APPLICATION NUMBER:
21-346

CHEMISTRY REVIEW(S)
NDA 21-346

Risperdal Consta™

Janssen Research Foundation

Gurpreet Gill-Sangha, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls
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1. NDA 21-346

2. REVIEW #: 2

3. REVIEW DATE: October 22, 2003

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

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7. NAME & ADDRESS OF APPLICANT:

   Name: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

   Address: 1125 Trenton-Harbourton Road, PO Box 200, Titusville, NJ 08560-0200

   Representative: Claude McGowan, Ph.D., Associate Director, Regulatory Affairs

   Telephone: (609) 730-3025

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Risperdal Consta™
   b) Non-Proprietary Name (USAN): Risperidone
   c) Code Name/# (ONDC only): None
   d) Chem. Type/Submission Priority (ONDC only):
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Schizophrenia

11. DOSAGE FORM: Intramuscular Injection

12. STRENGTH/POTENCY: 25, 37.5, and 50 mg

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

___ SPOTS product – Form Completed

_X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

USAN Name: Risperidone

Chemical Formula: C_{23}H_{27}FN_{4}O_{2}

Molecular Weight: 410.48

CAS registry #: 106266-06-2

Structure:
17. RELATED/SUPPORTING DOCUMENTS:

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2 – Type 1 DMF
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

\(^2\) Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NA

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The Chemistry Review for NDA 21-346

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

N21-346 for Risperdal Consta™ is recommended for APPROVAL from the CMC standpoint. The approval from the CMC standpoint is based on acceptable response to CMC deficiencies and an acceptable cGMP recommendation from FDA Compliance for all the manufacturing, packaging and testing sites.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Risperdal Consta™ Long Acting Injection for the treatment of schizophrenia is to be marketed as 25, 37.5 and 50 mg intramuscular injection. Risperdal Consta will be provided in a kit which includes a vial of risperidone extended release microspheres, 2 mL diluent in a pre-filled syringe, and one Needle Pro™ 20 G 2 inch TW safety needle with needle protection device for injection and a SmartSite® Needle-Free Access device for reconstitution. The labels on the vials and the kit cartons are color coded for the dose strengths as pink for 25 mg, green for 37.5 mg and blue for 50 mg.

The drug product Risperdal Consta™ comprises of risperidone extended release microspheres and a diluent to suspend the microspheres for intramuscular injection. The manufacturing of the microspheres and diluent is performed using . Risperidone extended release microspheres for injection are manufactured by encapsulating risperidone in polylactide-co-glycolide polymer microspheres to provide the extended release properties. These microspheres are suspended in a diluent composed of carboxymethylcellulose sodium — — — — Adequate in-process controls are provided for the diluent manufacture during compounding, filling and after filling of syringes.
The release and stability specifications for risperidone extended release microspheres are the same for __________. Deficiencies identified for the regulatory release specifications of risperidone microspheres related to impurities and residual solvents were resolved as per this review and J&J has accepted certain changes in impurity limits for risperidone microspheres. Refer to the updated table of Risperidone Extended Release Microspheres drug product following the executive summary. __________ was recommended for continued monitoring in the future stability studies. However, based on extensive data J&J has demonstrated that __________.

The drug substance risperidone is a ______ white powder, practically insoluble in water, freely soluble in methylene chloride and soluble in methanol and 0.1 N HCl. Risperidone consists of ______ with a molecular weight of 410.48. The ______ specifications by

__________ Risperidone drug substance is manufactured by Johnson at the County Cork, Ireland (CFN #9611011) site as described in Type II DMF __________ DMF __________ has been reviewed and found adequate by Dr. Gurpreet Gill-Sangha on June 12, 2002. Risperidone manufactured by Janssen is used to synthesize the risperidone extended release microspheres by Alkermes, Ohio. A re-test of __________ was granted for risperidone drug substance.

The theoretical formulations of risperidone extended release microspheres and diluent are similar for the clinical and commercial supply samples. The early phase I and II clinical studies used drug product from ________ batches ________ while the phase III and commercial drug product is from ________ batches. There are small differences in the formulations of microspheres and diluent from __________ scale to the __________ scale batches attributed to higher encapsulation efficiency of drug product resulting in slightly higher drug content in phase III and commercial samples. The phase III clinical and commercial samples of drug product are similar in the microsphere and diluent formulations and, therefore, did not require any compatibility studies.

