates	30 April 2015 to 12 May 2015
Principal Analytical Investigator	(b) (4)
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	106 days -20°C

Assessor's Note: The pilot BE study was conducted at different clinical and analytical sites from the pivotal BE study.

4.1.2.1.2 Product Information

Product	Test products	Reference product
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Treatment ID	A	B
Product Name	Risperidone LAI	Risperdal Consta (risperidone) Long-Acting Injection, 25 mg/vial
Manufacturer	(b) (4)	
Batch No./Lot No.	RLAI1402	411682
Manufacturing Date	Nov/2014	NA
Expiration Date	Retest Date: May/2015	Sep/2016
Strength	25 mg	25 mg
Dosage Form	Powder and solvent for (b) (4) suspension for injection	Powder and solvent for (b) (4) suspension for injection
Bio-batch Size	(b) (4)	N/A
Production Batch Size	N/A	NA
Assay*	99.2%	100.1%
Content Uniformity* (mean, %CV)	mean: 99.4% %CV: 2.12	N/A
Dose Administered	1x 25 mg	1x 25 mg
Route of Administration	IM	IM

Formulation Data

Ingredient of microparticles dry powder	Amount (mg) / Unit	Amount (%) / Unit
	Strength 1 (25mg)	Strength 1 (25mg)
Risperidone	25.00 (b) (4)	37.80
Poly(lactide-co-glycolide) polymer (PLGA 75:25)	(b) (4)	62.20
Total	66.14	100.00

Assessor's Note: The formulation of the microparticles dry powder used in the pilot study (Lot # RLAI1402, above) is similar to the formulation of the microparticles dry powder of the pivotal study (Lot #4700023B). The difference in the amount of Poly(lactide-co-glycolide) polymer (PLGA 75:25) is (b) (4).

4.1.2.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 51 Dosed: 48 (Test: 24 subjects; Reference: 24 subjects) Completed: 48 (Test: 24 subjects; Reference: 24 subjects) Samples Analyzed: 48 Statistically Analyzed: 48
No. of Sequences	1
No. of Periods	1
No. of Treatments	2
No. of Groups	1
Washout Period	N/A
Randomization	☒ Yes ☐ No
Blood Sampling Times	A total of (32) blood samples were collected for this study in 10 ml tubes containing lithium-heparin, according to the following schedule: Pre-dose (Blank), 1.00HR, 2.00HR, 4.00HR, 8.00HR, 12.00HR, Day 2, Day 3, Day 5, Day 8, Day 11, Day 15, Day 18, Day 22, Day 24, Day 26, Day 28, Day 29, Day 30, Day 31, Day 32, Day33, Day 34, Day 35, Day 36, Day 38, Day 40, Day 43, Day 47, Day 51, Day 57, Day 64 post dosing.
IRB Approval	☒ Yes Date: 07 December 2014 (Rev 00) ☐ No
Informed Consent	☒ Yes Date: 07 December 2014 (Rev 00) ☐ No
Length of Fasting	Subjects were fasted overnight for at least 10 hours.
Length of Confinement	Subjects were housed from approximately 10 hours prior to drug administration and until 24 hours post dose.
Was the drug product administered per labeling (for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A IM injection
Safety Monitoring	☒ Yes ☐ No

Note: The duration of the study treatment period was 65 days.

Comments on Study Design:

The pilot study was a single dose study conducted in healthy subjects, which is **not** in line with the recommendations provided in the current product specific BE guidance for this drug.¹⁸

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. PHA-RIP.I-01.15-208/147			
		Treatment Groups	
		Test Product (A), N=24	Reference Product (B), N=24
Age (years)	Mean $\pm$ SD	30 $\pm$ 9.2	29 $\pm$ 6.8
	Range	19-48	20-46
Age Groups	< 18	NA	NA
	18 – 40	20	23
	41 – 64	04	01
	65 – 75	NA	NA
	> 75	NA	NA
Sex	Male	24	24
	Female	NA	NA
Race	Asian	NA	NA
	Black	NA	NA
	Caucasian	24	24
	Hispanic	NA	NA
	Other	NA	NA
BMI (Kg/m ²)	Mean $\pm$ SD	24.70 $\pm$ 2.598	24.97 $\pm$ 2.991
	Range	19.36-29.62	20.22-29.41
Height (cm)	Mean $\pm$ SD	1.76 $\pm$ 0.056	1.76 $\pm$ 0.050
	Range	1.64-1.88	1.66-1.84
Weight (Kg)	Mean $\pm$ SD	77 $\pm$ 9.4	77 $\pm$ 9.5
	Range	60-96	62-95

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?

☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Study No. PHA-RIP.I-01.15-208/147				
Subject No	Reason for dropout/ replacement	Period	Replaced?	Replaced with
None				

Are dropouts appropriate? If no, please comment.

☐ Yes ☐ No ☒ NA

¹⁸

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Risperidone_intramuscular%20injection_RLD%2021346_RV08-16%20separate%20post.pdf

4.1.2.2.3

Study Adverse Events

Body System / Adverse Event	Reported Incidence by Treatment Groups	
	Fasting Bioequivalence Study	
	Study No. PHA-RIP.I-01.15-208/147	
	Test Product (A)	Reference Product (B)
Body System: Infections and infestations		
Influenza	01 (25.00%)	00 (00%)
Body System: Gastrointestinal disorders		
Diarrhea	01 (25.00%)	00 (00%)
Dry Mouth	01 (25.00%)	00 (00%)
Body System: Respiratory, thoracic and mediastinal disorders		
Short of breath	01 (25.00%)	00 (00%)
Total	04 (100.00%)	00 (00%)

Table 9 Listing of AEs by Subject

Subject No.	AE No.	Study Period	Treatment Code	Drug administration Date/Time (dd/mm/yyyy) /hr:min	Adverse Event Description	Onset Date (dd/mm/yyyy)	Onset time hr: min	Time from drug administration hr:min	Resolution Date/Time (dd/mm/yyyy) /hr:min	Duration of event hr:min	AE classification 1-Not serious 2-Serious	Intensity 1-Mild 2-Moderate 3-Severe	Relationship to treatment 1-Not related 2-Possible 3-Probable 4-Definite 5-other etiology	Action taken 1-None 2-Treatment given** 3-Participation termination 4-Medical state examination	Outcome 1-Complete recovery 2-Ongoing event 3-Disability 4-Death
(b) (6)	01	I	A	(b) (6)	Influenza	(b) (6)	08:00	119:56	(b) (6)	84:00	1	1	2	2-Treatment given:- Chlorpheniramine tablet 4 mg per OS 1x1x3 at 20:00 on (b) (6) Paracetamol 500 mg tablet per OS 2x1x3 at 12:00 on (b) (6)	2
	02	I	A		Shortness of breath		20:00	131:00		84:00	1	1	2	2	2
	03	I	A		Dry Mouth		20:00	131:00		84:00	1	1	2	2	2
	01	I	A		Diarrhea		06:00	741:10		28:30	1	1	1	2-Treatment given: Imodium tablet 5 mg per OS 2x2x2 start at 10:30	2

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
None					

Were subjects who experienced vomiting included in statistical analysis?

☐ Yes ☐ No ☒ N/A

If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.

☐ Yes ☐ No ☒ N/A

Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No Note: All AEs were mild in severity.
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.2.4 Protocol Deviations

Study No. PHA-RIP.I-01.15-208/147		
Type	Subject #s (Test)	Subject #s (Ref.)
Drug Administration: Deviation # 01: The drug administration procedure was delayed from the protocol specified time (Section 6.15.4 Drug Administration: "Dosing should be staggered at 2 minutes time interval starting at approximately 08:00 with the first subject"). Actual dosing time for first subject ended up starting at 08:08. There were also minor variations in the 2-minute staggering time between subjects. The delay was due to: 1- Delay in the reconstitution of the Risperidone by the pharmacist. 2- The dosing room was not ready. Deviation #03: Dosing was performed in the Emergency room instead of the Biological fluid sampling room as stated in section no 6.2:" Facilities". <u>Reason for departure:</u> Risperidone 25 mg should be given intramuscularly in the gluteal muscle; dosing was performed in the emergency room instead, for safety reasons and upon Principle Investigator's/ Clinical Investigator's request, since the latter is better equipped for the handling of any potential emergencies that might occur during the dosing process	All subjects (test and reference)	
Bioanalysis: Deviation # 05: Incurred sample reanalysis as described in protocol section 6.18 Bio-analysis" was not done. Reason for departure: As this was a pilot study it was not deemed as necessary per SOP (b) (4) Deviation # 06: PK samples storage and analysis in external lab outside (b) (4) As per Pharmathen request, the plasma samples of the study were shipped to an external lab (b) (4) for repeat analysis for confirmation purposes	All subjects (test and reference)	

Sample Collection and Handling: Deviation/Variation #02: Deviations from sampling timing were noted in the first (time: 1-hour post dose) sample after dosing as well as on sampling Days 3 - 64. All sample deviations were adjusted to dosing time delays (refer to Deviation #01) and captured accordingly.	All subjects (test and reference)	
Deviation # 04: Hemolyzed samples due to: 1. Difficulty of obtaining blood from vein 2. Rapid blood withdrawal from subject's vein by using the syringe 3. Blood emptying from the syringe into the tube was done in a rapid vertical way and not in a slow diagonal way toward the blood tube wall as appropriate.	Subjects no. (b) (6) 	Subjects no. (b) (6)

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time.	☒ Actual ☐ Nominal
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Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☐ Yes ☐ No ☒ N/A
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4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		The Determination of Risperidone and 9-Hydroxyrisperidone In Human Plasma By LC-MS/MS Using Risperidone-D4 and 9-Hydroxyrisperidone-D4 as an Internal Standard

4.1.2.3.2 Bioanalytical Method Validation -Risperidone

Information Requested	Data							
Analyte	Risperidone							
Internal standard (IS)	Risperidone-d ₄							
Method description	LC-MS/MS							
Limit of quantitation	0.100 ng/mL							
Average recovery of drug (%)	Between 83.82% and 87.14%							
Average recovery of IS (%)	83.06%							
Standard curve concentrations (ng/mL)	Cal 1	Cal 2	Cal 3	Cal 4	Cal 5	Cal 6	Cal 7	Cal 8
	0.100	0.200	0.800	2.000	8.000	16.000	20.000	25.000
QC concentrations (ng/mL)	QC low			QC med			QC high	
	0.300			12.500			17.500	
QC Intraday precision range (%) for Day One Precision	4.45% to 11.59%							

QC Intraday accuracy range (%) for Day One Precision	82.00% to 101.90%		
QC Intraday precision range (%) for Day Three Precision	1.21% to 6.36%		
QC Intraday accuracy range (%) for Day Three Precision	87.00% to 100.00%		
QC Intraday precision range (%) for Day Five Precision	2.54% to 13.39%		
QC Intraday accuracy range (%) for Day Five Precision	94.67% to 118.00%		
QC Interday precision range%)	2.93% to 18.65%		
QC Interday accuracy range (%)	93.00% to 104.00%		
Bench-top stability	6 hours @ room temperature		
Stock stability	19 days & 20 hrs @ 2-8°C		
Stock stability	42 hrs @ room temperature		
Processed stability	7 days & 22 hrs & 32min @ 15°C		
Freeze-thaw stability	9 cycles at -20°C		
Long-term storage stability	121 days @ -20°C		
Dilution integrity		Accuracy	Precision
	50.00 ng/mL diluted 2.5X	88.69	6.86
	75.00 ng/mL diluted 4X	88.28	6.13
Selectivity	No significant interferences from endogenous plasma samples at retention time for analyte and internal standard was observed.		

4.1.2.3.3 Bioanalytical Method Validation – (9-OH Risperidone)

Information Requested	Data							
Bioanalytical method validation report location	Module 5.3.1.2 Page #s 1909-1958 of PHA-RIP.I-01.15-208-147-study-summary-report.pdf							
Analyte	9-Hydroxyrisperidone							
Internal standard (IS)	9-Hydroxyrisperidone-d4							
Method description	LC-MS/MS							
Limit of quantitation	0.100 ng/mL							
Average recovery of drug (%)	Between 69.31% and 74.04%							
Average recovery of IS (%)	73.73%							
Standard curve concentrations (ng/mL)	Cal 1	Cal 2	Cal 3	Cal 4	Cal 5	Cal 6	Cal 7	Cal 8
	0.10	0.20	0.80	2.00	8.00	16.00	20.00	25.00
QC concentrations (ng/mL)	QC low			QC med		QC high		
	0.30			12.50		17.50		
QC Intraday precision range (%) for Day One Precision	5.81% to 10.80%							
QC Intraday accuracy range (%) for Day One Precision	96.10% to 112.00%							
QC Intraday precision range (%) for Day Three Precision	1.99% to 14.90%							

QC Intraday accuracy range (%) for Day Three Precision	95.41% to 102.00%		
QC Intraday precision range (%) for Day Five Precision	4.44% to 18.48%		
QC Intraday accuracy range (%) for Day Five Precision	89.33% to 105.00%		
QC Interday precision range%)	4.89% to 15.75%		
QC Interday accuracy range (%)	93.33% to 106.00%		
Bench-top stability	6 hours @ room temperature		
Stock stability	19 days & 20 hrs @ 2-8°C		
Stock stability	42 hrs @ room temperature		
Processed stability	7 days & 22 hrs & 32min @ 15°C		
Freeze-thaw stability	9 cycles at -20°C		
Long-term storage stability	121 days @ -20°C		
Dilution integrity		Accuracy	Precision
	50.00 ng/mL diluted 2.5X	97.56%	3.76
	75.00 ng/mL diluted 4X	96.94%	3.77
Selectivity	No significant interferences from endogenous plasma samples at retention time for analyte and internal standard was observed.		

4.1.2.3.4 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. PHA-RIP.I-01.15-208/147 Risperidone								
Parameter	Standard Curve Samples							
Concentration (ng/mL)	Cal 1	Cal 2	Cal 3	Cal 4	Cal 5	Cal 6	Cal 7	Cal 8
	0.100	0.200	0.800	2.000	8.000	16.000	20.000	25.000
Inter day Precision (%CV)	9.61	8.77	5.07	5.68	4.57	4.05	3.95	3.60
Inter day Accuracy (%Actual)	103.00	97.50	100.75	102.10	94.98	98.76	100.26	101.88
Linearity	0.9989							
Linearity Range (ng/mL)	0.100-25.00 ng/mL							
Sensitivity/LOQ (ng/mL)	0.100 ng/mL							

Bioequivalence Study No. PHA-RIP.I-01.15-208/147 Risperidone				
Parameter	Quality Control Samples			
Concentration (ng/mL)	QC low	QC med-1	QC med-2	QC high
	0.300	12.500	1.000	17.500
Inter day Precision (%CV)	12.23	6.36	7.76	6.03
Inter day Accuracy (%Actual)	103.00	103.00	100.20	100.56

Summary of Standard Curve and QC Data for Bioequivalence Sample Analyses- 9-OH Risperidone Analyte

Bioequivalence Study No. PHA-RIP.I-01.15-208/147 9-OH Risperidone				
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Parameter	Standard Curve Samples							
Concentration (ng/mL)	Cal 1	Cal 2	Cal 3	Cal 4	Cal 5	Cal 6	Cal 7	Cal 8
	0.100	0.200	0.800	2.000	8.000	16.000	20.000	25.000
Inter day Precision (%CV)	7.68	5.66	4.46	4.86	4.52	3.80	4.87	4.44
Inter day Accuracy (%Actual)	99.00	102.50	102.75	101.55	92.41	98.55	99.82	103.12
Linearity	0.9969							
Linearity Range (ng/mL)	0.100-25.00 ng/mL							
Sensitivity/LOQ (ng/mL)	0.100 ng/mL							

Bioequivalence Study No. PHA-RIP.I-01.15-208/147 9-OH Risperidone				
Parameter	Quality Control Samples			
Concentration (ng/mL)	QC low	QCmed1	QCmed2	QC high
	0.300	12.500	17.500	17.500
Inter day Precision (%CV)	8.48	5.54	6.90	5.61
Inter day Accuracy (%Actual)	103.33	101.11	104.20	99.81

