

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-043

CHEMISTRY REVIEW(S)



CHEMISTRY REVIEW



NDA 22-043

**INVEGA™ (paliperidone)
Extended Release Tablets**

**Johnson & Johnson Pharmaceutical Research and
Development L.L.C.**

Division of Psychiatry Products

**Chhagan G. Tele, Ph.D.
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment**

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA: 22-043
 2. REVIEW #: 1
 3. REVIEW DATE: February 1, 2007
 4. REVIEWER: Chhagan G. Tele, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	27-JUN-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	Janssen, L.P.
Address:	1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560
Representative:	Hedddie Martynowicz, Director, Regulatory Affairs
Telephone:	(609) 730-7028

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: INVEGA™
 b) Non-Proprietary Name (USAN-2004): Paliperidone
 c) Code Name/# (ONDC only): Oaliperidone
 d) Chem. Type/Submission Priority (ONDC only):
 • Chem. Type: 6
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1); INVEGA® (paliperidone) Extended-Release Tablets, 3 mg, 6 mg, and 9 mg Strengths.



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Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Maintenance of clinical stability in adult patients with Schizophrenia.
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 3 mg, 6 mg, and 9 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed
 Not a SPOTS product

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

USAN Name (2004): Paliperidone

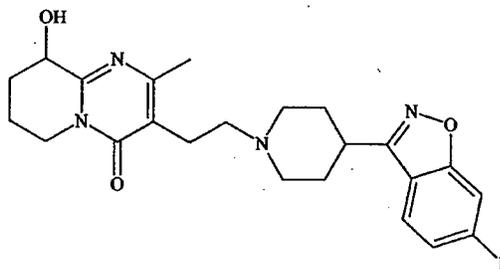
Non-Proprietary Name: (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

Chemical Formula: $C_{23}H_{27}FN_4O_3$

Molecular Weight: 426.49

CAS registry #: 144598-75-4

Structure:



Paliperidone (R076477) contains one chiral center. Racemic mixture of drug substance is used to manufacture drug product.



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Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
18915	II	Janssen Pharmaceutica, NV	Drug Substance	1	Adequate 21-JUN-06 Dr. Chhagan Tele	LOA 29 NOV-05
	III			4		LOA 25-JAN-05
	III			4		LOA 05-JAN-05
	III			4		LOA 29-AUG-05
	III			4		LOA 31-AUG-05
	III			4		LOA 05-JAN-05
	III			4		LOA 30-AUG-05
	III			4		LOA 29-AUG-05
	III			4		LOA 22-DEC-04
	III			4		LOA 06-JAN-05
	III			4		LOA 06-JAN-05

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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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	65,850	Commercial IND (Schizophrenia) Approved 19-DEC-2006
NDA	21-999	

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation Acceptable	30-JAN-07	D Ambrogio, Janine M (HFD-322)



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Pharm/Tox			
Biopharm	Acceptable		Ron Kavanagh, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	Proprietary name INVEGA acceptable		Tina Tesky, Pharm.D.
EA	Acceptable, categorical exclusion granted as per information from J&J PRD in this NDA	As per this review	Chhagan G. Tele, Ph.D. (ONDQA-Branch I)
Microbiology	N/A	N/A	N/A

Appears This Way
On Original

Appears This Way
On Original



The Chemistry Review for NDA 22-043

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time NDA 22-043 for INVEGA™ (paliperidone) Extended Release Tablets is recommended **APPROVAL** from the CMC standpoint. See Section II C for approval recommendation basis

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)

NDA 21-999 [INVEGA (paliperidone), Indication: For the treatment of schizophrenia] was approved on 19-DEC-2006. Janssen submitted NDA 22-043 as an extension of the label claim (Maintainance of clinical stability in adult patients with Schizophrenia). The paliperidone dosage forms are extended release tablets using ALZA's OROS® Push-Pull™ technology to deliver the paliperidone drug substance in a controlled manner over 24 hours, thereby achieving an effective once-a-day treatment for schizophrenia. The maximum recommended dose is 12 mg/day. The paliperidone extended release (ER) tablets (3 mg, 6, mg, and 9 mg strengths) contain 3, 6, or 9 mg of paliperidone drug substance.

The formulations provide dose proportional in-vivo and in-vitro release functionality. Paliperidone ER tablets across all doses have the same geometry, the same layer weights, and exhibit dose proportionality over the entire range of doses (3- to 15-mg).¹

All tablets are overcoated with different color overcoats to provide color differentiation between the different dosage strengths. The applicant provided adequate information on components and composition of the proposed commercial drug product for unit dose formulation for — strengths. The composition of all components (USP/NF or Ph. Eur. grades) is common to all — strengths of the INVEGA Extended Release Tablets. The amount of active ingredient, paliperidone used in each tablet is proportional in each strength.

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Executive Summary Section

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Adequate information was provided for the manufacturing of the drug product. There are no intermediates in the manufacture of paliperidone ER tablets. The applicant provided information about controls of Critical Steps in the manufacture of registration batches of the INVEGA Extended Release Tablets. Registration batches of drug product were manufactured at the commercial manufacturing site, [┌] at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches.

