

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-999

CHEMISTRY REVIEW(S)

NDA 21-999

██████████
(paliperidone)
Extended Release Tablets

DIVISION DIRECTOR REVIEW #2

Applicant: Janssen, L.P.
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 08560

Indication: Treatment of Schizophrenia

Presentation: Supplied as 3 mg (white), 6 mg (beige), 9 mg (pink), 12 mg (dark yellow) ██████████ strength extended release tablets in ██████ bottles, 30 count or 350 count, with desiccant pouch, and in ██████ unit-dose blister packages, 100 count.

Original Submission: 30-NOV-2005

██████████ is a new molecular entity (NME) and contains a racemic mixture of paliperidone. Paliperidone is named (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4Hpyrido[1,2-a]pyrimidin-4-one and has a molecular formula of $C_{23}H_{27}FN_4O_3$ giving a molecular weight of 426.49 Da. Drug substance is satisfactory.

██████████ (paliperidone) Extended-Release Tablet utilizes OROS® osmotic drug-release technology designed to deliver the drug substance in a controlled manner over 24 hours. Drug product is satisfactory.

Requested expiration of ██████████ (paliperidone) Extended-Release Tablets for all presentations is granted for 24 months at 25° C (77° F); excursions permitted to 15 - 30° C (59 - 86° F).

In the action letter dated 29-SEP-2006, the applicant was advised to change the drug release specification, a change that would affect the release and stability specifications for the drug product. Evaluation of the stability data provided in the complete response 20-OCT-06 by the applicant indicated no significant change in drug release profiles during ██████████ storage for all strengths.

Overall Conclusion: From a CMC perspective, the application is recommended for **Approval**.

Blair Fraser, Ph.D.
Director
DPA I/ONDQA

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this page is the manifestation of the electronic signature.**

/s/

Blair Fraser
12/14/2006 07:48:06 AM
CHEMIST



NDA 21-999

**_____ (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: 21-999
2. REVIEW #: 2
3. REVIEW DATE: November 21, 2006
4. REVIEWER: Chhagan G. Tele, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	30-NOV-2005
Amendment N-000 (BC)	04-MAY-2006
Amendment N-000 (BC)	26-MAY-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N-014 (AZ)	20-OCT-2006

7. NAME & ADDRESS OF APPLICANT:

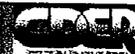
Name:	Janssen, L.P.
Address:	1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560
Representative:	Hedddie Martynowicz, Director, Regulatory Affairs
Telephone:	(609) 730-7028

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN-2004): Paliperidone
- c) Code Name/# (ONDC only): Oaliperidone
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S



CHEMISTRY REVIEW



Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1); (paliperidone) Extended-Release Tablets, 3 mg, 6 mg, 9 mg, and 12 mg Strengths.
10. PHARMACOL. CATEGORY: For the treatment of Schizophrenia.
11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 3 mg, 6 mg, 9 mg, and 12 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

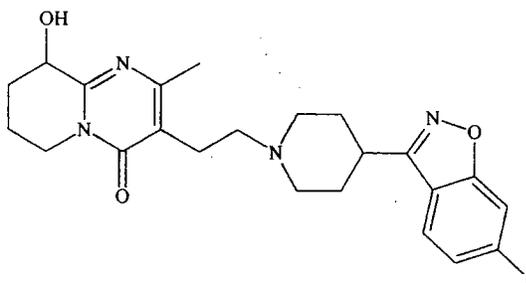
Non-Proprietary Name: (9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

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

Molecular Weight: 426.49

CAS registry #: 144598-75-4

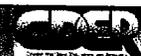
Structure:



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



CHEMISTRY REVIEW



Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	COMMENTS
18915	II	Janssen Pharmaceutica,	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
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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

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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)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Overall Recommendation Acceptable	08-SEP-06	S. Ferguson (HFD-322)
Pharm/Tox	Pending		



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Biopharm	Acceptable, provided that currently outstanding issues are adequately resolved, (e.g. agreement on dissolution and labeling).	12-SEP-06	Ron Kavanagh, Ph.D.
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	DMETS does not recommend the use of the proprietary name due to its potential to look similar to Meridia	23-JUN-06	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



The Chemistry Review for NDA 21-999

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

At this time NDA 21-999 for [REDACTED] (paliperidone) Extended Release Tablets is recommended **APPROVAL** from the CMC standpoint.