4.1.2.3.5 Reanalysis of Study Samples

Study No. PHA-RIP.I-01.15-208/147 Risperidone Module 5.3.1.2 Page #s 425- 1175 of PHA-RIP.I-01.15-208-147-study-summary-report.pdf								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Reason (Technical Error)	8	4	0.52	0.26	8	4	0.52	0.26
Reason (IR) (Inconsistent Results)	28	30	1.81	1.94	12	18	0.77	1.16
Reason (IP) (Interfering peak)	1	0	0.06	0.00	1	0	0.06	0.00
Total	37	34	2.39	2.20	21	22	1.35	1.42

Reanalysis of Study Samples -9-OH Risperidone Analyte

Study No. PHA-RIP.I-01.15-208/147 9-OH Risperidone Module 5.3.1.2 Page #s 1177 - 1859 of PHA-RIP.I-01.15-208-147-study-summary-report.pdf								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Reason (Technical Error)	16	29	1.03	1.87	16	29	1.03	1.87
Reason (IR) (Inconsistent Results)	6	7	0.39	0.45	2	6	0.13	0.39

Total	22	36	1.42	2.32	18	35	1.16	2.26
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4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters

Summary of Pharmacokinetic Parameters of Risperidone after administration of Treatments A (Test) and B (Reference) in Healthy subjects under fasting conditions (N=48)

MEAN AND SD PHARMACOKINETIC DATA FOR RISPERIDONE		
Pharmacokinetic Parameter	Test Product A (mean ± SD) N= 24	Reference Product (mean ± SD) N= 24
C_{max} (ng/ml)	4.341 ± 3.5642	2.538 ± 1.4093
AUC_{last} (ng*hr/ml)	1311.365 ± 1111.2577	833.277 ± 401.4794
AUC_{0-888} (ng*hr/ml)	826.972 ± 678.1722	471.436 ± 264.3696
$AUC_{888-1521.18}$ (ng*hr/ml)	503.812 ± 620.7815	374.130 ± 266.3048
$AUC_{0-\infty}$ (ng*hr/ml)	1356.159 ± 1126.6463	875.595 ± 410.3939
T_{half} (hr)	78.52 ± 40.745	98.34 ± 59.172
$K_{elimination}$ (hr ⁻¹)	0.0105 ± 0.00389	0.0092 ± 0.00422
	Test Product A (median, (Range)), N= 24	Reference Product (median, (Range)), N= 24
T_{max}	840.67, (337.37-1106.43)	888.87, (47.65-1108.60)
T_{max} (Mann Witney U test)	0.2398	

Summary of Pharmacokinetic Parameters of 9-OH Risperidone after administration of Treatments A (Test) and B (Reference) in Healthy subjects under fasting conditions (N=48)

MEAN AND SD PHARMACOKINETIC DATA FOR 9-OH RISPERIDONE		
Pharmacokinetic Parameter	Test Product A (mean ± SD) N=24	Reference Product (mean ± SD) N=24
C_{max} (ng/ml)	8.532 ± 4.8057	9.531 ± 3.7523
AUC_{last} (ng*hr/ml)	3014.557 ± 1303.5809	3248.221 ± 803.3676
AUC_{0-888} (ng*hr/ml)	1636.862 ± 885.10	1627.458 ± 659.9324
$AUC_{888-1521.18}$ (ng*hr/ml)	1280.121 ± 507.4203	1628.003 ± 668.4187
$AUC_{0-\infty}$ (ng*hr/ml)	2864.691 ± 970.6828	3325.552 ± 805.7381
T_{half} (hr)	97.28 ± 27.153	113.58 ± 50.998
$K_{elimination}$ (hr ⁻¹)	0.0076 ± 0.00202	0.0068 ± 0.00192
	Test Product (median, (Range)), N=24	Reference Product (median, (Range)), N=24
T_{max}	889.07, (767.60-1346.57)	892.56, (96.80-1108.60)

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Applicant Calculated

Risperidone Long-Acting Injection Dose (25 mg Risperidone), n=48 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fast Bioavailability Study (Study No.: PHA-RIP.I-01.15-208/147)						
Parameter	Test	N	Reference	N	Ratio	90% C.I.
LnC_{max} (ng /ml)	3.242	24	2.268	24	142.96	105.00- 194.63
$LnAUC_{0-t}$ (ng*hr/mL)	978.546	24	747.973	24	130.83	96.28- 177.77

LnAUC_{0-∞} (ng*hr/mL)	1023.745	24	791.374	24	129.36	95.89- 174.53
LnAUC₀₋₈₈₈ (ng*hr/mL)	608.635	24	410.640	24	148.22	106.53- 206.22
LnAUC_{888-1521.18} (ng*hr/mL)	323.743	24	290.786	24	111.33	73.86- 167.83

Comments on PK results:

- Based on the applicant's submitted results, the pilot single dose BE study did not meet the acceptance criteria of 80 -125% for 90% CIs of the test/reference ratios of the least squares geometric means PK parameters, LnC_{max}, LnAUC_{0-t}, LnAUC_{0-∞}, LnAUC₀₋₈₈₈, and LnAUC_{888-1521.18}. It is noted that T/R ratio for all parameter except for LnAUC_{888-1521.18} are not within 0.8-1.25.

4.2.1 Test Formulation

3.2.P.1 - Table 19: Quantitative Composition and Function of the Microspheres

[illegible]

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(b) (4)

Composition of Diluent²⁰

Table 3: Quantitative Composition and Function of the Diluent

Ingredient	Quality Standards	Function	mg/ unit ²	mg injected (mg) (b) (4) (2 mL)	% w/w (%/unit)	% content (w/v)
Carboxymethyl cellulose sodium salt ¹ (b) (4)	USP/NF/EP					(b) (4)
Polysorbate 20	USP/NF/EP					
Disodium hydrogen phosphate (b) (4)	USP/NF/EP					
Citric acid (b) (4)	USP/NF/EP					
Sodium chloride	USP/NF/EP					
Sodium hydroxide	USP/NF/EP					
Water for injection	USP/NF/EP					
Total weight (mg)	-	-		(b) (4)	100.0	100.00
Total volume (mL)	-	-	2.29 ²	2.00	--	--

(b) (4)

(b) (4)

²⁰ DARRTS 214068, dated 12/16/2019, M.3.2.P.1, Discription and composition of the drug product – Diluent, \\cdsesub1\evsprod\anda214068\0001\m3\32-body-data\32p-drug-prod\dp-diluent\32p1-desc-comp\desc-comp-of-the-drug-prod-diluent.pdf

(b) (4)

Applicant's Justification of Excipients in the Diluent²¹

Material	Function	Grade	CAS	UNII	mg (b) (4) (2mL)	% content (w/w)	% content (w/v)	eIID by FDA Maximum Potency per unit dose	Justification
Carboxymethyl cellulose sodium salt 1,2									(b) (4)
Polysorbate 20									
Disodium hydrogen phosphate dihydrate									
Citric acid anhydrous									
Sodium chloride									
Sodium hydroxide									
Water for injection									
Total	--	--	--	--	(b) (4)	100.00	100.00	NA	(b) (4)

²¹ DARRTS 214068, dated 12/16/2019, M.3.2.P.1, Formulation Review (IID Evaluation); [\lcdsesub1\evsprod\anda214068\0001\m3\32-body-data\32p-drug-prod\diluent\32p1-desc-comp\formulation-review-diluent.pdf](#)

(b) (4)

Table 1: Inactive Ingredient Levels in Risperidone Long Acting Injection, 12.5 mg/vial

Material	Function	Grade	CAS	UNII	mg/Injecte d ²	% content (w/w)	eIID by FDA Maximum Potency per unit dose	Justification
Risperidone	API	USP	106266062	L6UH7ZF8HC	12.5 mg	(b) (4)	-	NA

Excipients in dry powder

7525 polylactide-co-glycolide (PLG)	(b) (4)	(b) (4)
Water for Injection ¹	(b) (4)	(b) (4)

Table 2: Inactive Ingredient Levels in Risperidone Long Acting Injection, 25 mg/vial

Material	Function	Grade	CAS	UNII	mg injected ²	% content (w/w)	eIID by FDA Maximum Potency per unit dose	Justification
Risperidone	API	USP	106266062	L6UH7ZF8HC	25 mg	(b) (4)	-	NA
Excipients in dry powder								
(b) (4)								
7525 polylactide-co-glycolide (PLG)								
(b) (4)								
Water for Injection ¹								
(b) (4)								

Table 4: Inactive Ingredient Levels in Risperidone Long Acting Injection, 50 mg/vial

Material	Function	Grade	CAS	UNII	mg Injected ²	% content (w/w)	eHID by FDA Maximum Potency per unit dose	Justification
Risperidone	API	USP	106266062	L6UH7ZF8HC	50 mg	(b) (4)	-	NA

Excipients in dry powder

7525 polylactide-co-glycolide (PLG)

(b) (4)

*Water for Injection*¹

²² DARRTS 214068, dated 12/16/2019, M.3.2.P.1, Iron Content Calculation, [\\cdsesub1\evsprod\anda214068\0001\m3\32-body-data\32p-drug-prod\dp-diluent\32p1-desc-comp\iron-calc.pdf](#)

4.2.2 RLD Formulation

Not to be released under FOIA



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RLD (NDA 021346) Formulation Composition²⁵

3.2.P.1 Description and Composition of the Drug Product - RISPERDAL CONSTA®

Table 2: Overfill Factor and Corresponding Target Fill Weights Required to Obtain Risperidone Equivalent Dose Strengths of RISPERDAL CONSTA®

Target Fill Weight Including Overfill (Overfill Factor)			
Dose Strength	12.5 mg/vial	25 mg/vial	37.5 mg/vial 50 mg/vial
Risperidone ^a	(b) (4)		
PLG Polymer ^{a, b}	(b) (4)		
Microspheres	(b) (4)		

4.2.3 Comparison of Test and Corresponding Reference Formulations

Ingredients	Amount per mL		Percent Difference (%) (R-T)/R*100
	Test (mg/mL)	R.I.D. (mg/mL)	
(b) (4)			
polylactide-co-glycolide (PLG) 75:25	(b) (4)		
Diluent	(b) (4)		
Carboxymethyl Cellulose Sodium Salt	(b) (4)		
Polysorbate 20	(b) (4)		
Sodium Hydrogen Phosphate Dihydrate	(b) (4)		
Citric Acid Anhydrous	(b) (4)		
Sodium Chloride	(b) (4)		
Sodium Hydroxide	(b) (4)		

²⁵ DARRTS NDA 021346, dated 06/19/2006, M3.2.P.1, Description and Composition of the Drug Product (active, powder);
[\\cdsesub1\evsprod\nda021346\0000\un3\32-body-data\32p-drug-prod\active-powder-common\32p1-desc-comp\description-and-composition.pdf](#)

Control Correspondences (CC) that are pertained to the current ANDA
[Below summary of the applicant's communication with the Agency]²⁶

A. CC 02407 (dated 05/15/2019)²⁷

Inquiry submitted: Teva submitted a control to request the Agency's Q1/Q2 determination on its proposed test formulation and the RLD. In this control, Teva's proposed test formulation is considered Q1/Q2 the same as the RLD.

Agency response: *The assessment conclusion is Teva's test product is considered Q1/Q2 the same as the RLD.* The assessment report (cc 02407) provided the following formulation comparison, table below:

Ingredient	Proposed formulation Teva	RLD Risperdal Consta	% Difference to RLD (T-R)/R*100%
Microsphere composition (mg/vial)			
Risperidone			(b) (4)
Poly-(d,l-lactide-co-glycolide) 75:25			(b) (4)
Diluent composition (mg/mL)			
Citric acid, anhydrous			(b) (4)
Disodium hydrogen phosphate dihydrate			(b) (4)
Polysorbate 20			(b) (4)
Sodium carboxymethyl cellulose			(b) (4)
Sodium chloride			(b) (4)
Sodium hydroxide			(b) (4)
Water for Injection			(b) (4)

OGD's response to the applicant is provided below:

²⁶ <\\cdsesub1\evsprod\anda214068\0001\ml\us\controlled-correspondences.pdf>

²⁷ <\\cdsesub1\evsprod\anda214107\0001\ml\us\controlled-correspondence-24683031.pdf>

CC 02407, for convenience of the reviewing process, a copy of the cc is provided in the Attachment section of this review report.;
<https://panorama.fda.gov/task/view?ID=5c9007bf0101b74ba52ffa32f4ab416b>

OGD provides the following comments:

After reviewing your controlled correspondence submitted on March 18, 2019, the Office of Generic Drugs (OGD) has made a preliminary determination that OGD would not likely refuse to receive an abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act and its implementing regulations based on your proposed formulation pursuant to the requirements pertaining to inactive ingredients described in 21 CFR 314.101(d)(3) and 21 CFR 314.94(a)(9).

Reference is made to the definition of quantitative sameness to the reference listed drug (RLD) as stated in the guidance for industry *ANDA Submissions - Refuse-to-Receive Standards* (May 2015).

In addition, please note the following comments:

- Please make sure comparative physicochemical characterization studies of PLGA are conducted on three batches each of both your test and the reference products. If there are differences in physicochemical characteristics of PLGA, please include a justification of why these differences would not impact bioavailability in your ANDA submission.
- We acknowledge you have provided justification of the proposed overfill for your test product. Please note that overfill is out of the scope for Q1/Q2 assessment. Therefore, the submitted information/data regarding overfill was not reviewed at this time. The acceptance of your proposed overfill is a review issue and will be determined during ANDA review.

This response closes out the above controlled correspondence.

B. CC 1524801 (dated: 18 September 2015)

Inquiry submitted: Controlled Correspondence - Q1 and Q2 comparison between Risperdal® Consta® (risperidone) Injection **50 mg/vial** and proposed generic equivalents submitted by Teva Pharmaceuticals USA.

Agency response: After reviewing the proposed generic formulations, the OGD has made a preliminary determination that your proposed generic microsphere formulation titled –Teva Proposed Formulation (mg/vial) and your proposed diluent formulation titled –Teva Formulation #1 (mg/2 mL) are Q1/Q2 (qualitatively and quantitatively the same) to the Reference Listed Drug (RLD). Reference is made to the definition of quantitative sameness to the RLD as stated in the RTR guidance.

C. CC 1524802 (dated: 18 September 2015)

Inquiry submitted: Controlled Correspondence - Q1 and Q2 comparison between Risperdal® Consta® (risperidone) Injection **37.5 mg/vial** and proposed generic equivalents submitted by Teva Pharmaceuticals USA.

Agency response: Agency response: After reviewing the proposed generic formulations, the Office of Generic Drugs has made a preliminary determination that your proposed generic microsphere formulation titled –Teva Proposed Formulation (mg/vial) and your proposed diluent formulation titled –Teva Formulation #1 (mg/2 mL) are Q1/Q2 (qualitatively and quantitatively the

same) to the Reference Listed Drug (RLD). Reference is made to the definition of quantitative sameness to the RLD as stated in the Refuse-To-Receive guidance document.

D. CC 1524803 (dated: 18 September 2015)

Inquiry submitted: Controlled Correspondence - Q1 and Q2 comparison between Risperdal® Consta® (risperidone) Injection 12.5 mg/vial and proposed generic equivalents submitted by Teva Pharmaceuticals USA.

Agency response: After reviewing the proposed generic formulations, the Office of Generic Drugs has made a preliminary determination that your proposed generic microsphere formulation titled –Teva Proposed Formulation (mg/vial) and your proposed diluent formulation titled –Teva Formulation #1 (mg/2 mL) are Q1/Q2 (qualitatively and quantitatively the same) to the Reference Listed Drug (RLD). Reference is made to the definition of quantitative sameness to the RLD as stated in the RTR guidance.

E. CC 1524804 (dated: 18 September 2015)

Inquiry submitted: Controlled Correspondence - Q1 and Q2 comparison between Risperdal® Consta® (risperidone) Injection 25 mg/vial and proposed generic equivalents submitted by Teva Pharmaceuticals USA.

Agency response: After reviewing the proposed generic formulations, the Office of Generic Drugs has made a preliminary determination that your proposed generic microsphere formulation titled –Teva Proposed Formulation (mg/vial) and your proposed diluent formulation titled –Teva Formulation #1 (mg/2 mL) are Q1/Q2 (qualitatively and quantitatively the same) to the Reference Listed Drug (RLD). Reference is made to the definition of quantitative sameness to the RLD as stated in the RTR guidance.