**B. Description of How the Drug Product is Intended to be Used**

Risperdal Consta™ will be provided in a kit including a vial of risperidone extended release microspheres, 2 mL diluent in a pre-filled syringe, and one Needle Pro™ 20 G 2 inch TW safety needle with needle protection device for injection and a SmartSite® Needle-Free Access device for reconstitution. The diluent is used to reconstitute the microspheres to form a suspension.

The drug product is to be administered every 2 weeks by deep intramuscular (IM) gluteal injection. Each injection should be administered by a health care
professional using the enclosed safety needles. The recommended dose is 25 mg IM every two weeks. The maximum dose should not exceed 50 mg every two weeks. Oral risperidone or other antipsychotic medication should be given with the first injection of Risperdal Consta™ and continued for 3 weeks to ensure adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site. Detailed instructions for use with the SmartSite® kit are provided on the package insert and kit carton or leaflet inside the cartons. As of September 30, 2003, J&J notified FDA that only the SmartSite® device will be used for reconstitution for Risperdal Consta.

A 24 month shelf life (expiration period) under refrigerated conditions of 2 – 8 °C (36 – 46 °F) is granted based on acceptable 24 month real time data at 5 °C ± 3 °C from primary and supportive stability studies for 25 and 75 mg strengths. The simulated shipping studies support up to — of storage for microspheres and diluent packaged in the kit at temperatures — The studies document that no special light protective handing is required. However, based on data from J&J the — and hence, the precautionary protection from light statement is included in the label. The reconstituted microspheres in the diluent should be used within 6 hours when stored at controlled room temperature of 25 °C (77 °F) based on data from in-use stability studies.

C. Basis for Approvability or Not-Approval Recommendation

N21-346 (Risperdal Consta™) is recommended for APPROVAL from the CMC standpoint based on adequate responses to the CMC deficiencies and an acceptable cGMP recommendation from FDA Compliance.

III. Administrative

Reviewer – Gurpreet Gill-Sangha, Ph.D.
Chemistry Team Leader – Thomas F. Oliver, Ph.D.
Project Manager – Steven Hardeman, R.Ph.
33 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
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Gurpreet Gill-Sangha
10/22/03 12:01:36 PM
CHEMIST

CMC Review #2 for N21-346

Thomas Oliver
10/22/03 12:25:55 PM
CHEMIST

APPROVED ON
22-OCT-03
NDA 21-346

Risperdal Consta™

Janssen Research Foundation

Gurpreet Gill-Sangha, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
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1. NDA 21-346

2. REVIEW #: 1

3. REVIEW DATE: June 21, 2002

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

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   Name: Janssen Research Foundation
   Address: 1125 Trenton-Harbourton Road, PO Box 200, Titusville, NJ 08560-0200
   Representative: Claude McGowan, Ph.D., Associate Director, Regulatory Affairs
   Telephone: (609) 730-3025

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Risperdal Consta™
   b) Non-Proprietary Name (USAN): Risperidone
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type: 3
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Schizophrenia

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12. STRENGTH/POTENCY: 25, 37.5, and 50 mg

13. ROUTE OF ADMINISTRATION: Intramuscular

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   ___ SPOTS product – Form Completed

   ___X___ Not a SPOTS product

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   USAN Name: Risperidone

   Chemical Formula: C_{23}H_{27}FN_{4}O_{2}

   Molecular Weight: 410.48

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CHEMISTRY REVIEW
Chemistry Review Data Sheet

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<td>Acceptable</td>
<td>April 9, 2002</td>
<td>Vinayak Pawar</td>
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The Chemistry Review for NDA 21-346

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

N21-346 for Risperdal Consta™ is recommended Approvable from the CMC standpoint. The approval from the CMC standpoint is contingent on pending acceptable cGMP recommendation from FDA Compliance for all the manufacturing, packaging and testing sites and adequate responses to CMC deficiencies related to the drug product noted in this review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Risperdal Consta™ Long Acting Injection for the treatment of schizophrenia is to be marketed as 25, 37.5 and 50 mg intramuscular injection. The injection will be provided in_____ kits. Each kit will include a vial of risperidone extended release microspheres, 2 mL diluent in a pre-filled syringe, and one Needle Pro™ 20 G 2 inch TW safety needle with needle protection device for injection. In addition, the kit will contain _______________ SmartSite® Needle-Free Access device for reconstitution. The labels on the vials and the kit cartons are color coded for the dose strengths as pink for 25 mg, green for 37.5 mg and blue for 50 mg.