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)

The drug product [REDACTED] Extended Release Tablets (Paliperidone) are indicated for the treatment of Schizophrenia in adults. 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 paliperidone extended release (ER) tablets contain 3, 6, 9, 12 [REDACTED] of paliperidone drug substance. [REDACTED]

[REDACTED] 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 [REDACTED]. 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 [REDACTED] strengths. The composition of all components (USP/NF or Ph. Eur. grades) is common to all [REDACTED] strengths of the [REDACTED] Extended Release Tablets. The amount of active ingredient, paliperidone used in each tablet is proportional in each strength.

The core of the paliperidone ER tablet consists of 2 drug layers and a push layer. Drug Layer 1 contains [REDACTED] than Drug Layer 2, which provides the drug concentration gradient necessary to achieve an ascending release rate pattern. Additionally, the [REDACTED] push layer contributes to the drug delivery. The tablet core is surrounded by a [REDACTED] which enhances robustness of the drug release pattern. The semipermeable membrane, also referred to as rate controlling membrane, which is applied over the subcoat provides the main mechanism of drug delivery rate control as well as mechanical durability of the ER tablet. Two orifices are drilled on the drug layer dome of the tablet to provide exit ports for the drug. The color overcoat provides differentiation between the different dosage strengths. Print applied on the color overcoat along the side of the tablet offers additional product and dose differentiation. The tri-layer core OROS® Push-Pull™ system is designed to offer precise control of drug release over prolonged periods of



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time for both soluble and insoluble agents. The Push-Pull™ platform offers the versatility required to achieve the appropriate patterned drug delivery through the establishment and maintenance of an osmotic activity gradient across a semipermeable membrane. The osmotic gradient controls the flux of water through the membrane and into the core, which in turn controls the rate of drug delivered from the tablet. Since rate control resides within the semipermeable membrane, the drug substance is released essentially independently of environmental pH, agitation, and other conditions encountered in the gastrointestinal tract. In the gastrointestinal tract, the water-dispersible color overcoat erodes quickly. Water is then imbibed through the semipermeable, rate-controlling membrane into the core as a result of the osmotic activity gradient established across the membrane by the osmotic excipients (e.g., sodium chloride). As the drug layers hydrate, a gel-like suspension of paliperidone is formed in situ. As the push layer similarly imbibes water, the hydrophilic, osmotically active expansion polymers hydrate and the push layer begins to expand. Water is continuously imbibed into the trilayer core at a consistent rate controlled by the membrane. Delivery of the drug substance begins when the volumetric expansion of the osmotic push layer begins to “push” the drug suspension through the orifices, which are drilled through the membrane and subcoat on the first drug layer side of the elongated core. Since the volume of the paliperidone extended release tablet remains essentially constant during water imbibition, the delivery rate of drug is proportional to the rate at which water permeates the membrane and the drug concentration at the orifice. Such a rate of delivery can be expressed in terms of release duration (i.e., the time of complete delivery of drug from the tablet) or, more specifically, by t_{90} , which is defined as the time required to deliver 90 percent of the drug content from the tablet. Moreover, drug is expelled from the core continuously as the tablet travels along the gastrointestinal tract.

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 [redacted] Extended Release Tablets. Registration batches of drug product were manufactured at the commercial manufacturing site, Cork, Ireland at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches.

In-process tests for [redacted]

[redacted] The specifications for Tablets included Description, Appearance, Identification (HPLC and FTIR), Assay (HPLC), Degradation Products (HPLC), Drug release (HPLC), Content Uniformity (HPLC), Residual solvents (GC), and Water content. The batch analysis was provided for three batches of [redacted] 3 mg; [redacted] strengths and one batch of each, 6 mg, 9 mg, and 12 mg of strengths. Validated analytical methods were provided in the submission.