There was a discussion on polymer attributes at pre-ANDA meeting (submitted in Module 1.2)²⁸. The acceptability of physicochemical characteristic of polymer (i.e., PLG and sodium carboxymethyl cellulose) is deferred to OPQ.

Comment from Division of Clinical Review (DCR):

The office of Pharmaceutical Quality (OPQ) consulted DCR on determination of the safety and acceptability of three excipients, i.e., polylactide-co-glycolide (PLG), sodium carboxymethyl cellulose, and (b) (4), in the proposed generic risperidone long acting injection. PLG (75:25) in the proposed generic have the same (b) (4) but the molecular weight (MW) of the PLG in the proposed generic (b) (4) differs from the (b) (4) of the PLG in the RLD (b) (4). The MDIs of sodium carboxymethyl cellulose in the RLD and the proposed generic product are the same at (b) (4). It is also stated that sodium

²⁸ \\cdsesub1\evsprod\anda214068\0001\m1\us\controlled-correspondences.pdf

carboxymethyl cellulose in the proposed generic product is a (b) (4)

The DCR concluded for the consult as the following: From Clinical and Pharmacology/Toxicology perspectives, the MDIs of polylactide-co-glycolide (PLG), sodium carboxymethyl cellulose (NaCMC), and disodium hydrogen phosphate dihydrate, in the proposed generic risperidone long acting injection (ANDA 214068) are supported by levels in FDA approved drug products with similar context of use and are therefore acceptable.²⁹

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No The proposed generic formulations for both diluent and powder are Q1 & Q2 same to the RLD

Comments on Formulation: Adequate

²⁹ GDRP: ANDA 214068, Application Life Cycle, file: A214068N000DCR-Consult Response-01_Risperidone_PLG excipient_final.pdf; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

4.3 In Vitro Drug Release and Dissolution Testing

4.3.1 Dissolution Data

Table 5.1: Summary of In Vitro Dissolution Studies-

Dissolution Conditions		Apparatus:		(b) (4)		(b) (4)		
Speed of Rotation:								
Medium:								
Volume:								
Temperature:								
Firm's Proposed Specifications				(b) (4)		(b) (4)		
Dissolution Testing Site (Name, Address)				(b) (4)		(b) (4)		
Study Ref No	Testing Date (dd/mm/yyyy)	Product ID \ Batch No. (Test - Manufacture Date) (Reference - Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (days)		Study Report Location	
REPRD001 COMPDISS _RISPUS/L AI	29/05/2018 – 09/06/2018	Test Product: Batch# 4700014A Mfg Date: 03/2018	Risperidone for injectable suspension 12.5mg	12	Mean	0.3	15.1	Module 2.7 (comparative-dissolution-report)
					Range	(b) (4)		
					% CV	7.10	7.17	
	14/01/2019- 25/01/2019	Test Product: Batch# 4700023B (bio-batch) Mfg. Date: 05/2017	Risperidone for injectable suspension 25mg	12	Mean	1.2	15.0	
					Range	(b) (4)		
					% CV	13.48	3.37	
26/06/2018 – 07/07/2018	Test Product: Batch# 4700013C Mfg. Date: 02/2018	Risperidone for injectable suspension 37.5mg	12	Mean	0.8	15.9		
				Range	(b) (4)			
				% CV	8.30	5.79		

29/05/2018 – 09/06/2018	Test Product: Batch# 4700014D Mfg. Date: 03/2018	Risperidone for injectable suspension 50mg	12	Mean	0.4	15.6	(b) (4)
				Range			
				% CV	7.34	6.62	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch #91889P1 Exp. Date: 12/2020	Risperdal Consta® 12.5mg strength	12	Mean	0.4	8.7	(b) (4)
				Range			
				% CV	3.27	3.78	
15/10/2018- 26/10/2018	Reference Product: Risperdal Consta Batch # 83365P2 (bio-batch) Exp. Date: 04/2019	Risperdal Consta® 25mg strength	12	Mean	1.3	13.9	(b) (4)
				Range			
				% CV	12.12	3.96	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch # 87385P1 Exp. Date: 02/2020	Risperdal Consta® 37.5mg strength	12	Mean	0.6	9.0	(b) (4)
				Range			
				% CV	3.71	2.95	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch # 92828P1 Exp. Date: 03/2021	Risperdal Consta® 50mg strength	12	Mean	0.8	8.6	(b) (4)
				Range			
				% CV	3.44	1.01	

Table 5.2: Summary of In Vitro Dissolution Studies-

Dissolution Conditions		Apparatus:																
		Speed of Rotation:																
		Medium:																
		Volume:																
		Temperature:																
Firm's Proposed Specifications		(b) (4)																
Dissolution Testing Site (Name, Address)		(b) (4)																
Study Ref No	Testing Date (dd/mm/yyyy)	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (hours)	Study Report Location												
							24h	72h	120h	144h	160h	168h	172h	184h	192h	210h	256h	
REPRD001 COMPDISS_RISPU US/LAI	29/05/2018 – 09/06/2018	Test Product: Batch# 4700014A Mfg Date: 03/2018	Risperidone for injectable suspension 12.5mg	12	Mean	1.1	2.0	8.1	21.7	54.5	68.8	75.5	89.1	91.2	94.1	97.8	(b) (4) 2.7 comparative-dissoluti on-report)	
					Range													
					% CV	5.78	4.26	11.19	7.98	2.16	2.24	2.94	2.78	2.58	1.72	3.3		
	14/01/2019- 25/01/2019	Test Product: Batch# 4700023B (bio-batch) Mfg. Date: 05/2017	Risperidone for injectable suspension 25mg	12	Mean	2.0	4.0	9.3	27.7	53.1	70.1	81.3	89.1	90.5	93.2	95.3	(b) (4)	
					Range													
					% CV	7.57	3.51	3.17	4.50	0.42	3.48	2.36	1.33	1.57	0.73	0.64		
26/06/2018 – 07/07/2018	Test Product: Batch# 4700013C Mfg. Date: 02/2018	Risperidone for injectable suspension 37.5mg	12	Mean	1.4	2.1	8.1	21.8	55.0	69.8	75.1	88.1	91.4	94.8	98.6	(b) (4)		
				Range														
				% CV	4.64	5.06	12.63	10.11	4.84	7.13	2.48	2.31	3.36	1.54	3.17			
	Test Product:			12	Mean	1.2	2.3	8.4	21.2	55.3	68.8	75.1	87.6	89.0	90.8	93.6		

29/05/2018 – 09/06/2018	Batch# 4700014D Mfg. Date: 03/2018	Risperidon e for injectable suspension 50mg	12	Range	(b) (4)											
				% CV	8.61	6.7	8.69	8.5	1.22	3.14	3.35	2.34	3.41	2.15	2.54	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch #91889P1 Exp. Date: 12/2020	Risperdal Consta® 12.5mg strength	12	Mean	1.0	2.7	8.3	24.2	53.1	67.5	74.1	86.8	91.9	92.6	93.1	
				Range	(b) (4)											
				% CV	1.37	2.51	1.26	1.48	2.94	1.26	3.68	1.34	0.62	0.82	0.71	
15/10/2018- 26/10/2018	Reference Product: Risperdal Consta Batch # 83365P2 (bio- batch) Exp. Date: 04/2019	Risperdal Consta® 25mg strength	12	Mean	1.0	3.8	7.0	22.0	47.5	64.6	79.0	86.9	90.5	90.8	94.9	
				Range	(b) (4)											
				% CV	2.65	5.08	2.89	0.54	4.55	3.59	0.55	2.02	0.53	1.94	1.05	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch # 87385P1 Exp. Date: 02/2020	Risperdal Consta® 37.5mg strength	12	Mean	1.3	3.4	9.5	22.5	58.5	71.8	77.5	86.1	88.1	91.1	94.4	
				Range	(b) (4)											
				% CV	2.27	1.29	1.59	3.41	1.22	0.76	0.75	0.83	0.49	0.57	0.91	
18/09/2019 – 29/09/2019	Reference Product: Risperdal Consta Batch # 92828P1 Exp. Date: 03/2021	Risperdal Consta® 50mg strength	12	Mean	1.4	3.4	9.1	20.1	54.9	68.0	73.6	83.1	86.6	92	97.1	
				Range	(b) (4)											
				% CV	1.40	1.56	1.92	3.00	2.6	2.58	2.33	1.60	1.60	1.12	0.54	

Dissolution Testing of Pilot Study

(b) (4)

Dissolution Conditions		Apparatus:		(b) (4)									
		Speed of Rotation:											
		Medium:											
		Volume:											
		Temperature:											
Firm's Proposed Specifications				(b) (4)									
Dissolution Testing Site (Name, Address)													
Study Ref No	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units	Collection Times (minutes or hours)						Study Report Location		
					1 day	4 days	10 days	16 days	20 days				
Study Report #: REPRD001COMPDISSPIL_RISPUS/LAI	19/12/2014-26/01/2015	Test Product: RLAI1402 Man. Date:11/2014	Risperidone for injectable suspension 25mg	12	Mean	1.1	1.0	1.5	2.4	3.4	Module 3.2.P.2 (pdr-powder)		
					Range	(b) (4)							
					% CV	6.76	7.49	7.68	3.43	2.25			
Study Report #: REPRD001COMPDISSPIL_RISPUS/LAI	19/12/2014-26/01/2015	Reference Product: Batch#: 411682 Exp. Date: 09/2016	Risperdal Consta® 25mg	12	Mean	1.8	1.4	2.5	3.2	4.2	(b) (4)		
					Range	(b) (4)							
					% CV	3.95	6.44	2.65	2.56	1.97			
Study Ref No	Collection Times (minutes or hours)												

	Testing Date	Product ID \ Batch No. (Test - Manufacture Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		26 days	28 days	31 days	34 days	36 days	38 days	Study Report Location
Study Report #: REPRD001COMPDISSPIL_RISPUS/LA I	19/12/2014 - 26/01/2015	Test Product: Batch#: RLAI1402 Man. Date:11/2014	Risperidone for injectable suspension 25mg	12	Mean	11.9	24.9	56.2	96.6	99.1	100.5	Module 3.2.P.2 (pdr-powder)
					Range							
					% CV	2.90	7.07	3.16	2.76	0.47	0.42	
					Mean	11.0	19.2	56.8	89.2	96.5	97.5	
Study Report #: REPRD001COMPDISSPIL_RISPUS/LA I	19/12/2014 - 26/01/2015	Reference Product: Batch#: 411682 Exp. Date: 09/2016	Risperdal Consta® 25mg	12	Range							(b) (4)
					% CV	1.93	8.06	1.10	6.25	0.40	0.57	

4.3.2 In Vitro Drug Release

Per current product specific guidance for Risperidone LA Injectable, an in vitro drug release study on the 25 mg/vial strength is recommended in addition to the in vivo BE study.

Dissolution Method:

Apparatus:	(b) (4)	
Medium:		
Volume:		
Temperature:		

Results (37.0 ± 0.3 °C):

		Day 1 Mean (range) (%)	Day 21 Mean (range) (%)
25 mg/vial	Test (#4700023B)	(b) (4)	
	Reference (#83365P2)		

Results (45.0 ± 0.3 °C):

	Test (#4700023B) Mean (range) (%)	Reference (#83365P2) Mean (range) (%)
24 h (Day 1)	(b) (4)	
72 h (Day 3)		
120 h (Day 5)		
144 h (Day 6)		
160 h (Day 6.67)		
168 h (Day 7)		
172 h (Day 7.17)		
184 h (Day 7.67)		
192 h (Day 8)		
210 h (Day 8.75)		
256 h (Day 10.67)		

Assessor's Comments:

- The applicant submitted dissolution method validation report (No. CC-2019-30-0190; issued on 11/28//2019)³⁰ and report addendum (No. CC-2019-10-1170; issued on 12/10/2019)³¹ and a comparative dissolution study report (No: CC-2019-10-1170; issued 11/27/2019)³². It is noted that the dissolution study report was issued before the method validation report. The applicant will be asked to explain it.

(b) (4)

- The % cumulative drug release for the test and reference products is comparable at Day 1 (1.2 vs. 1.3%) and Day 21 (15.0 vs. 13.9%) at 37 °C.
- At 45 °C, the cumulative drug release for the test and reference products is comparable at Day 8 (both having 90.5% release).
- The applicant did not submit the in vitro drug release data in an electronic file. Therefore, assessor cannot calculate the T_{50%} at 45 °C and the 90% confidence interval of the test/reference ratio of T_{50%}. The applicant will be asked to submit the requested dissolution data and provide analysis results of T_{50%} and the 90% confidence interval of the test/reference ratio of T_{50%}.
- Therefore, the in vitro drug release study is **inadequate**.

4.3.3 Dissolution Summary

- The dissolution testing for establishment of the regulatory method and specifications for the test product for quality control (QC) purpose was reviewed separately in a biopharmaceutics review and review is currently pending.³³
- The in vitro release testing data of all strengths are acceptable. The f2 similarity factor values for all strengths are acceptable (f2 > 50; see table below).

F2 metric, biostudy strength compared to other strength		
RISPERIDONE		
Dissolution Method: (b) (4)		
Biostudy Strength (Test bio-lot)	Other Strength (Test – lower strengths)	F2 metric
Test Bio-lot 25 mg (Lot #4700023B)	Reference Bio-lot 25 mg (Lot #83365P2)	74.26
Test Bio-lot 25 mg (Lot #4700023B)	Test lot 12.5 mg (Lot # 4700014A)	77.11
Test Bio-lot 25 mg (Lot #4700023B)	Test lot 37.5 mg (Lot #4700013C)	75.98
Test Bio-lot 25 mg (Lot #4700023B)	Test lot 50 mg (Lot #4700014D)	75.87

- The submitted dissolution data are adequate with respect to supporting the waiver requests for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths. However, at this time DBIII does not grant the waiver requests for in vivo BE study requirements for the 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial strengths based on criteria set forth in 21 CFR § 320.24 (b)(6).