The drug product Risperdal Consta™ comprises of risperidone extended release microspheres and a diluent to suspend the microspheres for intramuscular injection. The manufacturing of the microspheres and diluent is performed using _______________ Risperidone extended release microspheres for injection are manufactured by encapsulating risperidone in poly lactide-co-glycolide polymer microspheres to provide the extended release properties. These microspheres are suspended in a diluent composed of carboxymethylcellulose sodium. Adequate in-process controls are provided for the diluent manufacture including during compounding, filling and after filling of syringes.
The release and stability specifications for risperidone extended release microspheres are the same for Deficiencies identified for the regulatory release specifications of risperidone microspheres pertain to related substances and residual solvents. is recommended for continued monitoring in the future stability studies.

The drug substance risperidone with a re-test date of is a hite powder practically insoluble in water, freely soluble in methylene chloride and soluble in methanol and 0.1 N HCl. The molecular weight of risperidone is 410.48 with The specifications by ' 'are' value at no more than ' 'and 'value at not more than ' Risperidone drug substance is manufactured by Janssen at the County Cork, Ireland (CFN #9611011) site as described in Type II DMF DMF has been reviewed and found adequate by Dr. Gurpreet Gill-Sangha on June 12, 2002. Risperidone manufactured by Janssen is used to synthesize the risperidone extended release microspheres by Alkermes, Ohio.

The theoretical formulations of risperidone extended release microspheres and diluent are similar for the clinical and commercial supply samples. The early phase I and II clinical studies used drug product from scale batches while the phase III and commercial drug product is from scale batches. There are small differences in the formulations of microspheres and diluent from scale to the scale batches attributed to higher encapsulation efficiency of drug product resulting in slightly higher drug content in phase III and commercial samples. The phase III clinical and commercial samples of drug product are similar in the microsphere and diluent formulations and, therefore, did not require any compatibility studies.

B. Description of How the Drug Product is Intended to be Used

Risperdal Consta™ will be provided in kit kit will include a vial of risperidone extended release microspheres, 2 mL diluent in a pre-filled syringe, and one Needle Pro™ 20 G 2 inch TW safety needle with needle protection device for injection. In addition, the kit will contain SmartSite® Needle-Free Access device for reconstitution. The diluent is used to reconstitute the microspheres to form a suspension.
The drug product is to be administered every 2 weeks by deep intramuscular (IM) gluteal injection. Each injection should be administered by a health care professional using the enclosed safety needles. The recommended dose is 25 mg IM every two weeks. The maximum dose should not exceed 50 mg every two weeks. Oral risperidone or other antipsychotic medication should be given with the first injection of Risperdal Consta™ and continued for 3 weeks to ensure adequate therapeutic plasma concentrations are maintained prior to the main release phase of risperidone from the injection site. Detailed instructions for use with the SmartSite® kit are provided on the package insert and kit carton or leaflet inside the cartons.

24 month shelf life (expiration period) under refrigerated conditions of 2 – 8 °C (36 – 46 °F) is granted based on acceptable 24 month real time data at 5 °C ± 3 °C from primary and supportive stability studies for 25 and 75 mg strengths. The studies support up to of storage for microspheres and diluent packaged in the kit at temperatures. The studies document that no special light protective handling is required. The reconstituted microspheres in the diluent should be used within 6 hours when stored at controlled room temperature of 25 °C (77 °F) based on data from in-use stability studies.

C. Basis for Approvability or Not-Approval Recommendation

N21-346 (Risperdal Consta™) is recommended approvable from the CMC standpoint based on the following:

- Pending recommendation from FDA Compliance regarding cGMP status of manufacturing, controls and packaging facilities – in particular the facility Cilag for diluent manufacturing and testing will be inspected by FDA Compliance in July 2002,
- CMC concerns related to drug product section as:
  - Inadequate justification for the proposed regulatory specifications of
  - Lack of information for the SmartSite® device, and
  - Additional information necessary on the labels for vials, syringes and carton for safety purposes.

The deficiencies are detailed in the draft deficiency letter for CMC to be relayed to Janssen.

III. Administrative

Reviewer – Gurpreet Gill-Sangha, Ph.D.
Acting Chemistry Team Leader – Hasmukh Patel, Ph.D.
Project Manager – Steven Hardeman, R.Ph.
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☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(5) Draft Labeling
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/s/

Gurpreet Gill-Sangha
6/24/02 08:41:26 AM
CHEMIST

CMC review #1

Hasmukh Patel
6/24/02 04:21:33 PM
CHEMIST

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