Registration (primary) stability studies have been conducted with paliperidone 3 mg, 6 mg, 9 mg, 12 mg, [redacted] ER tablets (formulations F039, F040, F041, F045 [redacted] 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 Division. Each strength has been packaged in 3 different packaging configurations: [redacted]

[redacted] blister; [redacted] 75-mL bottle with induction sealing and [redacted] closure and desiccant pouch (30 tablets) and a [redacted] 160-mL bottle with induction sealing and desiccant pouch (350 tablets). Three batches of the

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bracketing strengths of 3 mg [REDACTED], and 1 batch of the intermediate strengths (6 mg, 9 mg, 12 mg tablets), in 3 different packaging configurations were placed on stability for a total of [REDACTED] primary stability studies. In addition, all strengths were studied for photostability in blisters and in-use stability in bottles.

[REDACTED]

[REDACTED]

In the action letter dated 29-SEP-06 from the Agency to the applicant indicated that before the application may be approved, it will be necessary for applicant to address the following:

Biopharm recommended **following** dissolution specifications:

2 hours:

8 hours:

14 hours:

18 hours:

24 hours:

Accordingly following CMC comments were included in the action letter:

1. As noted in comment 1 above, please update the release and stability specifications for the paliperidone drug product to include the recommendation made by the Office of Clinical Pharmacology (OCP).
2. Please also provide a revised post-approval stability protocol that includes 0-18 hr test data points for dissolution and all stability data at the 0-18 hr time points for the drug product.

In response to the action letter dated 29-SEP-06, the applicant asked a teleconference to discuss the issues of dissolution specifications. A teleconference was held on 13-OCT-2006 with representatives of the Division of Psychiatry Products, Office of New Drug Quality Assurance and the J&JPRD Office of Translational Sciences to discuss the in vitro release specifications for paliperidone ER Tablets proposed by FDA in the 29-SEP-2006 Approvable Letter. We asked applicant to submit in vitro results of primary stability batches for 14, 16, 18, 20, 22, and 24 hours time points along with other request by OCP (meeting minutes in DFS). The applicant submitted complete response from CMC standpoint to the requests discussed in teleconference held on 13-OCT-06 in the amendment dated 20-OCT-06.

In the complete response from the applicant, the dissolution specifications for 0-2 hours: [REDACTED], 0-8 hours: [REDACTED] and 0-24 hours: NLT: [REDACTED] of label claim was agreed by the applicant. For the remaining time points (0-14 hours: [REDACTED] and 0-18 hours: [REDACTED] of label claim), specifications proposed by the OCP were not agreed by the applicant. The applicant proposed a specification of [REDACTED] at the 0-14 hours and no specification at the 0-18 hours time points. J&J provided rationale



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for these specifications using in vitro release data of phase 3 clinical lots, comparison in vitro release data and in vivo PK parameter (AUC, Cmax, Tmax), and stability data. The adequacy of data of phase 3 clinical lots, comparison in vitro release data and in vivo PK parameter (AUC, Cmax, Tmax) will be reviewed by the OCP. The stability data of the primary stability batches were provided by the applicant. The long term stability data for [redacted] of 3 batches [redacted] of the bracketing strengths (3 mg [redacted] tablets), and 1 batch each of the intermediate strengths (6 mg, 9 mg, and 12 mg tablets), in three different packaging configurations were provided.

The evaluation of stability data provided by the applicant indicates that there is no significant change in drug release profiles during the long term storage conditions after [redacted] for all five strengths manufactured at two proposed sites. Overall there is no stability or manufacturing site (manufacturing capability) issues involved for having wide ranges in drug release at 14 or 18 h time point.

[redacted]

[redacted]

Overall conclusion is that the recommended 14 h and 18 h specifications by OCP are supported by the stability data provided by the applicant. I discussed my evaluation of stability data with OCP reviewer, Dr. Ron Kavanagh. He agreed with my conclusions. Based on the stability data provided in initial submission and dissolution data provided in complete response [Amendment N-014 (AZ), dated 20-OCT-06] to the action letter dated 29-SEP-06], month expiry is granted for [redacted] Extended Release Tablets.

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 [redacted] Letters of Authorization to access this DMF were provided for cross-reference. The DMF [redacted] 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 [redacted] has been established for the bulk Paliperidone drug substance by Janssen Pharmaceutical on the basis of [redacted] real time stability data for 3 commercial batches.