Overall Comments: Inadequate

³³ GDRP; ANDA-214068-ORIG-1; Biopharmaceutics review; file: ANDA 214068 biopharm review.docx; <https://panorama.fda.gov/project/view?ID=5df8e06a009a6974cfbc1f8cd8cd0e72>

4.4 Attachments

4.4.1 Subjects at Each Clinical Site

Study Number	CAC15003						
Study Title	Randomized, multiple-dose, multi-national, multi-center, open-label, two-way crossover pharmacokinetic study to assess the bioequivalence of Risperidone Long-Acting Injection, 12.5, 25, 37.5 and 50 mg, manufactured by Pharmathen International S.A. for Actavis Group PTC ehf (TEST) compared to RISPERDAL CONSTA® (risperidone) LONG-ACTING INJECTION, 12.5, 25, 37.5 and 50 mg, Janssen Pharmaceuticals, Inc., USA (REFERENCE), in patients						
Study Type	☒ In Vivo BE ☐ In Vitro BE ☐ Permeability ☐ Other (Specify)						
Clinical Site BG01 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital Pazardzhik, 28 Bolnichna Str., 4400 Pazardzhik Bulgaria						
	Related subjects						
	Subject Randomization number	Subject ID (in each designated site)	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment
	(b) (6)		BG01	T-R	(b) (6)	(b) (6)	
		BG01	T-R				
		BG01	T-R				
		BG01	R-T				
		BG01	R-T				
		BG01	R-T				
		BG01	T-R				
		BG01	R-T				
		BG01	R-T				
		BG01	T-R				
		BG01	T-R				
		BG01	R-T				
		BG01	R-T				
		BG01	T-R				
		BG01	R-T				
		BG01	T-R				
	Total number of patients in site BG01 = 16						
Clinical Site BG02 (Name, Address, Phone #, Fax #)	MHAT "Dr. Ivan Seliminski" JSC, 1 "Hristo Botev" Str., 8800 Sliven, Bulgaria						
	Related subjects						
	Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment
	(b) (6)		BG02	R-T	(b) (6)	(b) (6)	
		BG02	T-R				
		BG02	T-R				
		BG02	T-R				
		BG02	R-T				
		BG02	R-T				
		BG02	T-R				
		BG02	T-R				
		BG02	R-T				
		BG02	T-R				
		BG02	R-T				

	(b) (6) BG02 R-T (b) (6) Total number of patients in site BG02 = 12																																													
Clinical Site BG03 (Name, Address, Phone #, Fax #)	Military Medical Academy, 3 "Sveti Georgy Sofiyski" Str, 1000 Sofia, Bulgaria No Patients involved																																													
Clinical Site BG04 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital Tsarev brod, 30 "Hristo Botev" Str., 9747 Tsarev brod, Bulgaria <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="7">(b) (6)</td><td></td><td>BG04</td><td>T-R</td><td rowspan="7">(b) (6)</td><td></td><td></td></tr><tr><td></td><td>BG04</td><td>T-R</td><td>drop out</td></tr><tr><td></td><td>BG04</td><td>T-R</td><td></td></tr><tr><td></td><td>BG04</td><td>R-T</td><td></td></tr><tr><td></td><td>BG04</td><td>R-T</td><td></td></tr><tr><td></td><td>BG04</td><td>T-R</td><td></td></tr><tr><td></td><td>BG04</td><td>T-R</td><td></td></tr></table> Total number of patients in site BG04 = 7	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment	(b) (6)		BG04	T-R	(b) (6)				BG04	T-R	drop out		BG04	T-R			BG04	R-T			BG04	R-T			BG04	T-R			BG04	T-R	
Related subjects																																														
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																								
(b) (6)		BG04	T-R	(b) (6)																																										
		BG04	T-R		drop out																																									
		BG04	T-R																																											
		BG04	R-T																																											
		BG04	R-T																																											
		BG04	T-R																																											
		BG04	T-R																																											
Clinical Site BG05 (Name, Address, Phone #, Fax #)	Center for Mental Health - Sofia district, 309 "Slivnitsa" Blvd., Sofia Bulgaria <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="6">(b) (6)</td><td></td><td>BG05</td><td>T-R</td><td rowspan="6">(b) (6)</td><td></td><td></td></tr><tr><td></td><td>BG05</td><td>R-T/applied T-R</td><td>Wrong treatment sequence applied</td></tr><tr><td></td><td>BG05</td><td>R-T</td><td></td></tr><tr><td></td><td>BG05</td><td>R-T</td><td>drop out</td></tr><tr><td></td><td>BG05</td><td>T-R</td><td></td></tr><tr><td></td><td>BG05</td><td>T-R</td><td></td></tr></table> Total number of patients in site BG05 = 6	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment	(b) (6)		BG05	T-R	(b) (6)				BG05	R-T/applied T-R	Wrong treatment sequence applied		BG05	R-T			BG05	R-T	drop out		BG05	T-R			BG05	T-R					
Related subjects																																														
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																								
(b) (6)		BG05	T-R	(b) (6)																																										
		BG05	R-T/applied T-R		Wrong treatment sequence applied																																									
		BG05	R-T																																											
		BG05	R-T		drop out																																									
		BG05	T-R																																											
		BG05	T-R																																											
Clinical Site BG06 (Name, Address, Phone #, Fax #)	Center for Mental Health - Vratsa EOOD, 1 "Belasitsa" Str., 3000 Vratsa Bulgaria <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="6">(b) (6)</td><td></td><td>BG06</td><td>R-T</td><td rowspan="6">(b) (6)</td><td></td><td></td></tr><tr><td></td><td>BG06</td><td>T-R</td><td>drop out</td></tr><tr><td></td><td>BG06</td><td>R-T</td><td></td></tr><tr><td></td><td>BG06</td><td>T-R</td><td></td></tr><tr><td></td><td>BG06</td><td>R-T</td><td>drop out</td></tr><tr><td></td><td>BG06</td><td>T-R</td><td></td></tr></table> Total number of patients in site BG06 = 6	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment	(b) (6)		BG06	R-T	(b) (6)				BG06	T-R	drop out		BG06	R-T			BG06	T-R			BG06	R-T	drop out		BG06	T-R					
Related subjects																																														
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																								
(b) (6)		BG06	R-T	(b) (6)																																										
		BG06	T-R		drop out																																									
		BG06	R-T																																											
		BG06	T-R																																											
		BG06	R-T		drop out																																									
		BG06	T-R																																											

Clinical Site BG07 (Name, Address, Phone #, Fax #)	“State Psychiatric Hospital – Lovech”, 1 “Aleksandar Batenberg” str., Lovech 5500 Bulgaria																																															
<table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="6"></td><td rowspan="6">(b) (6)</td><td>BG07</td><td>R-T</td><td rowspan="6"></td><td rowspan="6">(b) (6)</td><td>drop out</td></tr><tr><td>BG07</td><td>T-R</td><td></td></tr><tr><td>BG07</td><td>R-T</td><td></td></tr><tr><td>BG07</td><td>T-R</td><td>drop out</td></tr><tr><td>BG07</td><td>R-T</td><td></td></tr><tr><td>BG07</td><td>T-R</td><td></td></tr></table> Total number of patients in site BG07 = 6							Related subjects							Subject Randomization	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	BG07	R-T		(b) (6)	drop out	BG07	T-R		BG07	R-T		BG07	T-R	drop out	BG07	R-T		BG07	T-R							
Related subjects																																																
Subject Randomization	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																										
	(b) (6)	BG07	R-T		(b) (6)	drop out																																										
		BG07	T-R																																													
		BG07	R-T																																													
		BG07	T-R			drop out																																										
		BG07	R-T																																													
		BG07	T-R																																													
Clinical Site BG08 (Name, Address, Phone #, Fax #)	State Psychiatric Hospital "Sveti Ivan Rilski", 140 Hristo Botev Str., Novi Iskar 1282, Bulgaria																																															
<table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="8"></td><td rowspan="8">(b) (6)</td><td>BG08</td><td>T-R</td><td rowspan="8"></td><td rowspan="8">(b) (6)</td><td></td></tr><tr><td>BG08</td><td>R-T</td><td></td></tr><tr><td>BG08</td><td>T-R</td><td>drop out</td></tr><tr><td>BG08</td><td>T-R</td><td></td></tr><tr><td>BG08</td><td>R-T</td><td></td></tr><tr><td>BG08</td><td>R-T</td><td>drop out</td></tr><tr><td>BG08</td><td>T-R</td><td></td></tr><tr><td>BG08</td><td>R-T</td><td></td></tr></table> Total number of patients in site BG08 = 8							Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	BG08	T-R		(b) (6)		BG08	R-T		BG08	T-R	drop out	BG08	T-R		BG08	R-T		BG08	R-T	drop out	BG08	T-R		BG08	R-T	
Related subjects																																																
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																										
	(b) (6)	BG08	T-R		(b) (6)																																											
		BG08	R-T																																													
		BG08	T-R			drop out																																										
		BG08	T-R																																													
		BG08	R-T																																													
		BG08	R-T			drop out																																										
		BG08	T-R																																													
		BG08	R-T																																													
Clinical Site BG09 (Name, Address, Phone #, Fax #)	Center for Mental Health - Plovdiv EOOD, 68 Peshetrsko shosse Blvd., 4002 Plovdiv, Bulgaria																																															
<table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="7"></td><td rowspan="7">(b) (6)</td><td>BG09</td><td>T-R</td><td rowspan="7"></td><td rowspan="7">(b) (6)</td><td></td></tr><tr><td>BG09</td><td>T-R</td><td>drop out</td></tr><tr><td>BG09</td><td>R-T</td><td></td></tr><tr><td>BG09</td><td>R-T</td><td></td></tr><tr><td>BG09</td><td>T-R</td><td></td></tr><tr><td>BG09</td><td>R-T</td><td>drop out</td></tr><tr><td>BG09</td><td>T-R</td><td></td></tr></table> Total number of patients in site BG01 = 7							Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	BG09	T-R		(b) (6)		BG09	T-R	drop out	BG09	R-T		BG09	R-T		BG09	T-R		BG09	R-T	drop out	BG09	T-R				
Related subjects																																																
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																										
	(b) (6)	BG09	T-R		(b) (6)																																											
		BG09	T-R			drop out																																										
		BG09	R-T																																													
		BG09	R-T																																													
		BG09	T-R																																													
		BG09	R-T			drop out																																										
		BG09	T-R																																													
Clinical Site BG10 (Name, Address, Phone #, Fax #)	MHAT - Levski EOOD, 5 Nikola Vaptsarov, 5900 Levski, Bulgaria																																															
<table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="2"></td><td rowspan="2">(b) (6)</td><td>BG10</td><td>R-T</td><td rowspan="2"></td><td rowspan="2">(b) (6)</td><td></td></tr><tr><td>BG10</td><td>T-R</td><td></td></tr></table>							Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	BG10	R-T		(b) (6)		BG10	T-R																			
Related subjects																																																
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																										
	(b) (6)	BG10	R-T		(b) (6)																																											
		BG10	T-R																																													

	<table><tr><td rowspan="4">(b) (6)</td><td>BG10</td><td>R-T</td><td rowspan="4">(b) (6)</td><td></td></tr><tr><td>BG10</td><td>T-R</td><td></td></tr><tr><td>BG10</td><td>T-R</td><td>drop out</td></tr><tr><td>BG10</td><td>R-T</td><td></td></tr></table> Total number of patients in site BG10 = 6	(b) (6)	BG10	R-T	(b) (6)		BG10	T-R		BG10	T-R	drop out	BG10	R-T													
(b) (6)	BG10		R-T	(b) (6)																							
	BG10		T-R																								
	BG10		T-R			drop out																					
	BG10	R-T																									
Clinical Site PL01 (Name, Address, Phone #, Fax #)	Instytut Psychiatrii i Neurologii, ul. Jana III Sobieskiego 9, 02-957 Warszawa, Poland No Patients involved																										
Clinical Site PL02 (Name, Address, Phone #, Fax #)	Zespół Poradni Zdrowia Psychicznego, ul. A. Mickiewicza 24/26, 87-100 Toruń Poland No Patients involved																										
Clinical Site PL03 (Name, Address, Phone #, Fax #)	Uniwersyteckie Centrum Kliniczne. Klinika Chorób Psychiczych i Zaburzeń Nerwicznych, ul. Dębinki 7 80-952 Gdańsk, Poland <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="2">(b) (6)</td><td></td><td>PL03</td><td>T-R</td><td rowspan="2">(b) (6)</td><td></td><td>Exclude from statistical analysis*</td></tr><tr><td></td><td>PL03</td><td>R-T</td><td></td><td>drop out</td></tr></table> Total number of patients in site PL03 = 2	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment	(b) (6)		PL03	T-R	(b) (6)		Exclude from statistical analysis*		PL03	R-T		drop out
Related subjects																											
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																					
(b) (6)		PL03	T-R	(b) (6)		Exclude from statistical analysis*																					
		PL03	R-T			drop out																					
Clinical Site PL04 (Name, Address, Phone #, Fax #)	Centrum Badań Klinicznych, Jagiellońskie Centrum Innowacji, Life Science Parkul. Bobrzyńskiego 14 30 - 348 Kraków, Poland No Patients involved																										
Clinical Site PL05 (Name, Address, Phone #, Fax #)	Milickie Centrum Medyczne Sp. z o.o., Wielospecjalistyczny Szpital w Miliczuul. Grzybowa 1, 56-300 Milicz, Poland No Patients involved																										
Clinical Site PL06 (Name, Address, Phone #, Fax #)	Rodzinne Centrum Medyczne LUBIMED, ul. Woronieckiego 1120-492 Lublin, Poland No Patients involved																										
Clinical Site PL07 (Name, Address, Phone #, Fax #)	Szpital Specjalistyczny im. Dr. J. Babińskiego, SP ZOZ, ul. Babińskiego 39, 30-393 Kraków, Poland No Patients involved																										
Clinical Site PL08 (Name, Address, Phone #, Fax #)	Podlaskie Centrum Psychogeriatry, ul. Swobodna 38/9, 15-756 Białystok, Poland No Patients involved																										
Clinical Site MD01 (Name, Address, Phone #, Fax #)	PMSI Clinical Psychiatric Hospital, Department no. 4, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>	Related subjects																									
Related subjects																											

	<table><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="10"></td><td rowspan="10">(b) (6)</td><td>MD01</td><td>T-R</td><td rowspan="10"></td><td rowspan="10">(b) (6)</td><td></td></tr><tr><td>MD01</td><td>R-T</td><td>drop out</td></tr><tr><td>MD01</td><td>R-T</td><td></td></tr><tr><td>MD01</td><td>T-R</td><td></td></tr><tr><td>MD01</td><td>R-T</td><td></td></tr><tr><td>MD01</td><td>T-R</td><td>Exclude from statistical analysis*</td></tr><tr><td>MD01</td><td>T-R</td><td>Exclude from statistical analysis*</td></tr><tr><td>MD01</td><td>T-R</td><td>drop out</td></tr><tr><td>MD01</td><td>R-T</td><td></td></tr><tr><td>MD01</td><td>R-T</td><td></td></tr></table> Total number of patients in site MD01 = 10	Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	MD01	T-R		(b) (6)		MD01	R-T	drop out	MD01	R-T		MD01	T-R		MD01	R-T		MD01	T-R	Exclude from statistical analysis*	MD01	T-R	Exclude from statistical analysis*	MD01	T-R	drop out	MD01	R-T		MD01	R-T	
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																				
	(b) (6)	MD01	T-R		(b) (6)																																					
		MD01	R-T			drop out																																				
		MD01	R-T																																							
		MD01	T-R																																							
		MD01	R-T																																							
		MD01	T-R			Exclude from statistical analysis*																																				
		MD01	T-R			Exclude from statistical analysis*																																				
		MD01	T-R			drop out																																				
		MD01	R-T																																							
		MD01	R-T																																							
Clinical Site MD02 (Name, Address, Phone #, Fax #)	PMSI Clinical Psychiatric Hospital, Department no. 3, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="4"></td><td rowspan="4">(b) (6)</td><td>MD02</td><td>R-T</td><td rowspan="4"></td><td rowspan="4">(b) (6)</td><td></td></tr><tr><td>MD02</td><td>T-R</td><td></td></tr><tr><td>MD02</td><td>R-T</td><td>drop out</td></tr><tr><td>MD02</td><td>R-T</td><td></td></tr></table> Total number of patients in site MD02 = 4	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	MD02	R-T		(b) (6)		MD02	T-R		MD02	R-T	drop out	MD02	R-T												
Related subjects																																										
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																				
	(b) (6)	MD02	R-T		(b) (6)																																					
		MD02	T-R																																							
		MD02	R-T			drop out																																				
		MD02	R-T																																							
Clinical Site MD03 (Name, Address, Phone #, Fax #)	Department of Psychiatry, Narcology and Medical Psychology, State University of Medicine and Pharmacy “Nicolae Testemitanu”, located in the PMSI Clinical Psychiatric Hospital, 3, Costiujeni str., Chisinau, MD2011, Republic of Moldova <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td rowspan="3"></td><td rowspan="3">(b) (6)</td><td>MD03</td><td>T-R</td><td rowspan="3"></td><td rowspan="3">(b) (6)</td><td>drop out</td></tr><tr><td>MD03</td><td>R-T</td><td>drop out</td></tr><tr><td>MD03</td><td>T-R</td><td></td></tr></table> Total number of patients in site MD03 = 3	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	MD03	T-R		(b) (6)	drop out	MD03	R-T	drop out	MD03	T-R															
Related subjects																																										
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																				
	(b) (6)	MD03	T-R		(b) (6)	drop out																																				
		MD03	R-T			drop out																																				
		MD03	T-R																																							
Clinical Site MD04 (Name, Address, Phone #, Fax #)	PMSI Psychiatry Hospital Balti, 114, Gagarin str., Balti, MD3110, Republic of Moldova <table><tr><th colspan="6">Related subjects</th><th></th></tr><tr><th>Subject Randomization number</th><th>Subject ID</th><th>Site</th><th>Treatment</th><th>Date (Period-1)</th><th>Date (Period-2)</th><th>Comment</th></tr><tr><td></td><td>(b) (6)</td><td>MD04</td><td>R-T</td><td></td><td>(b) (6)</td><td></td></tr></table>	Related subjects							Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment		(b) (6)	MD04	R-T		(b) (6)																					
Related subjects																																										
Subject Randomization number	Subject ID	Site	Treatment	Date (Period-1)	Date (Period-2)	Comment																																				
	(b) (6)	MD04	R-T		(b) (6)																																					