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Registration (primary) stability studies have been conducted with paliperidone 3 mg, 6 mg, 9 mg, 12 mg, and 15 mg ER tablets (formulations F039, F040, F041, F045, and F043, respectively) under various conditions on registration batches manufactured at ALZA Corporation, Mountain View, CA and ALZA Corporation, Vacaville, CA, in accordance with the pre-phase 3 meeting of June 12, 2003. At this meeting, the stability protocol was discussed and agreed to with the Chemistry



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Executive Summary Section

Division. Each strength has been packaged in 3 different packaging configurations: []

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The drug substance, Paliperidone, is manufactured and supplied to the applicant by Janssen Pharmaceutical, West Deptford, NJ according to the process and controls described in their DMF #18915. Letters of Authorization to access this DMF were provided for cross-reference. The DMF #18915 was reviewed and found adequate by Dr. Chhagan Tele (21-JUN-06). Paliperidone is a white to yellow powder with one chiral center. Racemic mixture of the drug substance is used in drug product. All the batches of Paliperidone drug substance presented in the original NDA were manufactured at the Janssen Pharmaceutical, West Deptford, NJ plant. Batch analysis data of three batches of drug substance used in manufacturing of drug product were provided. Validated analytical methods were provided in the DMF. A retest date of _____ has been established for the bulk Paliperidone drug substance by Janssen Pharmaceutical on the basis of _____ real time stability data for 3 commercial batches.

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

INVEGA™ (paliperidone) Extended Release Tablets will be marketed into bottles and blisters. The [] bottle are 75 mL/30 counts and 160 mL/350 counts with [] child resistant (CR) closure with desiccant pouch for all strengths (3 mg, 6 mg, and 9 mg, [] The blisters are []

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[] push-through blisters. The proposed packaging materials are well established for pharmaceutical use. The maximum recommended total daily dose is 12 mg/day. J&J PRD provided 18 months of stability data at 25° C/60% RH and 6 months stability data at 40° C/75% RH for registration batches of each strength. The applicant has requested 18 month expiration period (shelf life) for all strengths packaged in bottles (see memo dated 12-DEC-06 by Dr. Thomas Oliver). Based on the stability data, 18 month expiry is granted for INVEGA™ Extended Release Tablets.

Store up to 25° C (77° F); excursions permitted to 15 – 30° C (59 - 86° F) [see USP Controlled Room Temperature]. Protect from moisture. Keep out of reach of children.

C. Basis for Approvability or Not-Approval Recommendation

CMC section of this NDA is cross referenced to NDA 21-999. NDA 21-999 was approved on 19-DEC-2006. On this basis NDA 22-043 for INVEGA™ (paliperidone) Extended Release Tablets is recommended APPROVAL from the CMC standpoint.

This application qualifies for categorical exclusion from environmental assessment under the provisions in 21 CFR § 25.31(a).



Executive Summary Section

The Office of Compliance has found all manufacturing, testing, and packaging sites for drug substance and drug product acceptable.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

Chemist Name: Chhagan G. Tele, Ph.D.

Branch Chief Name: Ramesh Sood, Ph.D.

Project Manager Name: Keith Kiedrow, Pharm.D.

C. CC Block

See DFS.



CHEMISTRY REVIEW



Chemistry Assessment Section

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FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22043/000	Sponsor: JANSSEN-LP
Org Code : 130	1125 TRENTON HARBOURTON RD
Priority : 6S	TITUSVILLE, NJ 08560

Stamp Date : 27-JUN-2006	Brand Name : PALIPERIDONE
PDUFA Date : 27-APR-2007	Estab. Name:
Action Goal :	Generic Name: PALIPERIDONE
District Goal: 26-FEB-2007	Dosage Form: (EXTENDED-RELEASE TABLET)
	Strength : 3,6,9

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FDA Contacts:	K. KIEDROW	Project Manager	301-796-1924
	C. TELE	Review Chemist	301-796-1762
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation: ACCEPTABLE on 30-JAN-2007 by J. D AMBROGIO (HFD-322) 301-829073

Establishment : CFN : 2938701 FEI : 2938701
ALZA CORP
700 EUBANKS DR
VACAVILLE, CA 956889470

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile :	TTR	OAI Status: NONE
Last Milestone:	OC RECOMMENDATION	
Milestone Date:	11-JAN-07	
Decision :	ACCEPTABLE	



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Chemistry Assessment Section

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [] FEI : []

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DMF No: ADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUL-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2650104 FEI : 3002942061

JANSSEN ORTHO L.L.C.

CARR # 933 KM 0.1

GURABO, PR 007789626

DMF No: ADA:

Responsibilities: FINISHED DOSAGE PACKAGER



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Chemistry Assessment Section

30-JAN-2007

FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TTR OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 30-JAN-07
 Decision : ACCEPTABLE
 Reason : BASED ON PROFILE

Establishment : CFN : 9611011 FEI : 3002807361
 JANSSEN PHARMACEUTICA INC
 COUNTY CORK, , EI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 12-JUL-06
 Decision : ACCEPTABLE
 Reason : BASED ON PROFILE

Establishment : CFN : 9610028 FEI : 3002807336
 JANSSEN PHARMACEUTICA N V
 30, B-2340
 BEERSE, , BE

DMF No: AADA:

Responsibilities: INTERMEDIATE MANUFACTURER

Profile : CSN OAI Status: NONE
 Last Milestone: OC RECOMMENDATION
 Milestone Date: 13-JUL-06
 Decision : ACCEPTABLE

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

/s/

Chhagan Tele
2/2/2007 01:15:20 PM
CHEMIST

Ramesh Sood
2/2/2007 01:38:59 PM
CHEMIST