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

[redacted] (paliperidone) Extended Release Tablets will be marketed into bottles and blisters. The [redacted] bottle are 75 mL/30 counts and 160 mL/350 counts with induction sealing and [redacted] closure with desiccant pouch for all strengths (3 mg, 6 mg, and 9 mg, 12 mg, [redacted] Tablets). The blisters are [redacted] push-through blisters. The proposed packaging materials are well established for pharmaceutical use. The maximum recommended total daily dose is [redacted] J&J PRD provided 18 months of stability data at 25° C/60% RH and [redacted] stability data at 40° C/75% RH for registration batches of each strength. The applicant has requested a 24 month expiration period (shelf life) for all strengths packaged in bottles. Based on the stability data provided in initial submission and dissolution data provided in



CHEMISTRY REVIEW



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complete response [Amendment N-014 (AZ), dated 20-OCT-06] to the action letter dated 29-SEP-06], 24 month expiry is granted for [REDACTED] 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

NDA 21-999 for [REDACTED] (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).

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.

5 Page(s) Withheld

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Draft Labeling

Deliberative Process

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CHEMIST

Ramesh Sood
11/21/2006 08:25:01 AM
CHEMIST



NDA 21-999

**_____ (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: 21-999
- 2. REVIEW #: 1
- 3. REVIEW DATE: August 1, 2006
- 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	30-NOV-2005
Amendment N-000 (BC)	04-MAY-2006
Amendment N-000 (BC)	26-MAY-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: XXXXXXXXXX
- b) Non-Proprietary Name (USAN-2004): Paliperidone
- c) Code Name/# (ONDC only): Oaliperidone
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S



CHEMISTRY REVIEW



Chemistry Review Data Sheet

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11. DOSAGE FORM: Extended Release Tablets
12. STRENGTH/POTENCY: 3 mg, 6 mg, 9 mg, 12 mg,
13. ROUTE OF ADMINISTRATION: Oral
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 Not a SPOTS product

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

USAN Name (2004): Paliperidone

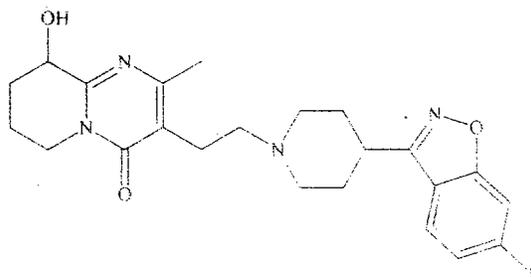
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Molecular Weight: 426.49

CAS registry #: 144598-75-4

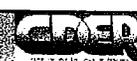
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At this time NDA 21-999 for [redacted] (paliperidone) Extended Release Tablets is recommended **APPROVAL** from the CMC standpoint.

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II. Summary of Chemistry Assessments

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

The drug product [redacted] Extended Release Tablets (Paliperidone) are indicated for the treatment of Schizophrenia in adults. 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 paliperidone extended release (ER) tablets contain 3, 6, 9, 12, [redacted] of paliperidone drug substance. The applicant [redacted]

[redacted] 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 [redacted]. 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 [redacted] strengths. The composition of all components (USP/NF or Ph. Eur. grades) is common to all [redacted] strengths of the [redacted] Extended Release Tablets. The amount of active ingredient, paliperidone used in each tablet is proportional in each strength.

The core of the paliperidone ER tablet consists of 2 drug layers and a push layer. Drug Layer 1 contains [redacted] than Drug Layer 2, which provides the drug concentration gradient necessary to achieve an ascending release rate pattern. Additionally, the [redacted] push layer contributes to the drug delivery. The tablet core is surrounded by a [redacted], which enhances robustness of the drug release pattern. The semipermeable membrane, also referred to as rate controlling membrane, which is applied over the subcoat provides the main mechanism of drug delivery rate control as well as mechanical durability of the ER tablet. Two orifices are drilled on the drug layer dome of the tablet to provide exit ports for the drug. The color overcoat provides differentiation between the different dosage strengths. Print applied on the color overcoat along the side of the tablet offers additional product and dose differentiation. The tri-layer core OROS® Push-Pull™ system is designed to offer precise control of drug release over prolonged periods of