	(b) (6) <table border="1"> <tr><td>MD04</td><td>R-T</td></tr> <tr><td>MD04</td><td>T-R</td></tr> <tr><td>MD04</td><td>R-T</td></tr> <tr><td>MD04</td><td>T-R</td></tr> </table> (b) (6) Total number of patients in site MD04 = 5	MD04	R-T	MD04	T-R	MD04	R-T	MD04	T-R
MD04	R-T								
MD04	T-R								
MD04	R-T								
MD04	T-R								
Clinical Site MD05 (Name, Address, Phone #, Fax #)	HOSPITAL OF PSYCHIATRY AND FTIZIOPNEUMOLOGY, 2 Dubasari str., Orhei, MD 3500, Republic of Moldova No Patients involved								

4.4.2 E-mail Communication and SAS Analysis

OSIS -PM Email communication for inspection- ANDA 214068.docx	 OSIS -Email communication for i
CC 02407 (dated 05/15/2019)	 C02407 Review Q1Q2.docx
The statistical analysis for this ANDA was done by Dr. Patel (Results on page 94 Of SAS output.	 A214068-SAS output 77 sub.pdf  214068-SteadyState 77sub.sas  A214068-data 77 subjects.xlsx  ANDA 214068 SAS Analysis from Patel.c
Email communication with Dr. Patel - Request for analysis of plasma and PK data - ANDA 214068.docx	 Email communication with
Email communication regarding in vivo and in vitro data.docx	 Email communication rega

Analysis using applicant submitted dataset (after 4th injection)

SUMMARY OF PHARMACOKINETIC PARAMETERS³⁴

Obs	trt	_TYPE_	_FREQ_	_STAT_	AUCT	cmax	cmin	cavg	FLUC1	tmax	LAUCT	LCMIN	LCMAX	LCAVG	LFLUC1	LTMAX
1	1	0	77	N	77.00	77.00	77.00	77.00	77.00	77.00	77.00	61.00	77.00	77.00	77.00	76.00
2	1	0	77	MIN	421.67	3.00	0.00	17.57	0.04	0.00	6.04	0.00	1.10	2.87	-3.30	1.39
3	1	0	77	MAX	16724.85	100.78	7.00	696.87	0.33	336.00	9.72	1.95	4.61	6.55	-1.10	5.82
4	1	0	77	MEAN	1932.65	11.51	1.46	80.53	0.12	94.44	7.28	0.45	2.13	4.10	-2.17	4.07
5	1	0	77	STD	2123.37	13.38	1.31	88.47	0.05	86.91	0.69	0.54	0.71	0.69	0.39	1.12

³⁴ The statistical analysis for this ANDA was conducted by Dev Patel, Pharm. D., the OB/DBIII consultant for statistical analysis (see the attachment section for email communication and SAS results).

6	2	0	77	N	76.00	77.00	77.00	76.00	76.00	77.00	76.00	63.00	77.00	76.00	76.00	76.00
7	2	0	77	MIN	451.81	2.62	0.00	18.83	0.04	0.00	6.11	-0.29	0.96	2.94	-3.34	1.39
8	2	0	77	MAX	20025.08	83.92	12.00	834.38	0.47	336.00	9.90	2.48	4.43	6.73	-0.74	5.82
9	2	0	77	MEAN	2319.27	12.24	1.89	96.64	0.12	105.14	7.41	0.57	2.22	4.23	-2.22	4.10
10	2	0	77	STD	2721.59	12.04	2.12	113.40	0.06	104.65	0.75	0.68	0.70	0.75	0.38	1.21
-	-	-	-	T/R	0.83	0.94	0.77	0.83	1.00	0.90	0.98	0.79	0.96	0.97	0.98	0.99

Units: AUC(Tau) [ng*h/mL], Cmax(SS) [ng/mL], Tmax (hr)

Risperidone Long-Acting Injection Dose (25 mg Risperidone), n=77 Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasting Bioequivalence Study (Study No. CAC15003)						
Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC(Tau) [ng*h/mL]	1450.79	77	1658.68	77	93.50%	81.39 - 93.99%
Cmax(SS) [ng/mL]	8.41	77	9.25	77	90.92%	81.91- 100.96%

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:	214068
APPLICANT:	Teva Pharmaceuticals USA Inc.
DRUG PRODUCT:	Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial

The Division of Bioequivalence III (DBIII) has completed its review and has identified the following deficiencies:

Deficiencies Related to Pre-study Method Validation:

1. Based on your submitted bioequivalence (BE) Summary Table 10 Study Information (Module 2.7) for the pivotal BE study No. CAC15003, the total sample storage duration is 625 days. Per your bioanalytical report, study samples were initially stored at clinical sites and then transferred to the bioanalytical sites, and storage duration was up to 414 days for sample aliquote-1 and up to 476 days for sample aliquote-2 at clinical sites (i.e., Subject (b) (6)). However, you only provided separate long-term storage stability data for 358 days at -70 °C and a total of 425 days at 2 different temperatures (417 days at -30 °C and 8 days at 5 °C or 351 days at -30 °C and then 74 days at -70 °C). It is also noted that during shipment of sample aliquote-2, the temperature was up to 22.2 °C for some subject samples. Please clarify the sample storage duration and temperature at clinical site and analytical site, as well as sample shipment time and temperature for each subject, and provide the additional long-term storage stability data to cover the study sample storage duration and condition.
2. Per your clinical study report (No. CAC15003), the bioanalytical lab was moved to a new location between 04/26 – 05/20/2019 during the conduct of study. Based on your bioanalytical report (Protocol #CAC15003; issued date: 11 December 2019), the study sample analysis was conducted initially at (b) (4)

_____. Please clarify if additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site and provide the required method validation information per FDA guidance for Bioanalytical Method Validation (May 2018).

Deficiencies Related to In Vivo Pivotal Bioequivalence Study (No. CAC15003):

3. Per your clinical study report, it is unclear about the length of confinement for patients at the clinical sites during the course of study. Please provide this information.
4. Your pivotal BE study was conducted at 14 clinical sites. You did not include group as a variable in the submitted dataset. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose Number, Time (hours), Concentration. Please also resubmit the pharmacokinetic (PK) dataset including

the following variable: Subject, Period, Sequence, Group, Treatment, Dose Number, and all relevant PK parameters (Cmax, AUCtau, Cavg, Cmin, Fluctuation, and Tmax).

5. Per product specific guidance for Risperidone Long-Acting Injectable, an intensive sampling is recommended for the 3rd dosing interval in period 2. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose Number, Time (hours), Concentration for the 3rd dosing interval in period 2. Please also provide PK parameters such as Cmin and Cmax for this dosing interval.
6. Per the FDA guidance for Industry: Bioequivalence studies with pharmacokinetic endpoint for drugs submitted under an ANDA (Issued December 2013), it is recommended that for steady-state study, applicant carry out appropriate dosage administration and sampling to document the attainment of steady-state. You collected multiple samples after 1st, 2nd, and 3rd injections. Please provide supporting document/data to demonstrate that individual patients have reached steady-state prior to conducting the BE analysis. Please also submit the dataset and SAS program for your analysis.

Deficiencies Related to In Vitro Drug Release Test:

7. For the in vitro release test, you did not submit the data for T50% and the 90% confidence interval of the test/reference ratio of T50%, as recommended in the product specific guidance for Risperidone Long-Acting Injectable. Please provide the requested data and also submit dataset and SAS program for your analysis. Additionally, please submit all data for the in vitro release test in Excel format.
8. It is noticed that your dissolution method validation (Report No. CC-2019-30-0190; issued on 11/28//2019 and report addendum No. CC-2019-10-1170; issued on 12/10/2019) was performed after the comparative dissolution testing (Report No: CC-2019-10-1170; issued 11/27/2019). Please provide explanation for this discrepancy.

Sincerely yours,

{ See appended electronic signature page }

April C. Braddy, Ph.D., RAC
Acting Director, Division of Bioequivalence III
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

ANDA: 214068

Completed Assignment for 214068 ID: 42087

Reviewer: Wahba, Zakaria

Date

Completed:

Verifier: ,

Date Verified:

Division: Division of Bioequivalence

Description: Risperidone Long-Acting Injection, 12.5 mg/vial, 25 mg/vial,
37.5 mg/vial, and 50 mg/vial

Items:

ID	Letter Date	Productivity Category	Sub Category	Score	Subtotal
42087	12/16/2019	BIO	ANDA Original [1]	1	1
42087	12/16/2019	Complexity	First Generic Drug Product Review [1]	1	1
42087	12/16/2019	Parallel	Fasting Study [1]	1	1
42087	12/16/2019	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation (as defined in Guidance) [0.25]	0.25	0.25
42087	12/16/2019	Parallel	Waiver Injectable (Per application) [1]	1	1
				Total:	4.25

CDER/OPQ/ONDP Biopharmaceutics Consult Review Memo

Consult Reference No.:	227231
Requesting Office/Division:	Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs (CDER/OGD/ORS/DTP)
Contact:	Yan Wang, Ph.D.
Application No.:	Pre-ANDA Meeting Package
Applicant:	TEVA Pharmaceuticals, Inc.
Product Name:	TEVA Risperidone Long-Acting Injection, 12.5 mg, 25 mg, 37.5 mg, and 50 mg per vial
Product Description:	Risperidone microspheres, packaged with a pre-filled syringe containing 2 mL of diluent, 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).
Proposed Indication:	For treatment of schizophrenia, and as monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of bipolar I disorder
Letter Date:	29 December 2015
FDA Stamp Date:	30 December 2015
Consult Request Date:	10 March 2016
Consult Request:	Comment on the DTP Response to TEVA's Question regarding <i>in vitro</i> drug release testing
Desired Completion Date	08 April 2016
Assigned Date	10 March 2016
Review Date:	31 March 2016
Primary Reviewer:	Gerlie Gieser, Ph.D.
Supervisory Concurrence:	Angelica Dorantes, Ph.D., Biopharmaceutics Branch Chief (Acting)

Summary of Consult Request

The Division of Therapeutic Performance at the Office of Research and Standards (ORS/DTP) within the Office of Generic Products is seeking the Division of Biopharmaceutics' concurrence on DTP's proposed response to TEVA Pharmaceutical's question regarding the *in vitro* drug release test of risperidone microspheres.

Background Information¹

Executive Summary of the Pre-ANDA Meeting Request

On December 30, 2015, the Office of Generic Drugs (OGD) received a meeting request package from Teva B.V. to discuss a potential ANDA submission for risperidone long-acting injection referencing RISPERDAL® CONSTA® from Janssen Pharmaceuticals, Inc. (NDA 21346, approved on 10-29-2003). TEVA states that the FDA has already confirmed that the composition of TEVA's product including both the microspheres and the diluent is qualitatively (Q1) and quantitatively (Q2) identical to the RLD in the response to control #1524802 on 11/08/2015. In

¹ *Verbatim* from the Consult Request

the current meeting request, TEVA proposes several CMC and clinical pharmacology development programs designed to demonstrate bioequivalence (BE) of its test product. The purpose of this meeting request is to obtain the FDA's agreement on the proposed programs.

The Division of Therapeutic Performance at OGD has granted the pre-ANDA meeting request and plans to meet with the firm in April/May, 2016.

Reference Product

The RLD, RISPERDAL® CONSTA® from Janssen Pharmaceuticals, Inc., is provided as a dose pack consisting of risperidone microspheres powder in a vial, a solvent in prefilled syringe, a West-Medimop Vial Adapter®, and two Terumo SurGuard®3 Needles (a 21 G UTW 1-inch needle with needle protection device for deltoid administration and a 20 G TW 2-inch needle with needle protection device for gluteal administration). Both the drug product and the diluent are manufactured by aseptic processing.

The microspheres are white to off-white powders, available in four strengths: 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial, which are identical to each other with respect to composition and manufacturing process (from the same bulk). At this time, the second lowest strength, 25 mg/vial, is listed as the Reference Listed Drug (RLD) strength. The formulation composition of risperidone microspheres is shown below. The active ingredient, risperidone, is a well characterized and commonly prescribed atypical antipsychotic available in oral and parenteral formulations.

Formulation composition of risperidone microspheres

Components	Function in Formulation
Risperidone Drug Substance	active ingredient
Polymer: 75:25 DL IN1 [poly-(d,l-lactide-co-glycolide)]	(b) (4) (u) (4)

Risperidone is encapsulated in 75:25 poly(lactide-co-glycolide) (PLG) at a concentration of 381 mg risperidone per gram of microspheres. PLG is (b) (4)

The diluent for preparing a suspension of risperidone microspheres for intramuscular injection 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 vial with diluent prior to injection.

With respect to clinical studies, according to the clinical review of Risperdal® Consta® for the NDA application, the pharmacokinetics of risperidone microspheres after single or repeated injection were dose-proportional from (b) (4) mg. The pharmacokinetics of the intermediate doses (b) (4) were evaluated after single injection and found to be dose-proportional to the 50 mg reference, based on dose-normalized C_{max} and AUC. Please note that the (b) (4) strengths were not marketed as no obvious advantages were observed compared to the 50 mg strength.

Bioequivalence Guidance

To date, OGD has posted product specific recommendations for this product to guide bioequivalence study design. The initial draft BE guidance for risperidone intramuscular injection was posted in February 2010², and the recommendations only included a single-dose in vivo study. In August 2013, a revised draft BE guidance which includes a steady-state in vivo study (instead of a single-dose study) and an in vitro drug release study³ was posted partly in response to a Citizen Petition (Docket No. FDA-2011-P-0086) submitted to FDA on February 11, 2011. In May 2015, an update of the in vitro dissolution medium was provided in the revised draft guidance⁴.

Below is the current recommendation posted in the draft BE guidance for the in vitro drug release test:

1. Type of study: In vitro drug release
Strength: 25 mg/vial

Medium: Dissolution medium (pH 7.4), prepared as indicated below
Volume: 400 mL (200 mL for each temperature)
Apparatus: Cylinder bottle
Temperature: 37°C and 45°C (water bath)
Sampling times: Day 1 and Day 21 for 37°C
Multiple time points from Days 0 to 8 for 45°C. Two sampling time points, that bracket $T_{50\%}$ (which is defined as the time of 50% drug release), are to be linearly interpolated to determine $T_{50\%}$.

Parameters to measure: Cumulative drug release at Days 1 and 21 at 37°C, cumulative drug release at Day 8 at 45°C, and $T_{50\%}$ at 45°C

Bioequivalence based on (90% CI): $T_{50\%}$. The 90% confidence interval (CI) of the test/reference ratio of $T_{50\%}$ should be within 80-125%.

These data are to be submitted in addition to the method specified in the Dissolution Methods Database (see below), which is to be used for stability and quality control testing.

Preparation of dissolution medium (makes 20 L):

- Add 40 g sodium azide into 760 g deionized water
- Add 18.76 kg deionized water into a 20 L container
- Add 200 g 1M HEPES buffer solution into the container
- Add 116 g sodium chloride to 1 kg deionized water
- Add sodium chloride solution into the container
- Add 80 mL sodium azide solution into the container
- Add 4 mL Tween 20 into the container

[The osmolality of the release medium should be 200 ± 20 mOsm.

As per 21 CFR § 314.94, the proposed parenteral drug product should be qualitatively (Q1) and quantitatively (Q2) the same as the reference product for all strengths (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial).

Waiver request of in vivo testing: 12.5 mg/vial, 37.5 mg/vial, and 50 mg/vial based on (i) acceptable in vitro and in vivo BE studies on the 25 mg/vial strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro drug release testing of all strengths.

Dissolution test method and sampling times: The dissolution information for this drug product can be found on the FDA-Recommended Dissolution Methods website available to the public at the following location: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).]

² Control #08-0114.

