CENTER FOR DRUG EVALUATION AND RESEARCH

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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List of Tables

Chemistry Review Data Sheet

1. NDA 21-346

2. REVIEW #: 2

3. REVIEW DATE: October 22, 2003

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 31, 2001
Amendment N(BC)	March 25, 2002
Amendment N(BC)	June 6, 2002
Chemistry Review #1	June 24, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Complete Response to NA Letter (June 28, 2002)	April 28, 2003
Amendment N-BL	May 7, 2003
Amendment N-BC	September 26, 2003

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):

- Chem. Type: 3
- Submission Priority: S

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-4*H*-pyrido[1,2-a]pyrimidin-4-one

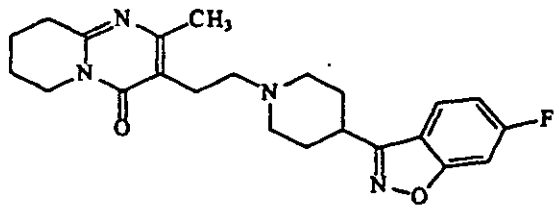
USAN Name: Risperidone

Chemical Formula: $C_{23}H_{27}FN_4O_2$

Molecular Weight: 410.48

CAS registry #: 106266-06-2

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable in the first review cycle	May 2, 2002	Sharon Yan
EES	Acceptable	September 17, 2003	FDA Compliance
Pharm/Tox	Pending		
Biopharm	Acceptable as in the first cycle		
LNC	USAN available	NA	NA
Methods Validation	Pending		Gurpreet Gill-Sangha, Ph.D.
OPDRA	Acceptable as in the first cycle		
EA	Acceptable, categorical exclusion granted as per information from J & J in original submission	As per CMC review #1	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Acceptable	April 9, 2002	Vinayak Pawar

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 [redacted]. 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. [redacted] was recommended for continued monitoring in the future stability studies. However, based on extensive data J&J has demonstrated that [redacted].

The drug substance risperidone is a [redacted] white powder, practically insoluble in water, freely soluble in methylene chloride and soluble in methanol and 0.1 N HCl. Risperidone consists of [redacted] with a molecular weight of 410.48. The [redacted] specifications by [redacted] Risperidone drug substance is manufactured by Janssen at the County Cork, Ireland (CFN #9611011) site as described in Type II DMF [redacted]. DMF [redacted] 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 [redacted] 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 [redacted] batches [redacted] while the phase III and commercial drug product is from [redacted] batches. There are small differences in the formulations of microspheres and diluent from [redacted] scale to the [redacted] 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 imtramuscular (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.

23 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

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

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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List of Tables and Figures

Chemistry Review Data Sheet

1. NDA 21-346

2. REVIEW #: 1

3. REVIEW DATE: June 21, 2002

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

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	August 31, 2001
Amendment N(BC)	March 25, 2002
Amendment N(BC)	June 6, 2002

7. NAME & ADDRESS OF APPLICANT:

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

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

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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-4*H*-pyrido[1,2-a]pyrimidin-4-one

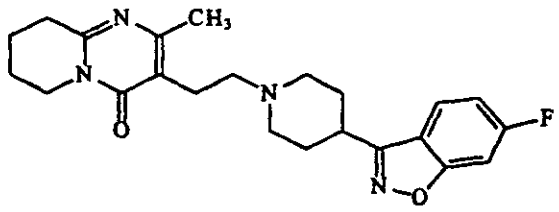
USAN Name: Risperidone

Chemical Formula: $C_{23}H_{27}FN_4O_2$

Molecular Weight: 410.48

CAS registry #: 106266-06-2

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Alkermes		1	Adequate	November 8, 2001 by Dr. Gurpreet Gill-Sangha	
	II	Janssen Research Foundation	Risperidone Drug Substance	1	Adequate	June 12, 2002 by Dr. Gurpreet Gill-Sangha	
	III			1	Adequate	November 21, 2001 by Dr. Gurpreet Gill-Sangha	
	III			1	Adequate	December 12, 2001 by Dr. Gurpreet Gill-Sangha	
	III			1	Adequate	February 11, 2002 by Dr. Gurpreet Gill-Sangha	
	III			1	Adequate	May 9, 2000 by Dr. David Lin	
	III			1	Inadequate	March 11, 2002 by Dr. Josephine Jee	Adequate for this NDA since information on — is included in the NDA.

[1] Action codes for DMF Table:
1 – DMF Reviewed.
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2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
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[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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	May 2, 2002	Sharon Yan
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Pending		
LNC	USAN available	NA	NA
Methods Validation	Pending		Gurpreet Gill-Sangha, Ph.D.
OPDRA	Pending		
EA	Acceptable, categorical exclusion granted as per information from Janssen	As per this review	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Acceptable	April 9, 2002	Vinayak Pawar

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 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 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 nas 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.

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The — studies document that no special light protective handing 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.

49 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/

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

CMC review #1

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