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time for both soluble and insoluble agents. The Push-Pull™ platform offers the versatility required to achieve the appropriate patterned drug delivery through the establishment and maintenance of an osmotic activity gradient across a semipermeable membrane. The osmotic gradient controls the flux of water through the membrane and into the core, which in turn controls the rate of drug delivered from the tablet. Since rate control resides within the semipermeable membrane, the drug substance is released essentially independently of environmental pH, agitation, and other conditions encountered in the gastrointestinal tract. In the gastrointestinal tract, the water-dispersible color overcoat erodes quickly. Water is then imbibed through the semipermeable, rate-controlling membrane into the core as a result of the osmotic activity gradient established across the membrane by the osmotic excipients (e.g., sodium chloride). As the drug layers hydrate, a gel-like suspension of paliperidone is formed in situ. As the push layer similarly imbibes water, the hydrophilic, osmotically active expansion polymers hydrate and the push layer begins to expand. Water is continuously imbibed into the trilayer core at a consistent rate controlled by the membrane. Delivery of the drug substance begins when the volumetric expansion of the osmotic push layer begins to “push” the drug suspension through the orifices, which are drilled through the membrane and subcoat on the first drug layer side of the elongated core. Since the volume of the paliperidone extended release tablet remains essentially constant during water imbibition, the delivery rate of drug is proportional to the rate at which water permeates the membrane and the drug concentration at the orifice. Such a rate of delivery can be expressed in terms of release duration (i.e., the time of complete delivery of drug from the tablet) or, more specifically, by t_{90} , which is defined as the time required to deliver 90 percent of the drug content from the tablet. Moreover, drug is expelled from the core continuously as the tablet travels along the gastrointestinal tract.

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 [REDACTED] Extended Release Tablets. Registration batches of drug product were manufactured at the commercial manufacturing site, Cork, Ireland at the commercial scale using commercial method. The applicant provided Certificates of Analysis (CoAs) of all of these batches.

In-process tests for [REDACTED]

[REDACTED] The specifications for Tablets included Description, Appearance, Identification (HPLC and FTIR), Assay (HPLC), Degradation Products (HPLC), Drug release (HPLC), Content Uniformity (HPLC), Residual solvents (GC), and Water content. The batch analysis was provided for three batches of [REDACTED] 3 mg [REDACTED] strengths and one batch of each, 6 mg, 9 mg, and 12 mg of strengths. Validated analytical methods were provided in the submission.

Registration (primary) stability studies have been conducted with paliperidone 3 mg, 6 mg, 9 mg, 12 mg, [REDACTED] ER tablets (formulations F039, F040, F041, F045, [REDACTED] 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 Division. Each strength has been packaged in 3 different packaging configurations: [REDACTED]

[REDACTED] blister; [REDACTED] 75-mL bottle with induction sealing and [REDACTED] closure and desiccant pouch (30 tablets) and a white [REDACTED] 160-mL bottle with induction sealing and desiccant pouch (350 tablets). Three batches of the

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bracketing strengths of 3 mg [redacted] and 1 batch of the intermediate strengths (6 mg, 9 mg, 12 mg tablets), in 3 different packaging configurations were placed on stability for a total of [redacted] primary stability studies. In addition, all strengths were studied for photostability in blisters and in-use stability in bottles.

[redacted]

[redacted]

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 [redacted] Letters of Authorization to access this DMF were provided for cross-reference. The DMF [redacted] 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 [redacted] has been established for the bulk Paliperidone drug substance by Janssen Pharmaceutical on the basis of [redacted] real time stability data for 3 commercial batches.

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

[redacted] (paliperidone) Extended Release Tablets will be marketed into bottles and blisters. The [redacted] bottle are 75 mL/30 counts and 160 mL/350 counts with induction sealing and [redacted] closure with desiccant pouch for all strengths (3 mg, 6 mg, and 9 mg, 12 mg, [redacted] Tablets). The blisters are [redacted] push-through blisters. The proposed packaging materials are well established for pharmaceutical use. The maximum recommended total daily dose is [redacted] J&J PRD provided 18 months of stability data at 25° C/60% RH and [redacted]; stability data at 40° C/75% RH for registration batches of each strength. The applicant has requested a 24 month expiration period (shelf life) for all strengths packaged in bottles. Based on the stability data, 24 month expiry is granted for [redacted] 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.



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C. Basis for Approvability or Not-Approval Recommendation

NDA 21-999 for [REDACTED] (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).

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.

106 Page(s) Withheld

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/s/

Chhagan Tele
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CHEMIST

Ramesh Sood
9/20/2006 11:07:19 AM
CHEMIST