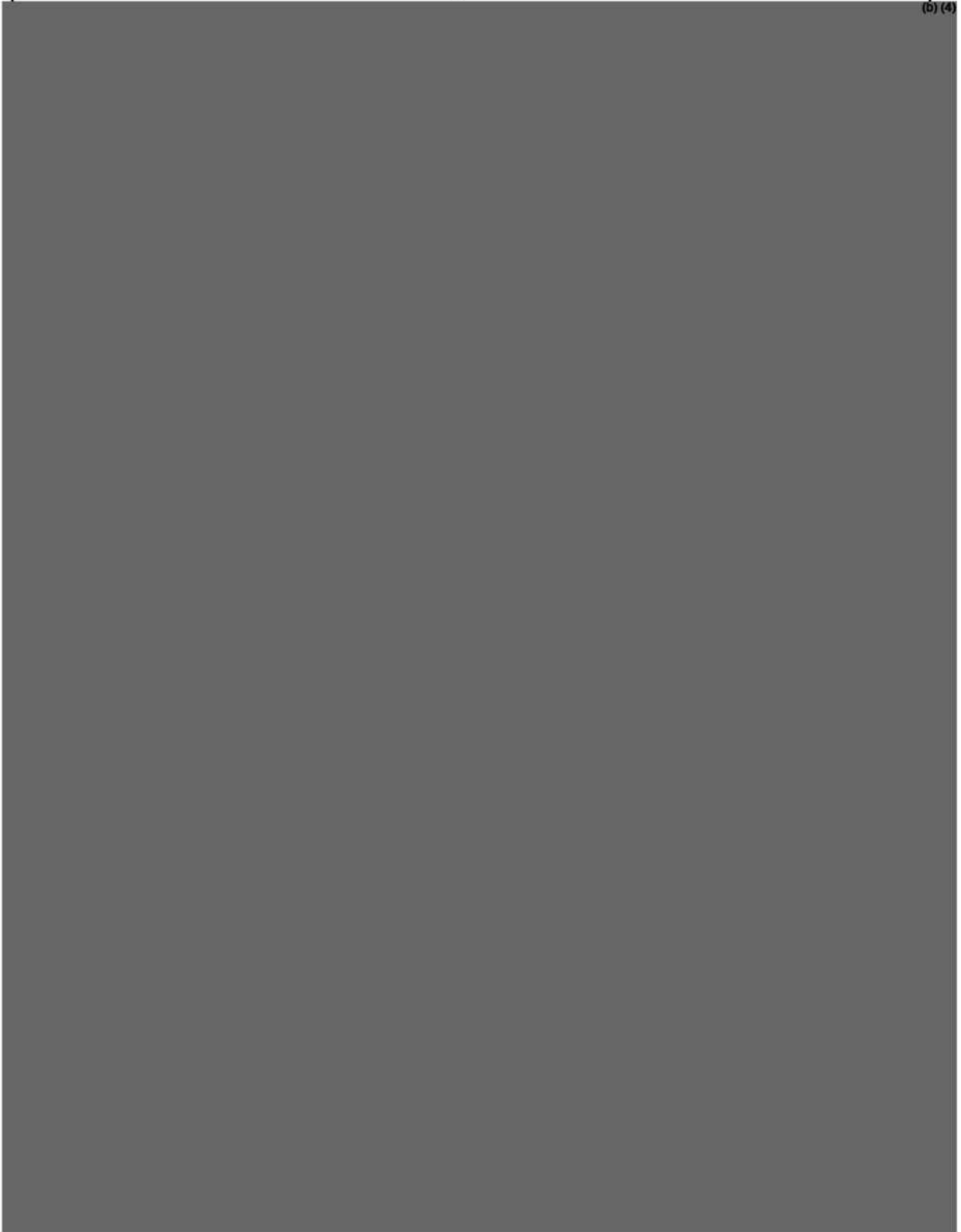
³ Control #13-0015.

⁴ Project #46773 in Panorama.

In the current meeting request, TEVA submitted one question with regard to the acceptance of the proposed in vitro drug release testing method.

Below are detailed information submitted by TEVA:

(b) (4)



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 208336

MICROBIOLOGY REVIEW(s)

CHAPTER VII: MICROBIOLOGY

[IQA ANDA Assessment Guide Reference](#)

Product Information	
ANDA Number	214068
Assessment Cycle Number	MR03
Drug Product Name / Strength	Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Route of Administration	Intramuscular Injection
Applicant Name	Teva Pharmaceuticals USA, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: view justification statements found at: [Justification Statements](#)

N/A
Other (Requires Division Director Approval) – Assessor writes-in justification here if “other” selected as theme.

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
0021	2/27/2023
0022	3/23/2023
0024	7/6/2023

Highlight Key Issues from Last Cycle and Their Resolution: A complete response letter (CRL) was issued on March 25, 2022 regarding deficiencies related to drug product, the DS manufacturing facility following Agency inspection, manufacturing process, labeling, and pharmacology/toxicology. Quality Microbiology was previously adequate.

Remarks: The 2/27/23 ANDA amendment is a response to the CRL dated 3/25/22 and references a post-CRL preliminary response dated 4/21/22 and an Agency email correspondence dated 7/8/22. A subsequent amendment to the CRL response was submitted on 3/23/23.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): Not applicable

Supporting Documents:

A214068MR01.docx (dated 5/21/2020; Overall inadequate, A214068MR02.docx (dated 12/23/2021; adequate) for original ANDA reviews.

Select Number of Approved Comparability Protocols: 0

Product Quality Microbiology Assessment

The proposed drug product, Risperidone (b) (4) Injection 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial, is provided as a dose pack, consisting of a vial containing the risperidone microspheres, a pre-filled syringe containing 2 mL of diluent, a 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). The product is (b) (4)

The ANDA was previously adequate for Quality Microbiology.

The 2/27/23 ANDA amendment is a response to the CRL dated 3/25/22. The amendment proposes a change in the (b) (4)

. There are no changes to the manufacturing process parameters or DP manufacturing facility.

12 Pages have been withheld in full as b4 immediately following this page

R REGIONAL INFORMATION

- **Executed Batch Records**

(b) (4)

Assessment: Adequate

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable

Primary Microbiology Assessor Name and Date: Dacie R. Bridge, July 7, 2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Yan Zheng, Ph.D., July 7, 2023



Dacie
Bridge

Digitally signed by Dacie Bridge
Date: 7/11/2023 07:45:48AM
GUID: 5a994d0c0051111bec366cf8880c9f85



Yan
Zheng

Digitally signed by Yan Zheng
Date: 7/11/2023 07:42:52AM
GUID: 58ca9ce301e697996a209b08cf0d70b6

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	Indicated for schizophrenia and bipolar disorder
ANDA Number	214068
Assessment Cycle Number	02
Drug Product Name / Strength	Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Route of Administration	Intramuscular deltoid or gluteal injection
Applicant Name	Teva Pharmaceuticals USA, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: Adequate

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☒ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: view justification statements found at: [Justification Statements](#)

N/A
Other (Requires Division Director Approval) – Assessor writes-in justification here if “other” selected as theme.

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0016	05/27/2021
Seq 0018	12/07/2021

Highlight Key Issues from Last Cycle and Their Resolution: This Amendment was submitted to the FDA as a response to a Complete Response letter that was dated

October 14, 2020. The submission also made reference to a post-complete response letter (CRL) teleconference between the FDA and Teva held on Nov 17, 2020 that involved issues surrounding the disciplines of Drug Product, Process, and Biopharmaceutics. Lastly, Teva made reference an email correspondence dated Jan 6, 2021 for clarification on Comment # 16 in the CRL which was issued by the Drug Product reviewer.

Remarks: The complete response letter contains 8 CRs issued by Microbiology. The information is reviewed below.

Concise Description of Outstanding Issues: None

Supporting Documents:

- Microbiology review A214068MR01.docx, dated 8/7/2020 (Inadequate – Minor).

Select Number of Approved Comparability Protocols: 0

Risperidone (b) (4) Injection (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial) is provided as a dose pack consisting of a vial containing the risperidone microspheres, pre-filled syringe containing 2 ml of diluent, vial adapter, and two needles for intramuscular injection (21 G UTW 1 inch needle with needle protection device for deltoid administration and 20 G TW 2-inch needle with needle protection device for gluteal administration). The drug product is (b) (4)

(b) (4)

P.3 Manufacture

(b) (4)

Reviewer's Assessment: *Adequate*

The firm provided sufficient CR responses (b) (4) for the proposed drug product.

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Jennifer Sykora, Ph.D. on 12/23/2021

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yan Zheng, Ph.D. on 12/23/2021



Jennifer
Sykora

Digitally signed by Jennifer Sykora

Date: 12/28/2021 07:24:57AM

GUID: 58012847014f3f7e82471ff535bb95cb



Yan
Zheng

Digitally signed by Yan Zheng

Date: 12/23/2021 11:37:04AM

GUID: 58ca9ce301e697996a209b08cf0d70b6

CHAPTER VII: MICROBIOLOGY

[IQA ANDA Assessment Guide Reference](#)

Product Information	Indicated for schizophrenia and bipolar disorder
ANDA Number	214068
Assessment Cycle Number	MR01
Drug Product Name/Strength	Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, 50 mg/vial
Route of Administration	Intramuscular deltoid or gluteal injection
Applicant Name	Teva Pharmaceuticals USA, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: Inadequate - Minor

Theme:

☐ N/A	☐ Depyrogenation Validation Data
☒ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: view justification statements found at: [Justification Statements](#)

N/A
Other (Requires Division Director Approval) – Assessor writes-in justification here if “other” selected as theme.

Assessment Summary: The drug product is (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

[Redacted text block]

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
eCTD sequence #0001	12/16/2019
eCTD sequence #0002	02/03/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: Risperidone Long Acting Injection (12.5 mg/vial, 25 mg/vial, 37.5 mg/vial, and 50 mg/vial) is provided as a dose pack consisting of a vial containing the risperidone microspheres, pre-filled syringe containing 2 ml of diluent, vial adapter, and two needles for intramuscular injection (21 G UTW 1 inch needle with needle protection device for deltoid administration and 20 G TW 2 inch needle with needle protection device for gluteal administration).

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): See "Microbiology List of Deficiencies"

Supporting Documents:

- Microbiology reviews A210317MR01.docx, dated 08/08/2018 (inadequate) and A210317MR02.docx, dated 01/17/2019 (adequate)

Microspheres Powder

- [Redacted text block]

(b) (4)

(b) (4)

Diluent

(b) (4)

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE – N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Microspheres Powder

Description of drug product – A sterile, white to off-white, free-flowing powder, consisting of the API micro-encapsulated in 75:25 polylactide-co-glycolide at a concentration of 381 mg risperidone per g of microspheres, supplied as (b) (4)

(b) (4)

Drug product composition –

Ingredient	Quality standards	Function	mg/unit ²			
			12.5 mg/vial	25 mg/vial	37.5 mg/vial	50 mg/vial
Risperidone	USP	API	(b) (4)			
75:25 Polylactide co-glycolide (Resomer)	Non-compendial					
Total	-	-	43.0	81.0	120.0	156.0

(b) (4)

Description of container closure system –

67 Pages have been withheld in full as b4 immediately following this page



Jesse
Wells

Digitally signed by Jesse Wells
Date: 8/07/2020 02:43:17PM
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Renee
Marcsisin

Digitally signed by Renee Marcsisin
Date: 8/07/2020 02:43:49PM
GUID: 58a215b40087203411c81698f83c8632

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 214068

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Narendra Racharla
Director Regulatory Affairs, US Generics

Dear Narendra Racharla:

This is in reference to your amendment received on September 6, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is December 6, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the

appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe
Date: 10/11/2023 12:30:02PM
GUID: 54205223000198472e8a989db47b1636



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This is in reference to your amendment received on September 6, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is December 6, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

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by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe

Date: 9/11/2023 11:48:24AM

GUID: 54205223000198472e8a989db47b1636



ANDA 214068

**INFORMATION REQUEST
QUALITY**

Teva Pharmaceuticals USA, Inc.
400 Interpace Pkwy
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, Us Generics

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on February 27, 2023, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Long Acting Injection, 12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Manufacturing

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

We request a complete written response, no later than September 1, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request¹, the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY
MINOR**

If you do not submit a complete written response by September 6, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at suzan.ghodasara@fda.hhs.gov or (301) 796 - 7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

¹ Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.



Suzan
Ghudasara

Digitally signed by Suzan Ghudasara
Date: 9/01/2023 08:06:06AM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT
Priority
Minor

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This is in reference to your amendment received on July 6, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a minor amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this priority minor amendment is October 6, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

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appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe
Date: 7/28/2023 04:00:29PM
GUID: 54205223000198472e8a989db47b1636



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Narendra Racharla
Director, Regulatory Affairs, US Generics

Dear Narendra Racharla:

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This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is October 6, 2023. We also note that, consistent with the GDUFA III Commitment Letter, your information request/discipline review letter (IR/DRL) response extends the goal date for your ANDA.

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by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe

Date: 7/26/2023 06:24:13PM

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ANDA 214068

**INFORMATION REQUEST
QUALITY**

Teva Pharmaceuticals USA Inc
400 Interpace Pkwy
Morris Corporate Center III
Parisppany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Long Acting Injection, 12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and request the following additional information/clarification and/or have the following comments:

QUALITY

A. Drug Product

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

B. Microbiology

1. [REDACTED] (b) (4)
[REDACTED]
a. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
b. [REDACTED] (b) (4)
[REDACTED]

- c. [REDACTED] (b) (4)
- d. [REDACTED] (b) (4)
- e. [REDACTED] (b) (4)

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a complete written response, no later than June 19, 2023 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. If you are responding to a late cycle information request¹, the goal date may be extended based upon the major or minor deficiencies included upon receipt of the response. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY
MINOR**

If you do not submit a complete written response by June 2, 2023, the listed information requests may be incorporated in a discipline review letter or complete response letter.

As described in FDA's draft guidance for industry *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the

appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at suzan.ghodasara@fda.hhs.gov or (301) 796 - 7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

¹ Late cycle defined as IRs or DRLs issued after the mid-cycle of an original ANDA or less than 90 days from the goal date for any ANDA amendment.



Suzan
Ghodasara

Digitally signed by Suzan Ghodasara
Date: 5/19/2023 11:03:15AM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT
Priority
Major

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This is in reference to your amendment received on February 27, 2023, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2022 (GDUFA III). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is August 27, 2023. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is December 27, 2023.

GDUFA provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the reference listed drug (RLD) that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

As described in FDA's Draft Guidance for Industry, *Cover Letter Attachments for Controlled Correspondences and ANDA Submissions*, FDA recommends that you include the appropriate attachment(s) along with the cover letter for your submission to help FDA ensure that your submission is properly triaged and assigned to the appropriate assessors. This will also ensure that submissions are effectively managed by FDA and acted upon within the performance review goal dates set by the Generic Drug User Fee Amendments.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Uzoma
Nnebe

Digitally signed by Uzoma Nnebe

Date: 3/24/2023 02:06:00PM

GUID: 54205223000198472e8a989db47b1636



ANDA 214068

COMPLETE RESPONSE

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

We acknowledge receipt of the May 27, 2021, submission, which constituted a complete response to our October 14, 2020, action letter, and to any amendments thereafter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Product

The Pharmaceutical Quality deficiencies have been classified as MAJOR because there is need for safety assessment of extractables and leachables, inadequate assessment of extractable and leachables, or submission of that assessment in an unsolicited amendment as noted in Appendix A, Section A(2)(o) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). This information is required for establishing safety of the drug product. Upon receipt, in FDA's judgement, the review of this information will require substantial expenditure of FDA resources.

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

Facility Inspection

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions - Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

3. During a recent inspection of the [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] Satisfactory resolution of the observations is required before this ANDA may be approved. Please list communications submitted to, or held with, the Agency to facilitate resolution of the observed objectionable conditions, or deficiencies, noted at the facility.

Process

4. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
5. [REDACTED] (b) (4)
[REDACTED].
6. [REDACTED] (b) (4)
[REDACTED].
7. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

Pharmacology/Toxicology

8. [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]

We refer you to any additional recommendations from the Drug Product Quality discipline with respect to your leachables study. We provide the following recommendations to address the safety of leachables in your proposed drug product:

- a. Identify and fully characterize all leachable compounds [REDACTED] (b) (4) with a CAS # and/or structure.
- b. Address the irritation/sensitization potential and general toxicity of leachable compounds with [REDACTED] (b) (4). Consider the context of use of your drug product, which is a long-acting injection administered intramuscularly. If you group compounds together and/or use surrogate compounds for safety assessment, provide a rationale for grouping and for the choice of surrogates.
- c. Address the mutagenicity of all leachable compounds with [REDACTED] (b) (4), using approaches described in ICH M7(R1) guidance. Mutagenic compounds should be limited to not-more-than [REDACTED] (b) (4). Please provide complete, legible copies of references and published information used to justify the safety of your leachables.

The acceptability of your safety assessment will be a review issue upon submission.

LABELING

1. CARTON LABELING

- a. On the PDP, revise [REDACTED] (b) (4) to read "SINGLE-DOSE PACK CONTENTS:".
- b. Under SINGLE-DOSE PACK CONTENTS:, second bullet: Revise to read "One single-dose pre-filled syringe container 2 mL of diluent".

- c. Revise [REDACTED] (b) (4) " to read "Do not substitute components of the single-dose pack".
- d. On the back panel, below IMPORTANT RESOURCES, revise [REDACTED] (b) (4) to read "PLEASE SEE ACCOMPANYING FULL PRESCRIBING INFORMATION."
- e. Revise [REDACTED] (b) (4) " associated with the strength statement on all panels to read "Single-Dose Pack".
- f. On the back panel, last paragraph, first sentence: Revise [REDACTED] (b) (4) to read "Remove the single-dose pack from refrigerator...."

2. PRESCRIBING INFORMATION

HIGHLIGHTS/RECENT MAJOR CHANGES: Revise this section to be in line with the RLD.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book (OB), and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

DRUG SUBSTANCE/MICROBIOLOGY/BIOPHARMACEUTICS/BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the

U.S. Food & Drug Administration
Silver Spring, MD 20993
www.fda.gov

compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence (21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

OTHER

On February 10, 2011, Janssen Research & Development, LLC, a company of Johnson & Johnson, (Petitioner) submitted a citizen petition to FDA (Docket No. FDA-2011-P-0086) (Petition) asking FDA to adopt specific bioequivalence requirements with respect to ANDAs and certain NDAs that reference Risperdal Consta (risperidone) Long-Acting Injection (NDA 021346) as a reference listed drug (RLD). Petitioner submitted four supplements to the Petition on December 10, 2013, July 27, 2015, February 25, 2016, and October 31, 2016 (collectively, Supplements). The deficiency comments included in this communication do not represent a final decision by the Agency on the issues raised in the pending Petition and/or Supplements.

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION
MAJOR
COMPLETE RESPONSE AMENDMENT
DRUG PRODUCT/PROCESS/FACILITY INSPECTION/
PHARMACOLOGY/TOXICOLOGY/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the

application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Uzoma Nnebe, Regulatory Project Manager, Division of Project Management, at (240) 402 - 5828.

Sincerely yours,

{See appended electronic signature page}

For Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Vincent
Sansone

Digitally signed by Vincent Sansone

Date: 3/25/2022 12:24:37PM

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ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone suspension injection, 12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Microbiology

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
 - a. [REDACTED] (b) (4)
[REDACTED]
 - b. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

We request a prompt written response, no later than December 8, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at Suzan.Ghodasara@fda.hhs.gov or (301) 796 - 7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Suzan
Ghodasara

Digitally signed by Suzan Ghodasara
Date: 11/08/2021 11:33:49AM
GUID: 5a85f77e000ee9ee78ef5d8694ea04bb



ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054
Attention: Ameya Kohojkar
Associate Director, Regulatory Affairs, US Generics

Dear Sir or Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Injection Suspension, 12.5mg/vial, 25mg/vial, 37.5mg/vial, 50mg/vial.

We are reviewing the Quality section of your submission and have the following comments and information requests:

**A. Manufacturing
Facility**

1. An inspection of the [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>.

We request a prompt written response, no later than August 19, 2021 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your

response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Suzan Ghodasara, Regulatory Business Process Manager, at suzan.ghodasara@fda.hhs.gov or (301) 796 - 7164.

Sincerely,

{See appended electronic signature page}

Suzan Ghodasara
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Suzan
Ghudasara

Digitally signed by Suzan Ghudasara
Date: 8/13/2021 09:47:07AM
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ANDA 214068

COMPLETE RESPONSE

Teva Pharmaceuticals USA Inc.
400 Interpace Parkway
Morris Corporate Center III
Parisspany, NJ 07054
Attention: Ameya Kohojkar
Senior Manager, Regulatory Affairs, US Generics

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Substance

1. [REDACTED] (b) (4)
[REDACTED]

Drug Product

2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
3. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

2 Pages have been withheld in full as b4 immediately following this page

25. [REDACTED] (b) (4)

26. [REDACTED] (b) (4)

27. [REDACTED] (b) (4)

Process

Diluent

28. [REDACTED] (b) (4)

a. [REDACTED] (b) (4)

b. [REDACTED] (b) (4)

29. [REDACTED] (b) (4)

30. [REDACTED] (b) (4)

31. [REDACTED] (b) (4)

7 Pages have been withheld in full as b4 immediately following this page

61. [REDACTED] (b) (4)

62. [REDACTED] (b) (4)

Please also note that the actual protocols, acceptance criteria, study outcomes, and supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Facility Inspection

The Pharmaceutical Quality deficiencies have been classified as MAJOR because one or more facilities were found inadequate at the time of action due to inspectional deficiencies as noted in Appendix A, Section A(6)(a) of the Guidance for Industry, ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (July 2018). Note that after the deficiencies have been purportedly resolved, FDA must assess the resolution of the cited deficiencies during the next review cycle. This assessment, upon receipt of an amendment responding to this deficiency, in FDA's judgement, will require substantial expenditure of FDA resources.

63. During a recent inspection of the [REDACTED] (b) (4)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response.

64. An inspection of the [REDACTED] (b) (4)

However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public

health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>

Biopharmaceutics

65. Provide the aqueous solubility data for the drug substance, risperidone, in your drug product over the physiological pH range [REDACTED] (b) (4) to support your claim regarding the solubility.

66. We acknowledge that you have adopted the dissolution method in the product specific guidance (PSG) for risperidone intramuscular injection for your proposed drug product. [REDACTED] (b) (4)

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

67. We acknowledge that you have evaluated the discriminating ability of your proposed dissolution method. However, the changes of the tested critical process parameters (CPPs) are beyond what the Agency typically recommended range, i.e., $\pm 20\%$ of target value, without appropriate justification. Re-evaluate the discriminating ability of your proposed dissolution method against critical material attributes (CMAs) and CPPs that affect dissolution of your product. Submit the following information and data to demonstrate the discriminating ability of the dissolution method.

- a. A list of CMAs and CPPs affecting the dissolution of your product.
- b. Percentage change of CMAs and CPPs of the tested aberrant batches.
- c. Complete in vitro dissolution data (individual, mean, SD, RSD) and similarity testing results obtained with appropriate statistical test (e.g., f_2 values) comparing the test and reference/target drug products.
- d. If available, data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference/target drug product.

Note that, if different dissolution medium volume is used for different strengths of your product, discriminating ability of the dissolution method needs to be demonstrated for each dissolution medium volume.

68. In your Table 34 of Pharmaceutical Development Report, one of the tested dissolution medium pH is (b) (4). In Table 35, Table 36, Figure 26, and Figure 27 of the same document, the pH value is (b) (4). Clarify your tested dissolution medium pH and update the information in your Pharmaceutical Development Report.

Microbiology

69. (b) (4)
(b) (4)
(b) (4)

a. (b) (4)
(b) (4)
(b) (4)
(b) (4)

i. (b) (4)
(b) (4)
(b) (4)
(b) (4)

ii. (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

b. (b) (4)
(b) (4)
(b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

c. (b) (4)
(b) (4)
(b) (4)
(b) (4)

2 Pages have been withheld in full asb4 immediately following this page

[REDACTED] (b) (4)
[REDACTED]
[REDACTED].

c. [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

d. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

76. [REDACTED] (b) (4)
[REDACTED]

a. [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

b. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

LABELING

1. CONTAINER LABEL (Drug Product and Diluent)

We acknowledge the request to revise the established name to read “Risperidone for Extended-Release Injectable Suspension”; however, revise the established name to include “Tall Man” lettering (i.e., risperiDONE for Extended-Release Injectable Suspension).

2. CARTON LABELING

Refer to comment 1 above.

3. PRESCRIBING INFORMATION

We recommend revising all instances of [REDACTED] (b) (4) to read “oral Risperdal®” when the RLD states “oral Risperdal®”.

4. INSTRUCTIONS FOR USE

- a. [REDACTED] (b) (4)
- b. [REDACTED] (b) (4)

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

BIOEQUIVALENCE

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be re-evaluated upon re-submission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are aware of FDA's recommendations for the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence

(21 CFR 320.24(a)), please continue to monitor for the availability of new and revised product-specific guidances in the *Federal Register* and on the FDA Web site at the following address:

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

OTHER

The resubmission to this CR letter will be considered to represent a **MAJOR AMENDMENT**, given that the deficiencies have been classified as **MAJOR**.

Prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission. If your submission includes gratuitous information in addition to the category or categories below, clearly identify the type of information submitted immediately following the wording below:

RESUBMISSION

MAJOR

COMPLETE RESPONSE AMENDMENT

DRUG SUBSTANCE/DRUG PRODUCT/PROCESS/MICROBIOLOGY /BIOPHARMACEUTICS/FACILITY INSPECTION/LABELING

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response as a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter does not fulfill the requirements in 21 CFR 314.110(b)(1) and therefore will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions¹ with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-

identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including by fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure you stay up to date with the Agency's current thinking on topics through guidances for industry, including product-specific guidances.

If you have any questions, call Uzoma Nnebe, Regulatory Project Manager, Division of Project Management, at (240) 402 - 5828.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
 Director, Division of Project Management
 Office of Regulatory Operations
 Office of Generic Drugs

¹ Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).



Denise
Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 10/14/2020 06:02:16PM
GUID: 5277df670008860f7e1231f730a8684c



ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA Inc
400 Interpace Pkwy
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Sr. Manager, Regulatory Affairs

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Injection, Suspension, 12.5mg/1vial, 25mg/1vial, 37.5mg/1vial, 50mg/1vial.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Manufacturing

a. Facility

1. An inspection of the [REDACTED] (b) (4) facility is required before the application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel we may be unable to conduct an inspection of the Pharmathen International S.A facility prior to the User Fee Date. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>.

We request a prompt written response, no later than **August 6, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the

response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 7/16/2020 02:45:58PM

GUID: 56f4536500ea9700421d7152e24f140d



ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc
400 Interpace Pkwy
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Sr. Manager, Regulatory Affairs

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Injection, Suspension, 12.5mg/1vial, 25mg/1vial, 37.5mg/1vial, 50mg/1vial.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. CDRH

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
3. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
4. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

5. [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than **July 10, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 6/15/2020 09:56:10AM

GUID: 56f4536500ea9700421d7152e24f140d



ANDA 214068

**DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE**

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054

Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

The following possible deficiencies have been identified by BIOEQUIVALENCE:

Deficiencies Related to Pre-study Method Validation:

1. Based on your submitted bioequivalence (BE) Summary Table 10 Study Information (Module 2.7) for the pivotal BE study No. CAC15003, the total sample storage duration is 625 days. Per your bioanalytical report, study samples were initially stored at clinical sites and then transferred to the bioanalytical sites, and storage duration was up to 414 days for sample aliquote-1 and up to 476 days for sample aliquote-2 at clinical sites (i.e., Subject (b) (6)). However, you only provided separate long-term storage stability data for 358 days at -70 °C and a total of 425 days at 2 different temperatures (417 days at -30 °C and 8 days at 5 °C or 351 days at -30 °C and then 74 days at -70 °C). It is also noted that during shipment of sample aliquote-2, the temperature was up to 22.2 °C for some subject samples. Please clarify the sample storage duration and temperature at clinical site and analytical site, as well as sample shipment time and temperature for each subject, and provide the additional long-term storage stability data to cover the study sample storage duration and condition.
2. Per your clinical study report (No. CAC15003), the bioanalytical lab was moved to a new location between 04/26 – 05/20/2019 during the conduct of study. Based on your bioanalytical report (Protocol #CAC15003; issued date: 11 December 2019), the study sample analysis was conducted initially at (b) (4)

(b) (4)

_____). Please clarify if additional method validation (i.e., partial validation) was performed prior to the sample analysis at the new bioanalytical site and provide the required method validation information per FDA guidance for Bioanalytical Method Validation (May 2018).

Deficiencies Related to In Vivo Pivotal Bioequivalence Study (No. CAC15003):

3. Per your clinical study report, it is unclear about the length of confinement for patients at the clinical sites during the course of study. Please provide this information.
4. Your pivotal BE study was conducted at 14 clinical sites. You did not include group as a variable in the submitted dataset. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose Number, Time (hours), Concentration. Please also resubmit the pharmacokinetic (PK) dataset including the following variable: Subject, Period, Sequence, Group, Treatment, Dose Number, and all relevant PK parameters (C_{max}, AUC_{tau}, C_{avg}, C_{min}, Fluctuation, and T_{max}).
5. Per product specific guidance for Risperidone Long-Acting Injectable, an intensive sampling is recommended for the 3rd dosing interval in period 2. Please resubmit the concentration dataset including the following variables: Subject, Period, Sequence, Group, Treatment, Dose Number, Time (hours), Concentration for the 3rd dosing interval in period 2. Please also provide PK parameters such as C_{min} and C_{max} for this dosing interval.
6. Per the FDA guidance for Industry: Bioequivalence studies with pharmacokinetic endpoint for drugs submitted under an ANDA (Issued December 2013), it is recommended that for steady-state study, applicant carry out appropriate dosage administration and sampling to document the attainment of steady-state. You collected multiple samples after 1st, 2nd, and 3rd injections. Please provide supporting document/data to demonstrate that individual patients have reached steady-state prior to conducting the BE analysis. Please also submit the dataset and SAS program for your analysis.

Deficiencies Related to In Vitro Drug Release Test:

7. For the in vitro release test, you did not submit the data for T50% and the 90% confidence interval of the test/reference ratio of T50%, as recommended in the product specific guidance for Risperidone Long-Acting Injectable. Please provide the requested data and also submit dataset and SAS program for your analysis. Additionally, please submit all data for the in vitro release test in Excel format.
8. It is noticed that your dissolution method validation (Report No. CC-2019-30-0190; issued on 11/28//2019 and report addendum No. CC-2019-10-1170; issued on

12/10/2019) was performed after the comparative dissolution testing (Report No: CC-2019-10-1170; issued 11/27/2019). Please provide explanation for this discrepancy.

In an addition, on February 10, 2011, Janssen Research & Development, LLC, a company of Johnson & Johnson, submitted a citizen petition to FDA (Docket No. FDA-2011-P-0086) regarding applications that reference Risperdal Consta (risperidone) Long-Acting Injection (NDA 021346) as a reference listed drug (RLD). The issues raised by this petition are currently under review by the Agency, and FDA has not made a final decision on the issues the petition raises. The comments included in this communication reflect only our current thinking, and this communication does not represent a final decision by the Agency on the issues raised in the pending citizen petition.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than 7/15/2020. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER BIOEQUIVALENCE

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Sylvia Park, Bioequivalence Project Manager, at Sylvia.Park@fda.hhs.gov or 301-796-5469.

Sincerely,

{See appended electronic signature page}

Sylvia Park, Pharm.D Project Manager
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Sylvia
Park

Digitally signed by Sylvia Park

Date: 6/15/2020 03:01:55PM

GUID: 5c8a87ae00acf2424a38962db1c1ad1d



ANDA 214068

**DISCIPLINE REVIEW LETTER
QUALITY**

Teva Pharmaceuticals USA Inc
400 Interpace Pkwy
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Senior Manager, Regulatory Affairs, US Generics

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Injection, Suspension, 12.5mg/1vial, 25mg/1vial, 37.5mg/1vial, 50mg/1vial.

Reference is also made to any amendments submitted prior to the issuance of this letter.

The following possible deficiencies have been identified by the Office of Pharmaceutical Quality:

A. Drug Substance

1. [REDACTED] (b) (4)
[REDACTED].

B. Drug Product

1. [REDACTED] (b) (4)
[REDACTED].
2. [REDACTED] (b) (4)
[REDACTED]
3. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED] (b) (4)
[REDACTED]

26. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

C. Manufacturing

a. Process

1. [REDACTED] (b) (4)
[REDACTED].

- a. [REDACTED] (b) (4)
[REDACTED]
[REDACTED].

- b. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

[REDACTED] (b) (4).

2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED].

3. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

4. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED].

7 Pages have been withheld in full as b4 immediately following this page

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]

32. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

33. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

34. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

35. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Please also note that the actual protocols, acceptance criteria, study outcomes, and supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

D. Microbiology

1. [REDACTED] (b) (4)
[REDACTED]

2. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

3. [REDACTED] (b) (4)
[REDACTED]

3 Pages have been withheld in full as b4 immediately following this page

d. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

10. [REDACTED] (b) (4)
[REDACTED]:

a. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

b. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

E. Biopharmaceutics

1. We acknowledge that you have adopted the dissolution method in the product specific guidance (PSG) for risperidone intramuscular injection for all strengths of your proposed drug product. In PSG, 200 mL medium volume is recommended for the 25 mg strength. [REDACTED] (b) (4)

[REDACTED]
[REDACTED] is proposed. Provide justification for using different medium volumes for different strengths.

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than **July 10, 2020**. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER

QUALITY

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.
2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 6/10/2020 12:02:20PM

GUID: 56f4536500ea9700421d7152e24f140d

ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parisppany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received on December 16, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED].

We request a complete written response no later than May 12, 2020 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST CLINICAL

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:

www.fda.gov/ectd.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

If you have any questions, please contact the Clinical Project Manager, at Karen.Townsend@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Karen Townsend
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Karen
Townsend

Digitally signed by Karen Townsend
Date: 5/05/2020 11:55:16AM
GUID: 5017fa0600000496295c39ed5304f64d



ANDA 214068

**DISCIPLINE REVIEW LETTER
LABELING**

Teva Pharmaceuticals USA, Inc.
400 Interpace Pkwy
Morris Corporate Center III
Parsippany, NJ 07054 USA
Attention: Ameya Kohojkar
Sr. Manager, Regulatory Affairs, US Generics

Dear Mr. Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

The following possible deficiencies have been identified by Labeling:

Labeling Deficiencies determined on April 7, 2020 based on your submission(s) received December 16, 2019:

1. GENERAL COMMENT

- a. Revise the name of your drug product to read "Risperidone for Extended-Release Injectable Suspension" to comply with USP nomenclature guidelines from USP General Chapter, General Information <1121> Nomenclature, on your labels and labeling.
- b. Comment as to whether text appears on your cap/ferrule overseal. Ensure your proposed cap/ferrule overseals are in compliance with the requirements of the USP, General Chapter <7> Labeling for Ferrules and Cap Overseals.

2. CONTAINER LABEL (Drug Product)

- a. Refer to comment 1a above.
- b. Revise the strength statement to express the strength in terms of the total amount of drug per vial. For example: XX mg/vial or XX mg per vial.

3. CONTAINER LABEL (Diluent)

Refer to comment 1a above.

4. CARTON LABELING

- a. Refer to comments 1a and 2b above.
- b. Revise [REDACTED] (b) (4)
[REDACTED] " on the side labels to read "PLEASE READ COMPLETE INSTRUCTIONS PRIOR TO USE."

5. PRESCRIBING INFORMATION

- a. Revise your labeling to be in accordance with the most recently approved labeling for the reference listed drug (RLD), Risperdal Consta, NDA 021346/S-063 approved on February 5, 2020 found on the Drugs@FDA website.
- b. Refer to comment 1a above.
- c. DESCRIPTION: Include "Sterile", as required for the proposed drug product. Refer to 201.57(c)(12)(D).

6. INSTRUCTIONS FOR USE

Refer to comment 1a above.

7. STRUCTURED PRODUCT LABELING (SPL)

- a. DATA ELEMENTS: Provide the data elements for the 25 mg, 37.5 mg, and 50 mg strengths.
- b. In the Prescribing Information portion of the SPL, steps 3 and 4 are not included in section 2.8 Instructions for Use. Ensure these steps are included.

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review cycle, we request a complete written response to this discipline review letter (DRL) no later than May 11, 2020. If you submit a written response during this review cycle, depending on the timing and/or the information contained in your response, we may not be able to consider your response before taking action on your application. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER LABELING

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter¹, these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified or additional deficiencies may be identified as we complete our review of your entire application.

Deficiencies addressed by applicants in a response to a DRL may appear in a Complete Response Letter (CRL) if FDA's review of the response has been deferred or if FDA has outstanding concerns after review of the response. The CRL will include all deficiencies that must be satisfactorily addressed before the ANDA can be approved.

If the applicant receives a CRL, but has already responded to some (or all) identified deficiencies in a DRL response, the applicant does not need to re-submit previously submitted information in a CRL amendment. However, the applicant should still submit a CRL amendment and should clearly identify the previously provided DRL response that renders its CRL amendment complete.

Additionally, please take note of the following if you choose to respond to these possible deficiencies before the end of this review cycle:

1. FDA will strive to review your response during the review cycle in which it is received if such review can be completed during such review cycle. However, if the Agency determines that it cannot review the response before a goal date or if a complete response letter is otherwise ready to be issued, the review of your response may be deferred. When FDA defers review of your response, it will be reviewed during the next review cycle for the application.

¹ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>).

2. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

If you have any questions, please contact Julie Call, Labeling Project Manager, at julie.call@fda.hhs.gov or 240-402-8598.

Sincerely,

{See appended electronic signature page}

Julie Call, PharmD, PMP
Labeling Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration



Julie
Call

Digitally signed by Julie Call
Date: 4/27/2020 09:32:14AM
GUID: 525d9e9d00038c406bce70608a211ab1

ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received on December 16, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

Please provide high resolution photos of the vial adapter without the blister packaging for both the test product and the RLD. The current photos, (b) (4)

We request a complete written response no later than April 29, 2020 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST CLINICAL

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:
www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Karen.Townsend@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Karen Townsend
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Karen
Townsend

Digitally signed by Karen Townsend
Date: 4/22/2020 03:03:21PM
GUID: 5017fa0600000496295c39ed5304f64d



INFORMATION REQUEST

4. [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED] (b) (4)
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than **April 22, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 4/02/2020 11:49:30AM

GUID: 56f4536500ea9700421d7152e24f140d



ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA Inc
400 Interpace Pkwy
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar
Senior Manager, Regulatory Affairs

Dear Ameya Kohojkar:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on December 16, 2019, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Risperidone Injection, Suspension, 50mg/1vial, 25mg/1vial, 37.5mg/1vial, 12.5mg/1vial.

We are reviewing the Quality section of your submission and have the following comments and information requests:

A. Manufacturing

a. Process

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]

Please inform us if any special handling requirements are advised. The samples can be mailed to the address below:

FDA/CDER/OPQ/OTR
Attn: Bryan Lowry
10903 New Hampshire Ave
WO Bldg 64, Room 1080
Silver Spring, MD 20993

b. Facility

1. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED],

(b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

If utilizing a streamlined approach, you must demonstrate compliance with (i) either the drug CGMP regulations or the device QS regulation in their entirety, and (ii) those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and device QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm>.

It is acknowledged that your application includes information intending to demonstrate compliance with the device QS regulation. However, this information has not been reviewed at this time because, based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection rather than reviewed as part of the quality assessment of your application. Therefore, this information must be available upon inspection, and assessment of this information has been deferred for possible review during inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

It has been determined that the quality assessment for this ANDA requires an additional technical consultation. Please note that the quality assessment of the ANDA cannot be fully completed until this technical consultation has been finalized. Therefore, additional requests for information and/or deficiencies may be issued based on the outcome of this technical consultation.

We request a prompt written response, no later than **March 19, 2020** in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. In addition, if your response contains either gratuitous information not requested by FDA or information that requires a more thorough review as determined by FDA, FDA may classify the

response as an amendment and assign an appropriate goal date for that amendment. The goal date assigned to the amendment may extend the review goal date for your current submission.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
QUALITY**

If you have any questions, please contact Temitope Oriola, PharmD, Regulatory Business Process Manager, at Temitope.Oriola@fda.hhs.gov or (240) 402 - 4646.

Sincerely,

{See appended electronic signature page}

Temitope Oriola, PharmD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



Temitope
Oriola

Digitally signed by Temitope Oriola

Date: 3/03/2020 10:46:05AM

GUID: 56f4536500ea9700421d7152e24f140d

ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received on December 16, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

We request 1 sample of the to-be-marketed proposed product for each strength and 1 sample of the RLD for each strength. The proposed product should be affixed with the to-be-marketed immediate container label, or a label that closely resembles the to-be-marketed product. For the proposed product, samples with a mocked label, i.e., non-commercially produced, depicting the actual label in both size, shape and font would be acceptable.

This request is separate from any request for samples that may come to you from the Office of Pharmaceutical Quality.

The samples do not need to be refrigerated during shipment.

We request a complete written response no later than March 17, 2020 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST CLINICAL

The requested samples should be submitted under a separate cover letter and mailed to the following address:

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Karen Townsend
Senior Regulatory Project Manager
Division of Clinical Review
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA
Bldg. 75, Room 2510
10903 New Hampshire Ave,
Silver Spring, MD 20993

If you do not submit a complete written response by March 17, 2020 the listed information requests may be incorporated in a complete response letter.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:
www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at
Karen.Townsend@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Karen Townsend
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



Karen
Townsend

Digitally signed by Karen Townsend
Date: 3/03/2020 12:35:37PM
GUID: 5017fa0600000496295c39ed5304f64d



ANDA 214068

**ACKNOWLEDGEMENT
ANDA RECEIPT**

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial

DATE OF APPLICATION: December 16, 2019

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: December 16, 2019

Reference is made to the information request dated January 29, 2020 and to any amendments thereafter.

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). We acknowledge that you have requested a priority review for this submission. However, your submission does not meet the criteria listed in section 505(j)(11)(A) of the FD&C Act or the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. The GDUFA goal date for review of this standard original ANDA is October 15, 2020.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP

monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:

www.fda.gov/ectd.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Uzoma Nnebe, Senior Regulatory Health Project Manager, at uzoma.nnebe@fda.hhs.gov¹ or (240) 402 - 5828. We also recommend that you sign up for Generic Drug e-mail updates,² which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bankim Patel, RPh
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

¹ A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

² <https://updates.fda.gov/subscriptionmanagement>



Bankim
Patel

Digitally signed by Bankim Patel

Date: 2/06/2020 12:52:00PM

GUID: 5423006c00721f7db511c8db220bd9cf

List of Deficiencies for ANDA #214068

A. Drug Substance Deficiencies

B. Drug Product Deficiencies

C. Microbiology Deficiencies

D. Process Deficiencies

Please submit samples (three each) of your finished product from batch 4800013A-P, 4700023B-P, 4800014C-P, and 4800014D-P, as well as the reference product for evaluation.

Please inform us if any special handling requirements are advised. The samples can be mailed to the address below.

FDA/CDER/OPQ/OTR
Attn: Bryan Lowry
10903 New Hampshire Ave
WO Bldg 64, Room 1080
Silver Spring, MD 20993

E. Facilities Deficiencies

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, you must demonstrate compliance with (i) either the drug CGMP regulations or the device QS regulation in their entirety, and (ii) those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and device QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance

for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm>.

It is acknowledged that your application includes information intending to demonstrate compliance with the device QS regulation. However, this information has not been reviewed at this time because, based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection rather than reviewed as part of the quality assessment of your application. Therefore, this information must be available upon inspection, and assessment of this information has been deferred for possible review during inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

F. Biopharmaceutics Deficiencies

List of Deficiencies for ANDA #214068

A. Drug Substance Deficiencies

1.

(b) (4)

B. Drug Product Deficiencies

(b) (4)

C. Microbiology Deficiencies

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D. Process Deficiencies

9 Pages have been withheld in full as b4
immediately following this page

E. Facilities Deficiencies

F. Biopharmaceutics Deficiencies

1. We acknowledge that you have adopted the dissolution method in the product specific guidance (PSG) for risperidone intramuscular injection for all strengths of your proposed drug product. In PSG, 200 mL medium volume is recommended for the 25 mg strength. It is noted (b) (4)

Provide justification for using different medium volumes for different strengths.

Question from FDA: Process Deficiency # 56

(b) (4)

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Teva's Clarifying Question 3:

(b) (4)

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FDA Response to Question 3 (OPMA):

(b) (4)

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FDA Deficiency #9 and #10

(b) (4)



e

Question from FDA: Drug Product Deficiency # 11

11. Please provide the method validation for the determination of critical attributes for PLG, such as Intrinsic Viscosity, Molecular Weight and Polymer Composition.

Teva's Clarifying Question 2:

(b) (4)



FDA Comments:

[REDACTED] (b) (4)

ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received on December 16, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

Please provide high resolution photos of the vial adapter without the blister packaging for both the test product and the RLD. The current photos, previously provided, have the vial adapter in the packaging.

We request a complete written response no later than April 29, 2020 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST CLINICAL

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit:
www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at Karen.Townsend@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Karen Townsend
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



ANDA 214068

INFORMATION REQUEST

Teva Pharmaceuticals USA, Inc.
400 Interpace Parkway
Morris Corporate Center III
Parispany, NJ 07054
Attention: Ameya Kohojkar

Dear Ameya Kohojkar:

This is in reference to your abbreviated new drug application (ANDA) received on December 16, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone Long Acting Injection, 12.5 mg/vial, 25 mg/vial, 37.5 mg/vial and 50 mg/vial.

Your submission remains under review, and we require additional information in order to complete our Clinical Consultation review.

We refer to your Threshold Analysis Report, your Clinical/Response to Information Request dated 3/27/2020, and your proposed labeling dated 5/11/2020.

[REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

We request a complete written response no later than June 9, 2020 in order to continue our evaluation of your ANDA. We will not process or review a partial response. Facsimile or e-mail responses will not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

**INFORMATION REQUEST
CLINICAL**

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD

Guidance will be subject to rejection. For more information please visit:
www.fda.gov/ectd.

If you have any questions, please contact the Clinical Project Manager, at
Karen.Townsend@fda.hhs.gov.

Please also confirm receipt of this letter.

Sincerely,

{See appended electronic signature page}

Karen Townsend
Clinical Project Manager
Division of Clinical Review
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research



ANDA 214068

AMENDMENT ACKNOWLEDGEMENT

**Priority
Major**

Teva Pharmaceuticals USA Inc.
400 Interpace Parkway
Morris Corporate Center III
Parsippany, NJ 07054
Attention: Ameya Kohojkar
Senior Manager, Regulatory Affairs, US Generics

Dear Sir:

This is in reference to your amendment received on May 27, 2021, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Risperidone for Extended-Release Injectable Suspension, 12.5 mg per vial, 25 mg per vial, 37.5 mg per vial, and 50 mg per vial.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). FDA has made an initial determination that this is a major amendment and it meets the criteria for a priority review per the Center for Drug Evaluation and Research's Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*. If FDA determines that an inspection is not required to validate the information contained in this priority major amendment, the GDUFA goal date for review of this priority major amendment is November 26, 2021. If FDA determines that an inspection is required to validate the information contained in this priority major amendment and a Pre-Submission Facility Correspondence was not submitted or not accepted, the GDUFA goal date for review of this priority major amendment is March 26, 2022.

GDUFA II provides important program enhancements that are designed to improve the predictability and transparency of ANDA assessments and to minimize the number of review cycles necessary for approval, including fostering the development of high-quality applications. While FDA will communicate deficiencies identified during our assessment of your application, it is each applicant's responsibility to submit and maintain a high-quality application that FDA can approve. To this end, you should ensure your application addresses any changes to the RLD that occur after the submission of your ANDA, such as changes in labeling, patent or exclusivity information, or marketing status. You should also ensure your application stays up to date with the Agency's current recommendations on demonstrating bioequivalence reflected in relevant product specific guidances.

If you have any questions, contact Uzoma Nnebe, Regulatory Project Manager, at (240) 402 - 5828.

Sincerely,

{See appended electronic signature page}

Uzoma Nnebe
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration