CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-264 Resubmission** **Sponsor's responses to FDA's Complete Response letter of August 25, 2008**
SERIAL NUMBER:	**0000**
DATE RECEIVED BY CENTER:	**February 3, 2009**
PRODUCT:	**Paliperidone palmitate (Invega® Sustenna™)**
INTENDED CLINICAL POPULATION:	**adults with schizophrenia (acute and maintenance treatment)**
SPONSOR:	**Ortho-McNeil-Janssen Pharmaceuticals, Inc.**
AGENT:	**Johnson & Johnson Pharmaceutical R & D, L.L.C., 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560**
DOCUMENTS REVIEWED:	**electronic submission**
REVIEW DIVISION:	**Division of Psychiatry Products (HFD-130)**
PHARM/TOX REVIEWER:	**Elzbieta Chalecka-Franaszek, Ph.D.**
PHARM/TOX TEAM LEADER:	**Aisar Atrakchi, Ph.D.**
PHARM/TOX SUPERVISOR:	**Barry Rosloff, Ph.D.**
DIVISION DIRECTOR:	**Thomas Laughren, M.D.**
PROJECT MANAGER:	**Kimberly Updegraff, R.Ph.**

Date of review submission to Division File System (DFS): June 17, 2009

Content of submission:

This is a resubmission to the NDA 22-264 addressing comments raised by the Division in the Complete Response letter dated August 25, 2008 including items agreed to during the Sponsor's meeting with the Division on November 21, 2008.

In this resubmission reference is made to the original NDA 22-264 for paliperidone palmitate (b) (4) that was submitted by Johnson & Johnson Pharmaceutical Research and Development, L.L.C. on October 25, 2007 for the treatment of schizophrenia in adults on behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc. Reference is also made to the Division's Complete Response letter dated August 25, 2008 and to Sponsor's meeting with the Division on November 21, 2008 to discuss the content of this resubmission.

During the November 21, 2008 meeting, the Sponsor indicated that the paliperidone palmitate development program included the use of a clinical 150 mg eq. dose of paliperidone palmitate. According to the Sponsor, the nonclinical development program provided in the submitted NDA 22-264 was conducted to support the 150 mg eq. dose in addition to the 25 to 100 mg eq. dose range. No additional nonclinical studies were conducted to further support the 150 mg eq. dose, and no further information or analyses were planned to be included in the resubmission; (b) (4) The Division confirmed acceptability of this plan for the Sponsor's resubmission.

Therefore, no new pharmacology/toxicology data were submitted and/or reviewed at present.

Executive Summary

I. Recommendations

A. Recommendation on approvability:

The nonclinical studies submitted in support of the original NDA 22-264 for paliperidone palmitate were sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor revise the drug substance specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) µg per injection (b) (4) ppm). This recommendation was communicated to the Sponsor in the CMC information request letter dated April 24, 2009.

B. Recommendation for nonclinical studies:

No additional nonclinical studies are recommended.

C. Recommendations on labeling:

The Sponsor has accepted the labeling changes proposed by the Division based on the recommendations of the pharmacology/toxicology reviewer in sections 8.1 (Pregnancy), 12.1 (Mechanism of action), 12.2 (Pharmacodynamics), and 13.1 (Carcionogenesis, Mutagenesis, Impairment of Fertility). (b) (4)

The following labeling text is a version that includes changes proposed by the Division and Sponsor and should be considered as final with the exception of paliperidone palmitate units (mg eq.) which are still under consideration by the Division.

8.1 Pregnancy

(b) (4)

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m^2 basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see Risperdal package insert).

There are no adequate and well controlled studies of INVEGA® SUSTENNA™ in pregnant women. INVEGA® SUSTENNA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

12.1 Mechanism of Action

Paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3)]*. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist.

12.2 Pharmacodynamics

Paliperidone is a centrally active dopamine Type 2 (D_2) receptor antagonist and a serotonin Type 2 ($5HT_{2A}$) receptor antagonist. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors, which may explain some of the other effects of the drug. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro.*

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

(b) (4)

Mutagenesis
Paliperidone palmitate showed no genotoxic potential in the Ames reverse mutation test or the mouse lymphoma assay. No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test.

Impairment of fertility
Fertility studies of paliperidone palmitate have not been performed.

In a study of fertility conducted with orally administered paliperidone, the percentage of treated female rats that became pregnant was not affected at doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose (12 mg/day) of orally administered paliperidone (INVEGA®) on a mg/m^2 basis.

The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31 mg/kg - 5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued).

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Please see Dr. Chalecka-Franaszek's pharmacology/toxicology review of the NDA 22-264 for details.

B. Nonclinical safety issues relevant to clinical use

The nonclinical studies submitted in support of the original NDA 22-264 for paliperidone palmitate were sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor sets a specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) (b) (4) to no more than (b) (4) µg per injection (b) (4) ppm).

Two genotoxic impurities (b) (4) and (b) (4) are present in the synthesis batches of paliperidone palmitate. Both (b) (4) and (b) (4) showed genotoxic properties in an *in vitro* Ames bacterial reverse mutation test and an *in vitro* chromosome aberration assay in human lymphocytes. Previous batches have contained impurities (b) (4) and (b) (4) up to levels of (b) (4) and (b) (4) ppm, respectively. According to the Sponsor, these values are well below the concentration limit of (b) (4) calculated on the basis of the maximum

recommended human dose (MRHD) of 100 mg eq. of paliperidone palmitate per person given as a monthly i.m. injection (corresponding with 100 mg eq./28 days or approximately (b) (4)./person/day), and the Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day. However, this reviewer concluded in the review of the original application that the acceptance criteria for these two impurities in the drug substance should be equal to or less than (b) (4) ppm because this value should be calculated based on monthly (not daily) dose.

In a Complete Response letter dated August 25, 2008, the Sponsor was informed about these recommendations and asked to "establish an acceptance criteria equal to or less than (b) (4) ppm for the two genotoxic impurities, (b) (4) and (b) (4) ".

It was noted that the Sponsor is reproducibly capable of producing "crude" batches of paliperidone palmitate with undetectable (b) (4) ppm) levels of both impurities. Therefore, the Sponsor should, as the first principle, control both impurities at levels as low as reasonably practicable (please see Dr. Chalecka-Franaszek's pharmacology-toxicology review of the NDA 22-264 dated August 25, 2008 for further information regarding impurities).

In this resubmission, new clinical data to support the 150 mg eq. dose strength were submitted. Based on this change in the MRHD it is recommended at this time that the Sponsor sets a specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) per injection (b) (4)

In the CMC information request letter dated April 24, 2009, the following recommendations were conveyed to the Sponsor:

1. The presence of a significant level of impurities (b) (4) and (b) (4) in sterile grade drug substance lots is unlikely as both species are likely to undergo (b) (4) Provide evidence that the (b) (4) of (b) (4) and (b) (4) are present at less than (b) (4) ppm in the drug substance.
2. Revise the drug substance specification to include a limit of NMT (b) (4) ppm for potential genotoxic impurities (b) (4) and (b) (4) and their respective (b) (4)
3. Provide full details of the analytical method used to detect the potential genotoxic impurities ((b) (4) and (b) (4) and their respective esters).

Please see the CMC letter and CMC review for full list of recommendations and information.

The Sponsor responded in a submission dated May 22, 2009. The reviewing chemist will evaluate the adequacy of the Sponsor's response. Please see the CMC review for additional information.

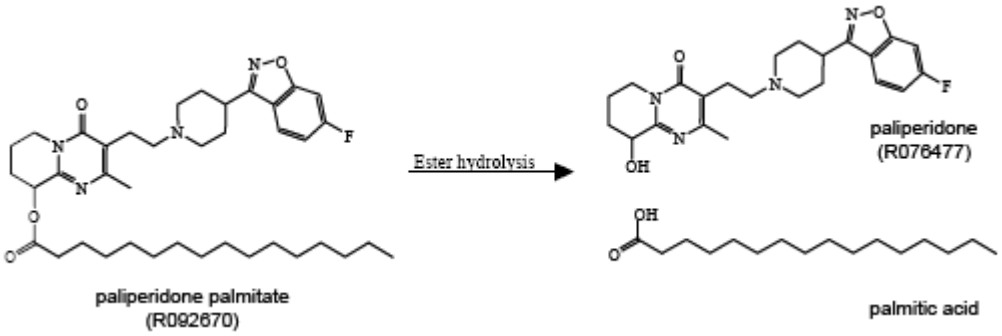
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-264
Review number: 2
Sequence number/date/type of submission: 0000/February 3, 2009/NDA resubmission
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: SPONSOR: Ortho-McNeil-Janssen Pharmaceuticals Inc.
AGENT: Johnson & Johnson Pharmaceutical R & D, L.L.C., 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560
Manufacturer for drug substance: Janssen Pharmaceutical Ltd., Cork, Ireland and Janssen Pharmceutica N.V., Beerse, Belgium
Reviewer name: Elzbieta Chalecka-Franaszek, Ph.D.
Division name: Division of Psychiatry Products
HFD #: 130
Review completion date: June 17, 2009

Drug:

Trade name: INVEGA SUSTENNA
Generic name: paliperidone palmitate
Code name: JNJ16977831; R092670
Chemical name: (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6, 7, 8, 9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate
CAS registry number: 199739-10-1
Molecular formula/molecular weight: $C_{39}H_{57}FN_4O_4$/664.9
Structure: Chemical structures of paliperidone palmitate and paliperidone and ester hydrolysis of paliperidone palmitate are shown below:



Relevant INDs/NDAs/DMFs: IND 67,356; DMF 20902; NDA 20-272 for Risperdal (risperidone), NDA 21-999 for Invega (paliperidone); NDA 22-043 for Invega

(paliperidone; for prevention of recurrence of schizophrenia), NDA 21-346 for Risperdal Consta (risperidone i.m.)

Drug class: Paliperidone palmitate injected intramuscularly is hydrolized to paliperidone, an atypical antipsychotic drug, which is an antagonist on serotonin 5-HT_{2A} and dopamine D_2 receptors.

Intended clinical population: adults with schizophrenia

Clinical formulation: An aqueous nanosuspension for injection with low solubility leading to extended release properties; strength: 25, 50, 75, 100, and 150 mg eq.

Route of administration: intramuscular injection (i.m.)

Studies reviewed within this submission: none

This resubmission includes a "Complete Response Document" that addresses the comments raised by the Division in the Complete Response letter dated August 25, 2008. It also includes a Chemistry, Manufacturing, Control (CMC) reviewer's guide that provides an overview of Module 3 updates presented in this Resubmission. As discussed during the November 21, 2008 meeting, this submission includes resubmission of the Pediatric Waiver request, an update to include Cork, Ireland, as an additional sterile drug substance manufacturing site and new clinical data to support the 150 mg eq. dose strength and the proposed initiation dosing regimen. It also contains a Safety Update document, patient case report forms, clinical study reports for R092670-PSY-3007 and R092670-PSY-3001, summaries of published clinical safety data, and updated draft Package Insert and package labeling. The package labeling also includes an Instruction For Use leaflet (b) (4) that is planned as a packaging component within each sample carton. That this updated draft labeling is intended to replace the labeling provided in the original NDA submission.

All pivotal studies submitted to the NDA 22-264 except toxicology and other studies were reviewed previously by Dr. Aisar Atrakchi under INDs 67,356 for paliperidone palmitate and Dr. Elzbieta Chalecka-Franaszek under the NDA 21-999 for paliperidone. Their reviews are available in the Division's file and DARRTS. In addition, the summaries of pivotal studies and conclusions taken directly from Dr. Atrakchi's and Chalecka-Franaszek's reviews are included in relevant sections of the review of the NDA 22-264.

Studies <u>not</u> reviewed within this submission: none

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Please see Executive Summary on page 2 of this review.

Unresolved toxicology issues (if any): Two genotoxic impurities (b) (4) and (b) (4) are present in the (b) (4) of paliperidone palmitate. Please see page 5 of this review for additional information.

Recommendations: The nonclinical studies submitted in support of the original NDA 22-264 for paliperidone palmitate were sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor revise the drug substance specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) µg per injection (b) (4) ppm). This recommendation was communicated to the Sponsor in the CMC information request letter dated April 24, 2009. The reviewing chemist will evaluate the adequacy of the Sponsor's response. Please see the CMC review for additional information.

Reviewer Signature: Elzbieta Chalecka-Franaszek, Ph.D. (signed electronically)

Supervisor Signature Aisar Atrakchi, Ph.D. (team leader) (signed electronically)

Concurrence Yes _ x__ No ___

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/s/

Elzbieta Chalecka-Franaszek
6/17/2009 12:08:57 PM
PHARMACOLOGIST

Aisar Atrakchi
6/18/2009 08:58:25 AM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
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PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**22-264**
SERIAL NUMBER:	**0000**
DATE RECEIVED BY CENTER:	**10/26/2007**
PRODUCT:	**Paliperidone palmitate (Invega Sustenna)**
INTENDED CLINICAL POPULATION:	**adults with schizophrenia** (b) (4)
SPONSOR:	**Ortho-McNeil-Janssen Pharmaceuticals Inc.**
AGENT:	**Johnson & Johnson Pharmaceutical R & D, L.L.C. 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560**
DOCUMENTS REVIEWED:	**electronic submission**
REVIEW DIVISION:	**Division of Psychiatry Products (HFD-130)**
PHARM/TOX REVIEWER:	**Elzbieta Chalecka-Franaszek, Ph.D.**
PHARM/TOX SUPERVISOR:	**Aisar Atrakchi, Ph.D.**
DIVISION DIRECTOR:	**Thomas Laughren, M.D.**
PROJECT MANAGER:	**Kimberly Updegraff, R.Ph.**

Date of review submission to Division File System (DFS): July 31, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

The preclinical studies submitted in support of the NDA for paliperidone palmitate are sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor sets a specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) per injection (b) (4) ppm). We note that the Sponsor is reproducibly capable of producing "crude" batches of paliperidone palmitate with undetectable (< 1 ppm) levels of both impurities. Therefore, the Sponsor should, as the first principle, control both impurities at levels as low as reasonably practicable (please see page 15 of the Executive Summary for further information regarding impurities).

B. Recommendation for nonclinical studies:

No additional preclinical studies are recommended.

C. Recommendations on labeling:

Note to the Sponsor: We have deleted the safety factor of 27 from the "Pregnancy" section and the safety factor of 1.7 from the "Impairment of fertility" section of the labeling. To help determine the validity of comparing the animal oral doses with i.m. doses in humans, please provide comparisons of exposure in humans receiving the maximum recommended oral and i.m. doses.

Note: All the doses of paliperidone palmitate are expressed as mg eq./kg, referring to mg paliperidone (base) equivalents (eq.)/kg body weight (f = 1.56). In the plasma and tissue samples, concentrations of paliperidone were measured unless stated otherwise.

8.1 Pregnancy

Sponsor's proposal:

(b) (4)

3 pp withheld in full immed. after this page as (b)(4) draft labeling.

paliperidone. There were no separate primary pharmacodynamics, secondary pharmacodynamics, safety pharmacology, or pharmacodynamic drug interaction studies submitted to the NDA 22-264 for paliperidone palmitate since pharmacology profile of paliperidone was evaluated during the development of p.o. paliperidone. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

General toxicology: The nonclinical toxicology program in support of paliperidone palimitate intramuscular formulation consisted of single-dose toxicity studies in dogs, pigs, and minipigs, repeat-dose toxicity studies in rats (3 months and two 6 months studies), dogs (6 months and 12 months studies), and minipigs (3 months study). These studies addressed both local tolerance at the i.m. injection site and systemic toxicity. Moreover, several nonclinical toxicology studies were previously conducted with p.o. paliperidone. The NDA 22-264 for i.m. paliperidone palmitate cross-references the toxicology study reports and nonclinical summaries submitted previously under NDA 21-999 for p.o. paliperidone (INVEGA). All pivotal toxicity studies were conducted in full compliance with the OECD Good Laboratory Practice guidelines.

Rats: In the 3 months and two 6 months repeat-dose toxicity studies in rats, paliperidone palimitate was injected i.m. once monthly at **0**, **20** (LD), **80** (MD), and **160** mg eq./kg (HD). Test article related mortalities occurred only in two HD females in the 3 months study; all animals survived in the 6 months studies. The following description is based on observations in the 6 months study in rats. However, in general, test article related effects were comparable in all studies. Clinical signs included ptosis and sedation at all dose levels. Body weight and body weight gain decreased in males and increased in females, with the greatest increases in the LD female group. Changes in food consumption in general paralleled changes in body weights in both sexes. Test article related changes in hematology and clinical chemistry parameters that reached statistical significance were small and may not have any toxicological significance. Mean weight of several organs/tissues were affected and correlated with histopathology findings: spleen weight was significantly and dose dependently increased in both sexes, kidney weight was significantly increased in HD males (but decreased in LD males), absolute adrenal weight was significantly and dose dependently increased in males (but relative weight decreased in females), and gonads weight of females were significantly reduced in the MD and HD groups compared to control. Gross morphological exam showed a white powdery deposit at injection site in all dose groups of both sexes. Mammary gland stimulation was observed in all female drug groups and occasionally in males. Histopathological exam revealed findings in the following organs/tissues: injection site, adrenals, kidneys, mammary glands, ovaries, prostate, seminal vesicles, spleen, testes, and pituitary. Similar to other toxicity studies, findings at injection site were those of inflammatory immunoreactive changes. In the adrenals, swollen cortical cells of *zona fasiculata* and *reticularis* were markedly increased in all male drug groups compared to control. Increased dilation of cortical renal collecting tubules was observed in HD males and females, and in all female drug groups relative to corresponding controls. There was female appearance (alveolar development) with increased secretion observed in mammary glands in all male drug groups; similarly, alveolar development and secretion

were increased in mammary glands of all female groups compared to controls. Focal hyperplasia of alveolar epithelium of mammary glands was seen in MD and HD males and in all female test article groups. Reduced cyclic activity was noted in the uterus. Male accessory sex organs showed low epithelium of ventral prostate, seminal vesicles, and coagulation gland. Increase in prolactin-immunoreactivie cells was observed in males. However, a decrease in these cell was seen in females. Serum prolactin was increased in all male test article treated groups and in HD females. The **MTD** was achieved in this study and in all repeat-dose toxicity studies in rats. Based on these results, the NOEL could not be determined due to presence of injection site reactions as well as other effects including histopathology at the LD of 20 mg eq./kg. However, **20** mg eq./kg may be considered the **NOAEL**.

Dogs: In the 6 months and 12 months repeat-dose toxicity studies in dogs, paliperidone palimitate was injected i.m. once monthly at **0**, **5** (LD), **20** (MD), and **80** (HD) mg eq./kg. However, the test article related injection site reactions led to decreasing the doses of 20 and 80 mg eq./kg to 10 and 40 mg eq./kg, respectively. The findings from pivotal 12 months repeat-dose toxicity study are described below. However, in general, test article related effects were comparable in all studies in dogs. The monthly injections were administered in the *m. semimembranosus/m. semitendinosus* of both hind legs using a 21 G needle. From the second dose onwards, the injections were given in the *m. biceps femoris* of both hind legs, because the *m. semitendinosus m. semimembranosus* were not healed yet.

Transient sedation was noted dose-dependently in all test article dosed groups. An acute, transient anaphylactic reaction (i.e., swollen eyelids, head and paws, red spots, sedation, decubitus, cyanosis and hyperpnea), probably related to the polysorbate 20 present in the vehicle, was seen in all animals of the vehicle and HD group after each injection. Some animals also had a slight anaphylactic reaction (i.e., swollen eyelids and/or sedation) after the first dose of 20 mg eq./kg/month. Slight decreases in body weight and food consumption were noted after single doses of 20 or 80 mg eq./kg/month.
There were no treatment-related effects on ECG, heart rate, ophthalmoscopy, and urinalysis. Systolic and diastolic blood pressure was decreased in the HD group.
Drug related changes in hematology and clinical chemistry were small, not dose dependent, and within the historical control range. Serum prolactin levels were increased in all dosed groups. Peak levels were mostly reached between 7 and 14 days after dosing, showing no clear-dose response relationship due to high variability. In the HD groups, the relative weights of the testes and ovaries were decreased, while the relative weight of the prostate was decreased at the MD and HD. The relative weight of the spleen was increased at the HD. This finding correlated with histopathology of the spleen (see below). A dose-related reaction was noted at all dose levels in the injection site as evidenced by hardening, swelling, abscess formation, subcutaneous nodules, and skin lesions. At necropsy, adhesions to the skin, white subcutaneous deposit, and nodules in the subcutis were noted as well. Slightly hardened iliac lymph nodes were observed macroscopically in a few animals of the LD and HD groups; this finding is likely related to the injection site changes.

The following description of the injection site findings at the microscopic level is taken directly from the Sponsor's toxicology summary: "The vehicle-dosed group exhibited only slight focal muscular degeneration with slight focally thickened endomysium. These findings were slightly to prominently increased in the test article-dosed groups. Perimysially located encapsulated histiocytic granulomas with necrotic center and granulocytic infiltration were prominent in all test article-dosed groups. These granulomas showed aspects of chronic inflammation and fibrosis. Volume- and dose-related differences were not found. Occasionally comparable inflammatory fibro-granulomatous reactions in the skin (subcutis) were seen near the injection site at all dose levels. In the iliac lymph nodes, particularly in high-dosed animals, pigmented macrophages were marginally to slightly more prominent than in vehicle control animals, as a reaction to the foreign material and the inflammation at the injection sites".

Additional histopathology findings included prostate atrophy in MD and HD males, slight resting appearance of the uterus and the absence of mitotic figures within the uterine epithelium at the HD, resting appearance of the ovaries, slightly increased number of prolactin-immuno reactive cells in the pituitary gland of HD females. These findings are prolactin-mediated. The splenic red pulp of high-dosed animals showed an increased accumulation of red blood cells due to the a-lytic properties of the active drug. The MTD was achieved in the 12 months study in dogs. A **NOAEL** could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.

Minipigs: In the 12 weeks local tolerance study of two paliperidone palmitate long acting injectable formulations in the minipig, intramuscular administration of the to be marketed F013 formulation of paliperidone palmitate by three consecutive injections once every 4 weeks at single **5** mg eq./kg dose (LD) resulted in slightly decreased general activity and slight tremors. The same formulation administered at **20** mg eq./kg (HD) showed slightly to moderately decreased general activity, slight tremors, excessive salivation, compulsive behavior, transient increase in white blood cells, neutrophiles, and monocytes, slight but transient decrease in red blood cell count, hemoglobin and hematocrit, and minimal decrease in plasma potassium and sodium. The following dose-related local reactions were noted at the injection sites: a dose-related minimal/slight inflammatory reaction with granulomata formation was observed in the HD groups, and a crystalline material was seen in the inflammatory cells. A **NOAEL** could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.

Genetic toxicology: The potential genotoxic effects of paliperidone palmitate were studied in an *in vitro* bacterial reverse mutation (Ames) test with *Salmonella typhymurium* and an *in vitro* mouse lymphoma assay. No genotoxic potential was identified. Moreover, a full battery of genotoxicity studies was previously conducted with p.o. paliperidone. These studies were submitted previously to the NDA 21-999 for p.o. paliperidone (please see pharmacology/toxicology reviews of the NDA 21-999 for more information). The studies with p.o. paliperidone included two *in vitro* bacterial reverse mutation (Ames) tests with *Salmonella typhimurium*, two mouse lymphoma, and an *in vivo* rat micronucleus test with p.o. dosing. All these genetic toxicology studies were

conducted in full compliance to GLP regulations. Paliperidone was not genotoxic in these studies.

Carcinogenicity: Carcinogenic potential of paliperidone palmitate was evaluated in the 24-month intermittent dose intramuscular carcinogenicity study in the rat. In general, the Agency requires studies in two rodent species for the carcinogenicity assessment. However, injected i.m. paliperidone palmitate is hydrolyzed to paliperidone. Marketed oral paliperidone (INVEGA) is the major active metabolite of marketed risperidone (RISPERDAL). Carcinogenicity studies with risperidone in rats and mice were conducted and previously reviewed by the Agency. Therefore, the Division agreed that only one species study (rat) was sufficient for the assessment of the carcinogenic potential of paliperidone palmitate.

Intramuscular administration of paliperidone palmitate for 104 weeks at dosages of **0**, **10** (LD), **30** (MD), and **60** mg eq./kg b.w./month (HD) resulted in increased mortality in male rats at MD and HD when compared to control groups (63% and 77% of animals died, respectively, compared to 49% in saline controls and 51% in vehicle controls). In female rats, minimally higher mortality was observed at the MD. Since the increase in mortality in female rats was not dose related, it was considered to be incidental. Dosing with paliperidone palmitate resulted in narrowing of the palpebral fissure in both sexes at all dose levels throughout the study. An increased incidence of small skin lesions located on subcutaneous tissue masses was observed in female rats at all dose levels and in MD and HD males. At terminal sacrifice, body weight in HD males was 9% and 11% less than that of the saline and vehicle control groups, respectively. In HD females, body weight was 11% and 13% less than that of the saline and vehicle control groups, respectively; therefore, the MTD was achieved in this study. There were no toxicologically significant changes in food consumption. A fibrohistiocytic inflammatory reaction was observed at the injection site mainly in HD and MD male and female rats. A prominent granulocytic reaction resulting in abscess formation was observed occasionally in HD animals of both sexes. Prolactin mediated effects were seen in both sexes, manifested by the slightly increased incidences of swollen pituitaries in both sexes and mammary gland secretion in males as well as the slightly lower incidence of cysts in the uterus in females. Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in male rats using the vehicle control and all treated groups but not using the saline control group. Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. The increased incidences of combined mammary gland tumors in male rats may be related to increased prolactin levels observed in male rats in this study. Prolactin levels were increased also in female rats. Neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors in female rats, except for the LD vs. the vehicle comparison of adenocarcinomas. However, the reviewer considers these findings to be of toxicological significance. There were no other test article related tumors.

Reproductive and developmental toxicology: Fertility and early embryonic development studies were not conducted with paliperidone palmitate. These studies were bridged to those conducted previously with p.o. paliperidone under NDA 21-999. Oral paliperidone was tested in male and female fertility studies in rats; please see the pharmacology/ toxicology review of the NDA 21-999 for more information.

The objective of the male fertility study was to investigate potential effects of paliperidone administered p.o. at **0**, **0.16** (LD), **0.63** (MD), and **2.5** mg/kg/day (HD) on male fertility. There were no test article related findings at dose level of 0.16 mg/kg/day. In rats dosed at the MD, clinical observations of subdued or decreased activity were noted from Week 1 to 5. Partially closed eyes were recorded from Week 2 to 13. Epididymides weights were lower by 6% than those of controls. In rats dosed at the HD, clinical observations were similar to those at the MD, and were recorded from Week 1 to 13 (subdued behavior or decreased activity) and Week 2 to 13 (both eyes partially closed). Body weights were moderately decreased (up to 6% lower than control). Food utilization was slightly reduced in Weeks 5 to 9 and 1 to 9. Epididymides weights were lower by 7% than those of controls. Findings in epididymides at the MD and HD were clearly not associated with any functional impairment and therefore not considered to be toxicologically significant. There were no effects on precoital interval. There were no effects on male fertility at any of the dose levels tested. There were no other test article related changes. The HD of **2.5** mg/kg/day was the **NOAEL** for fertility in male rats.

The objective of the female fertility study was to investigate any potential effects of paliperidone administered p.o. at **0**, **0.16** (LD), **0.63** (MD), and **2.5** mg/kg/day (HD) on female fertility and reproductive performance. There were no test article related findings at the LD level. Maternal toxicity was moderate in females receiving the MD as evidenced by ptosis, slightly decreased body weight gain during pregnancy, and decreased maternal corrected weight gain (defined as the maternal body weight on Day 14 of pregnancy minus body weight on Day 0 minus gravid uterus weight). During the preparing period, increased body weight gain and food consumption were noted. The pre-coital interval was increased from 3 (control) to 11 days, likely due to reduced estrus cycle activity. Pseudopregnancies were observed by vagina cytology in all females administered paliperidone. These pseudopregnancies are presumably a consequence of prolactin mediated effects. Copulation, fertility rates, and pregnancy parameters remained unaffected by treatment with paliperidone. In females receiving the HD, ptosis, lacrimation, increases in body weight gain and food consumption during the first week of treatment, and a slight reduction in food intake were noted. Moreover, the corrected maternal weight gain was decreased at the HD. These findings indicate that the selected HD was the MTD. The pre-coital interval was increased from 3 (control) to 10 days. Adverse effects on fertility and reproductive capacities at the HD were evidenced by increase in pre- and postimplantation loss (23% versus 14% in control group and 14% versus 8% in control group, respectively) resulting in decreases in the numbers of implantations (-13%) and live fetuses (-16%) as expressed per pregnant female, and lower weights of the gravid uterus. The LD of **0.16** mg/kg was the **NOAEL** for fertility

and reproductive capacity for female rats based on increased percoital interval (11 versus 3 days) and decreased by 20% corrected maternal weight at 0.63 mg/kg/day.

Paliperidone administered orally was tested in embryofetal development toxicity studies in rats and rabbits submitted to the NDA 21-999 (please see pharmacology/toxicology review of the NDA 21-999 for further details). Embryofetal developmental study in rabbits was not conducted with paliperidone palmitate. Paliperidone palmitate administered intramuscularly was tested in rats in the embryofetal development dose-range finding pilot and definitive studies.

In the pilot developmental toxicity study in rats, intramuscular administration of paliperidone palmitate at doses of **0, 20** (LD), **80** (MD), and **160** mg eq./kg b.w. (HD) resulted in ptosis in 6/8 rats of the MD and HD groups during a short period (Days 9-13 of pregnancy) overlapping with the anticipated period of main exposure. The mean maternal body weight gain was reduced in comparison with the control group by 35% and 55% in the MD and HD groups, respectively, during pregnancy Days 6-9. The corrected mean maternal weight gain was reduced by 30% at the MD and HD. Food consumption was reduced by 11% in MD and HD animals in comparison with the control group from pregnancy Day 14 to Day 20. There were no test article-related effects on pregnancy parameters including the numbers of corpora lutea, implantations, live fetuses, and pre- and postimplantation loss. A slight reduction (by 6%) in fetal weight was observed in the HD group. There were no test article-related effects on sex ratio or external malformations.

In the definitive embryofetal developmental study of paliperidone palmitate administered intramuscularly as a bolus on pregnancy Day 3, there were 22/24, 22/24, 23/24, and 24/24 pregnant female rats in the vehicle control and groups dosed at **0**, **20** (LD), **80** (MD), and **160** mg eq./kg (HD), respectively. All animals survived until scheduled sacrifice. Ptosis was observed on the day of dosing in all groups and between pregnancy Day 4 and 21 at the MD and HD. Body weight gain was decreased by 43% between pregnancy Days 6 and 9 in MD animals relative to controls. Body weight loss was observed between pregnancy Days 6 and 17 in HD animals. However, by the end of the study body weight gain was increased in the HD animals over the vehicle group. The corrected mean maternal weight gain was slightly reduced in the MD group and markedly reduced in the HD group. Food consumption was markedly decreased from pregnancy Day 8 to Day 17 in the HD group. There were no relevant changes in implantations, number of corpora lutea, pre- and post implantation loss, number of live and dead fetuses, mean litter size, early and late resorptions, and fetal sex ratio. Delayed ossification, including incomplete ossification of the hyoid and sternum bones, absent sternum bones and centra of cervical vertebrae, and reduced ossification of the metatarsal bones was observed in all groups. These findings were most pronounced in the HD group. There were no external malformations in any dose group. The incidence of malformed fetuses in the paliperidone palmitate treatment groups was 2/285, 1/284, and 2/275 at the LD, MD, and HD, respectively. In view of the isolated nature, these malformations are considered incidental. Therefore, **paliperidone palmitate was not teratogenic** under conditions of this study.

Prenatal and postnatal development study was not conducted with paliperidone palmitate. This study was bridged to the study conducted previously with p.o. paliperidone under the NDA 21-999 as a Phase IV commitment. Please see pharmacology/toxicology review No. 2 of the NDA 21-999 for further details.

Prenatal and postnatal developmental effects of orally administered paliperidone were initially assessed in the prenatal and postnatal developmental toxicity study in the rat submitted to the NDA 21-999. Doses used in this study were **0**, **0.08** (LD), **0.31** (MD), and **1.25** mg/kg/day (HD). Maternal treatment with paliperidone resulted in clinical signs of partially closed eyes with decreased activity during the gestation period. Decreased activity was observed also during the beginning of lactation. Body weight gain was slightly lower at the highest dose following the first day of dosing during gestation. However, after 7 days of dosing, mean body weight gains were similar to controls. There were no other test-article related findings. The **MTD** was not achieved in this study. The **NOAEL** for maternal treatment with p.o. paliperidone was the HD of **1.25** mg/kg/day, the highest dose administered. The same dose was the NOAEL for pup development, fertility, mating performance, or gestation of the F1 generation. Therefore, the dose selection was questionable for this study.

Based on the dose-range finding study, this reviewer concluded there was no reason to decrease the top dose of 2.5 mg/kg/day (the highest dose in the dose-range study) to the dose of 1.25 mg/kg/day in the first pivotal study because the dose of 2.5 mg/kg/day was not an MTD. At 2.5 mg/kg/day in the dose range-finding study, group mean maternal body weight and body weight gain were only slightly decreased (-6% and -8%, respectively). In conclusion, the dose selection for the prenatal and postnatal developmental toxicity study of p.o. paliperidone conducted in the rat was inadequate. This reviewer recommended that the prenatal and postnatal developmental study be repeated using higher doses and submitted during Phase IV of drug development.

The sponsor conducted the second prenatal and postnatal developmental study using higher doses of p.o. paliperidone as recommended by the Agency. The following document is the summary and conclusions taken directly from the review of final study report submitted to the NDA 21-999 as well as to IND 65,850, IND (b) (4), IND 67,356, IND (b) (4), and IND 76,952 on January 25, 2008 (received by CDER on January 28, 2008).

In the second prenatal and postnatal developmental toxicity study, paliperidone was administered p.o to mated female rats at **0**, **2.5** (LD), and **10** mg/kg b.w./day (HD) from Day 6 of gestation throughout lactation to investigate the effects on embryonic, fetal, and postnatal development, including behavior and reproductive performance of F1 generation, which was allowed to mature untreated. Although paliperidone was administered p.o. only at two dose levels, the study is considered acceptable because effects of lower paliperidone p.o. dosages had been evaluated in the first prenatal and postnatal developmental toxicity study in rats.

Marked clinical signs of partially closed eyes and decreased activity were observed in LD and HD females with a clear dose-relationship in severity and duration. Piloerection and labored breathing were observed during the initial dosing period (from Day 6 to Day 13 of gestation) in majority of LD and HD females. Food consumption was unaffected during the gestation period but decreased during the lactation period in both test article-treated groups relative to controls. Body weight gain was markedly decreased between Days 6 and 8 of gestation and between Days 1 and 4 of lactation in LD females. Body weight loss was observed in HD females during Days 6 and 7 of gestation. Body weight gain was decreased from Day 6 to Day 9 of gestation and between Days 1 and 4 of lactation in HD females. The duration of pregnancy was slightly increased in a dose related manner in test article treated females. Although pregnancy length was increased, there was no effect on parturition. There were no test article related effects on the number or sex of litter at birth, or maternal necropsy parameters. Dose-related reduction in survival of pups to Day 4 of age was observed in both treatment groups. In the LD group, half the litters had at least one dead pup and one litter was dead by Day 4 of lactation. In the HD group, thirteen litters had lost one or more pups and six litters were dead by Day 4 of age. Observations in pups that died early included the absence of milk in the stomach, pallor, and cold body. Survival of pups from Day 4 to Day 21 of lactation was unaffected. Body weight was decreased on Day 14 of age in LD and HD pups of both sexes and on Day 21 of age in HD females. A slight delay in sexual development was noted in HD F1 females as indicated by the mean day of vaginal opening (1.2 days longer than the controls). The percentage of litters with ears open, eyes open, righting reflex, startle response, and pupillary light reflex was not affected by the treatment with the test article. There were no test article-related mortalities, clinical observations, changes in body weight, behavioral development or reproduction in the F1 generation post-weaning that were considered by the Sponsor related to F0 maternal treatment. F2 generation was not assessed. In conclusion, the MTD for maternal treatment was achieved in this study based on decreased body weights in pregnant F0 females. Therefore, the study is considered adequate. The **NOAEL** for maternal treatment, pup survival between Days 1 and 4 of lactation, and pup development after maternal treatment is considered to be below the LD of **2.5** mg/kg/day. The **NOAEL** for behavioral development, fertility, or mating performance of F1 generation is considered to be the HD of **10** mg/kg/day.

B. Pharmacologic activity

Paliperidone palmitate (R092670) is a prodrug of paliperidone (R076477 or 9-hydroxy-risperidone). Paliperidone is the major active metabolite of risperidone. Paliperidone palmitate is formulated as an aqueous nansuspension with low solubility leading to extended release properties for once a month intramuscular (i.m.) injection. Paliperidone palmitate injected i.m. is hydrolyzed to paliperidone with low systemic exposure to paliperidone palmitate in laboratory animals and humans. Systemic concentrations of unhydrolyzed paliperidone palmitate in humans are below or marginally higher than the quantification limit of the bioanalytical method. Therefore, any systemic effect following the i.m. injection is most likely mediated through paliperidone. The pharmacological profile of paliperidone was evaluated during the development of paliperidone under NDA 21-999.

The exact mechanism of action of paliperidone, as well as other drugs used for treatment of schizophrenia, is unknown. However, it has been proposed that their therapeutic activity in schizophrenia is mediated through the central D_2 dopamine and 5-HT_{2A} serotonin receptor antagonism. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro*. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

C. Nonclinical safety issues relevant to clinical use

(b) (4) and (b) (4) Two genotoxic impurities (b) (4) and (b) (4) are present in the (b) (4) of paliperidone palmitate. Both (b) (4) and (b) (4) showed genotoxic properties in an *in vitro* Ames bacterial reverse mutation test and an *in vitro* chromosome aberration assay in human lymphocytes. Previous batches have contained impurities (b) (4) and (b) (4) up to levels of (b) and (b) (4) ppm, respectively. According to the Sponsor, these values are well below the concentration limit of (b) (4) calculated on the basis of the MRHD of 100 mg eq. of paliperidone palmitate per person given as a monthly i.m. injection (corresponding with 100 mg eq./28 days or approximately (b) (4) eq./person/day), and the Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day. However, this reviewer concluded that the acceptance criteria for these two impurities in the drug substance should be equal to or less than (b) (4) because this value should be calculated based on monthly (not daily) dose. The Sponsor was informed about these recommendations.

Genotoxic and carcinogenic degradants in paliperidone palmitate drug product:

(b) (4)

According to the chemistry reviewer, the Sponsor is scheduled to test for (b) (4) at the 24 month and 36 month pull points for the registration batches. In the action letter, the Sponsor was asked to include a test and an acceptance limit for (b) (4) in the drug product specification.

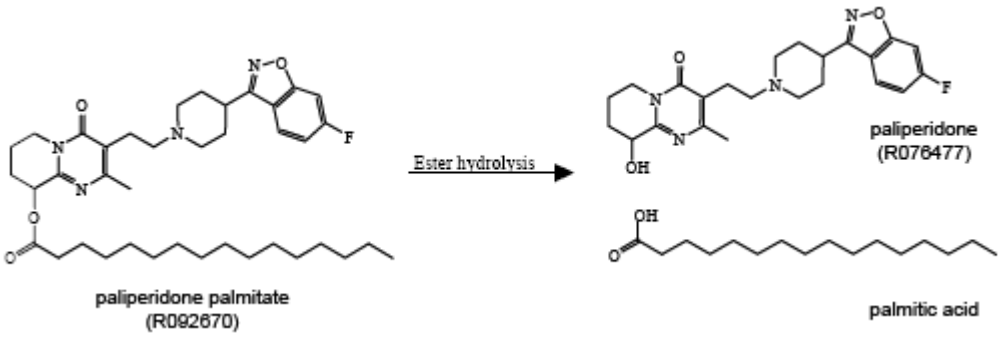
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-264
Review number: 1
Sequence number/date/type of submission: 0000
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: SPONSOR: Ortho-McNeil-Janssen Pharmaceuticals Inc.
AGENT: Johnson & Johnson Pharmaceutical R & D, L.L.C., 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560
Manufacturer for drug substance: Janssen Pharmaceutical Ltd., Cork, Ireland and Janssen Pharmceutica N.V., Beerse, Belgium
Reviewer name: Elzbieta Chalecka-Franaszek, Ph.D.
Division name: Division of Psychiatry Products
HFD #: 130
Review completion date: July 16, 2008

Drug:

Trade name: INVEGA SUSTENNA
Generic name: paliperidone palmitate
Code name: JNJ16977831; R092670
Chemical name: (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6, 7, 8, 9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-a]pyrimidin-9-yl hexadecanoate
CAS registry number: 199739-10-1
Molecular formula/molecular weight: $C_{39}H_{57}FN_4O_4$/664.9
Structure: Chemical structures of paliperidone palmitate and paliperidone and ester hydrolysis of paliperidone palmitate are shown below:



Relevant INDs/NDAs/DMFs: IND 67,356; DMF 20902; NDA 20-272 for Risperdal (risperidone), NDA 21-999 for Invega (paliperidone); NDA 22-043 for paliperidone (prevention of recurrence of schizophrenia), NDA 21-346 for Risperdal Consta (risperidone i.m.)

Drug class: Paliperidone palmitate injected intramuscularly is hydrolized to paliperidone, an atypical antipsychotic drug, which is an antagonist on serotonin 5-HT_{2A} and dopamine D_2 receptors.

Intended clinical population: adults with schizophrenia

Clinical formulation: An aqueous nanosuspension for injection with low solubility leading to extended release properties; strength: 25, 50, 75, and 100 mg eq. Composition of paliperidone palmitate eq. 100 mg/mL suspension for injection (F013 formulation) is shown in the following sponsor's table:

Component	Reference to Quality Standard	Function	Concentration (mg/mL)
R092670 sterile grade[a]	Company Specifications[b]	Active drug substance	156
Polysorbate 20	NF	(b) (4)	
Polyethylene glycol 4000	NF		
Citric acid monohydrate	USP		
Disodium hydrogen phosphate anhydrous	USP		
Sodium dihydrogen phosphate monohydrate	USP		
Sodium hydroxide	NF		
Water for Injection	USP		

[a] 156 mg R092670 (paliperidone palmitate) is equivalent to 100 mg R076477 (paliperidone) active moiety.

[b] Reference is made to Module 1 of this dossier where the letter authorizing the FDA to review the DMF in conjunction with this dossier is included.

Route of administration: intramuscular injection (i.m.)

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: All pivotal studies submitted to the NDA 22-264 except toxicology and other studies reviewed previously by Dr. Aisar Atrakchi under INDs 67,356 for paliperidone palmitate and Dr. Elzbieta Chalecka-Franaszek under NDA 21-999 for paliperidone. Their reviews are available in the Division's file and DARRTS. In addition, the summaries of pivotal studies and conclusions taken directly from Dr. Atrakchi's and Chalecka-Franaszek's reviews are included in relevant sections of this review.

Studies not reviewed within this submission: Selected dose-ranging and other supportive, non-pivotal studies that do not have impact on the evaluation of the safety of paliperidone palmitate administration have not been reviewed.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Paliperidone palmitate (R092670) is a prodrug of paliperidone (R076477 or 9-hydroxy-risperidone). Paliperidone is the major active metabolite of risperidone. Paliperidone palmitate is formulated as an aqueous nansuspension with low solubility leading to extended release properties for once a month intramuscular (i.m.) injection. Paliperidone palmitate injected i.m. is hydrolyzed to paliperidone with low systemic exposure to paliperidone palmitate in laboratory animals and humans. Systemic concentrations of unhydrolyzed paliperidone palmitate in humans are below or marginally higher than the quantification limit (b) (4)) of the bioanalytical method. Therefore, any systemic effect following the i.m. injection is most likely mediated through paliperidone. The pharmacological profile of paliperidone was evaluated during the development of paliperidone. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

2.6.2.2 Primary pharmacodynamics

Mechanism of action and drug activity related to proposed indication:

Paliperidone palmitate injected i.m. is hydrolyzed to paliperidone. The mechanism of action of paliperidone, as well as other drugs used for treatment of schizophrenia, is unknown. However, it has been proposed that their therapeutic activity in schizophrenia is mediated through the central D_2 dopamine and 5-HT_{2A} serotonin receptor antagonism. Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H_1 histaminergic receptors. Antagonism at receptors other than D_2 and $5HT_{2A}$ may explain some of the other effects of paliperidone. Paliperidone has no affinity for cholinergic muscarinic or β_1- and β_2-adrenergic receptors. The pharmacological activity of the (+)- and (-)- paliperidone enantiomers is qualitatively and quantitatively similar *in vitro*. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

2.6.2.3 Secondary pharmacodynamics

There were no separate secondary pharmacodynamics studies submitted to the NDA 22-264 for paliperidone palmitate. The secondary pharmacodynamics profile of paliperidone was evaluated during the development of p.o. paliperidone and was described in the pharmacology/toxicology review of the NDA 21-999 for p.o. paliperidone. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

2.6.2.4 Safety pharmacology

There were no separate safety pharmacology studies submitted to the NDA 22-264 for paliperidone palmitate. The safety pharmacology profile of paliperidone was evaluated

during the development of p.o. paliperidone and was described in the pharmacology/ toxicology review of the NDA 21-999 for p.o. paliperidone. Please see pharmacology/ toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

In summary, paliperidone tested in parallel with risperidone produced similar effects on behavior and other body functions in animals. Paliperidone and risperidone elevated serum prolactin levels. This effect was expected, given the known pharmacodynamics of the dopamine D_2 receptor antagonists. Safety pharmacology concerning the CNS was assessed within the toxicology testing program. As with risperidone, paliperidone induced palpebral ptosis, general sedation and depression of motor activity. Cardiovascular safety pharmacology studies indicated inhibition of the potassium channel in the HERG model with IC_{50} of 1.2 μM. Action potential duration was increased by paliperidone in many models at concentrations of 1 μM or above. Early depolarizations and TdPs were induced occasionally at higher concentrations in some models. In several animal studies in pigs, dogs and rats, paliperidone increased heart rate and decreased blood pressure. QTc interval was slightly prolonged in some studies in dogs. There were no effects on respiration in the safety pharmacology study. Based on safety pharmacology and other data, the CNS and cardiovascular system are targets of paliperidone toxicity.

2.6.2.5 Pharmacodynamic drug interactions

There were no separate pharmacodynamic drug interaction studies submitted to the NDA 22-264 for paliperidone palmitate. The pharmacodynamic drug interaction profile of paliperidone was evaluated during the development of p.o. paliperidone and was described in the pharmacology/toxicology review of the NDA 21-999 for p.o. paliperidone. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Note: The summary of the available data on the absorption, distribution, metabolism and excretion (ADME) of the prodrug paliperidone palmitate and its active drug paliperidone provided below is taken directly from the Sponsor's NDA 22-264 submission (with some modification):

Paliperidone palmitate (R092670) is formulated as an aqueous nanosuspension with prolonged release properties for intramuscular (i.m.) injection. In humans, as well as in

laboratory animals, i.m. injected paliperidone palmitate is converted to paliperidone (R076477 or 9-hydroxy-risperidone) with minimal systemic exposure to paliperidone palmitate.

The pharmacokinetics of paliperidone palmitate and its active drug paliperidone have been examined in both *in vitro* and *in vivo* test systems. *In vitro* studies were conducted with blood, plasma, hepatocyte suspensions, primary hepatocyte cultures, liver microsomes, and 12,000 x g supernatants of male and female Wistar rats, male Beagle dog and man. In addition, human liver subcellular fractions, 12,000 x g fractions of human kidney and muscle tissue and plasma of hepatic impaired patients was used. *In vivo* studies were conducted in Sprague-Dawley rats, Wistar rats, Beagle dogs, Belgian Stress-negative (BN) pigs and Göttingen minipigs. In the nonclinical toxicology studies, the same species and strains were used. A number of studies were conducted in compliance with the Good Laboratory Practices (GLP) of the Organization for Economic Co-operation and Development (OECD). As paliperidone palmitate is converted to paliperidone with minimal systemic exposure to paliperidone palmitate, this pharmacokinetics program on the i.m. administered paliperidone palmitate prodrug for paliperidone therefore builds on the large dataset of nonclinical pharmacokinetic studies previously generated with oral (p.o.) paliperidone.

Absorption and Plasma Kinetics

During the development of paliperidone palmitate, several formulations were tested in order to obtain an optimal long lasting formulations. In support of the exploration of the human pharmacokinetic properties of the formulation concept of micronized paliperidone palmitate suspended in an aqueous formulation for intramuscular injection, the concept was tested in 6-month rat and dog toxicity studies. Peak plasma concentrations of paliperidone were attained within 1 or 2 weeks after i.m. dosing with paliperidone palmitate but remained fairly constant thereafter for the rest of the 4-week dosing interval. The human pharmacokinetic trial with the similar clinical F001 formulation (i.e. the first clinical formulation) revealed equally that the release of paliperidone from this formulation was too slow for a monthly injection interval. The formulation F001 was therefore not considered for further development.

The pharmacokinetics of paliperidone following formulation F004 (the second clinical formulation), with (b) (4) of paliperidone palmitate, were studied after single and repeated i.m. dosing in rats, dogs and pigs. The pharmacokinetic profile of paliperidone following the F004 formulation was consistent with administration intervals of 1 month: peak plasma concentrations were attained within 1 or 2 weeks following injection and slowly declined thereafter. Steady state was reached already with the 2nd administration. The doses used in the toxicity studies produced a dose-proportional increase in AUCs in rats, dogs and pigs. No relevant sex differences were observed.

Measurable concentrations of paliperidone palmitate prodrug in plasma (LLOQ 0.2 ng/mL) were observed for the first 8 days after a single dose of F004 in dogs at 5 mg eq/kg. The average of the highest paliperidone palmitate plasma concentrations was about

250-fold lower than the average C_{max} value for paliperidone. Formulation F011, investigated in phase 1, 2 and 3 clinical trials, was tested in single and repeat dose i.m. studies in rats, dogs and minipigs. The prolonged release profile of paliperidone produced after i.m. injection of F011 was comparable to that of F004. Intravenous (i.v.) and intralipomatous (i.l.) injection of F011 in minipigs was also performed to investigate the effect of a possible dosing error on the pharmacokinetic profile of paliperidone. On average, the peak plasma concentrations of paliperidone following i.l. administration were about 20% lower than after i.m. administration. Following i.v. administration of paliperidone palmitate, the plasma concentrations of the prodrug and the active drug paliperidone dropped at a similar rate, with a half-life of 6 days for paliperidone. Since the paliperidone half-life following an immediate release i.m. injection in minipigs was only 0.2 days, it was apparent that the release of paliperidone even after an i.v. injection of paliperidone palmitate still provided a prolonged release of paliperidone.

Formulation F011 exhibited an acceptable stability profile at refrigerated conditions, but showed an increase in (b) (4) content due to (b) (4) at higher temperatures. In order to inhibit this (b) (4), was added, resulting in the final clinical formulation F013. The F013 formulation was used in further Phase 3 clinical trials and is also the formulation intended for marketing.

The to-be-marketed formulation F013 was evaluated in rats and minipigs. The pharmacokinetic profile of paliperidone following F013 was similar to that following F011. Paliperidone palmitate was measured in rats after 56 and 336 days of repeated dosing with the F013 formulation. The paliperidone palmitate exposure (AUC) in this study represented 2.9 to 6.7 % of the paliperidone exposure. The overview of the studied formulations is shown in the following Sponsor's table:

Table 1: Overview of the Studied Formulations

	Formulation (mg/mL)							
Ingredients (mg)	**F001**	**F004**	**F007**	**F008**	**F009**	**F010**	**F011**	**F013**
Paliperidone palmitate	(b) (4)							
Polysorbate 20								
PEG 4000								
(b) (4)								
Citric acid monohydrate								
Na_2HPO_4 anhydrous								
$NaH_2PO_4.H_2O$								
NaOH								
(b) (4)								
Water for injection								
(b) (4)								
(b) (4)								

Distribution

In a quantitative whole body autoradiography (QWBA) study male rats were dosed with labeled paliperidone palmitate (^{14}C-paliperidone palmitate and paliperidone- ^{3}H-palmitate). Following sectioning, a white deposit was observed in the injection site muscle, which was probably due to an aggregation of radiolabelled paliperidone palmitate particles after injection. This agglomerate served as the depot from where the drug substance was released. The dissociation of the ^{14}C- and ^{3}H-moieties and the subsequent differential disposition of the moieties in the muscle, confirmed the muscle as a first site of hydrolysis. Inside the core of the agglomerate there was no indication of hydrolysis. Around the core there was a small layer with lower radioactivity probably serving as the interface between the nanoparticles and the surrounding injection site tissue.

The tissue distribution in dogs was studied with the F001 and the F004 formulations. After 6 months of dosing with the F001 formulation, highest tissue to plasma ratios of paliperidone were found in the lymph nodes (tissue to plasma (T/P) ratio of 119) and in the injection site muscle (T/P ratio up to 91). After 12 months of dosing with the F004 formulation, highest concentrations were found at the injection site muscle (mean T/P-ratio of 78). The T/P-ratios in kidney, lymph nodes, lung and liver were on average 6. Concentrations in brain and in non-injected muscle were comparable to somewhat lower than in plasma. In minipigs, between 1 week and 5 months after a single i.m. dose of F013 formulation at 5 and 20 mg eq./kg, T/P-ratios of paliperidone in the injection site muscle ranged from 71 to 489.

No data on the plasma protein binding and distribution of paliperidone palmitate in blood cells were generated. Studies on placental transfer were not conducted with paliperidone palmitate or paliperidone. Studies with risperidone indicated that placental transfer of paliperidone, a major risperidone metabolite, was limited.

Metabolism

The ester hydrolysis of the prodrug paliperidone palmitate to palmitic acid and the active compound paliperidone was studied *in vitro*. The *in vitro* hydrolysis was most extensive in liver cells and subcellular fractions; injection muscle showed also significant hydrolysis capacity; the extent of hydrolysis in blood was limited in dog and human, but higher in the rat. There was stereoselectivity in hydrolysis of the ester favoring the formation of the (+)-enantiomer over the (-)-enantiomer. Results of a chiral inversion experiment indicated that there was some extent of chiral inversion of the (+)-enantiomer to the (-)-enantiomer, but the extent of chiral inversion in liver-derived matrices of human was minor. Chiral inversion from the (-)-enantiomer to the (+)-enantiomer was not observed. The involvement of serine esterases in the hydrolysis of paliperidone palmitate was demonstrated, but a possible role of other esterases in the hydrolysis cannot be ruled out. There was no involvement of oxidoreductase enzymes (cytochrome P450 enzymes) in the hydrolysis.

All other *in vitro* and *in vivo* metabolism data are based on the experiments conducted with paliperidone.

Excretion

After the ester hydrolysis of paliperidone palmitate to paliperidone and palmitic acid in the muscle, paliperidone enters the blood circulation from where it is eliminated via metabolism and excretion in feces and urine.

Pharmacokinetic drug interactions

All data on pharmacokinetic drug interactions are based on the studies performed with paliperidone.

2.6.4.2 Methods of Analysis

see under individual study reviews

2.6.4.3 Absorption

See page 20 of this review

2.6.4.4 Distribution

1. Study title: Injection site and tissue distribution of ^{3}H radioactivity and ^{14}C radioactivity in male Sprague Dawley rats following single intramuscular injection of an aqueous suspension of ^{14}C-paliperidone palmitate (^{14}C-R092670) and paliperidone ^{3}H-palmitate (^{3}H-R092670) at 10 mg paliperidone equivalents (Study No. R092760/FK5747)

Tissue distribution of paliperidone palmitate was studied in Sprague Dawley rats using quantitative whole-body authoradiography (QWBA). Rats received a single intramuscular injection of an aqueous suspension of paliperidone palmitate (10 mg paliperidone eq./animal) radiolabel led with a 1:40 mixture of ^{14}C paliperidone palmitate and paliperidone ^{3}H palmitate. One rat was sacrificed and sectioned for QWBA at each selected time point after dosing up to 21 days post dose. Sections were exposed for 1 hour or for 4 days to two types of image plates to capture either only ^{14}C-related radioactivity or total radioactivity (^{14}C plus ^{3}H). Radioluminograms obtained after image plate scanning were analyzed quantitatively. Blood radioactivity was determined with liquid scintillation counting.

A macroscopically visible white deposit was observed at the injection site in the muscle. This area contained substance particles that aggregated after injection of the formulation. The radioactivity at the injection site muscle was very high. ^{3}H-related palmitate radioactivity and ^{14}C paliperidone radioactivity were detected at different concentrations in the areas around the white deposits. The gradient of radioactivity indicated that the drug substance was released into the surrounding tissue from the deposits. Based on the increase of the $^{3}H/^{14}C$ concentration ratio with time, it can be concluded that the

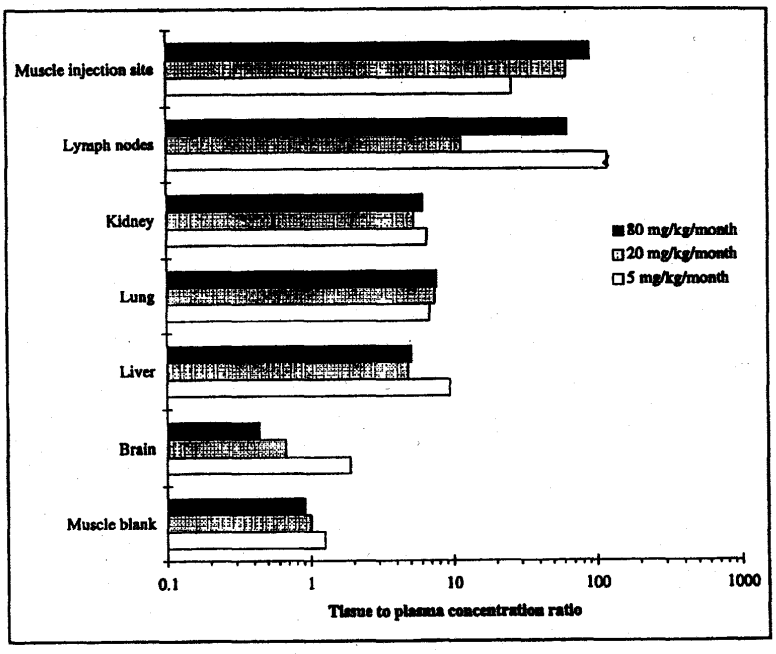
palmitate was retained longer at the injection site as compared to the paliperidone. The highest ^{14}C-paliperidone radioactivity level was observed in intestinal content, urinary content, salivary gland, prostate, liver, kidney, spleen, and adrenal glands. The general tissue distribution of ^{14}C paliperidone-related radioactivity following i.m. administration was similar to that observed after an oral dose of ^{14}C paliperidone in rats (please see the review of the NDA 21-999 for oral paliperidone for more information).

2. Study title: Toxicokinetics and tissue distribution of 9-hydroxy-risperidone (R076477) in beagle dogs in a 6-month intramuscular toxicity study (Exp. No. 3849) on an aqueous depot suspension formulation of the prodrug R092670 at 2.5, 10 and 40 mg (R076477-eq.)/kg/month for the first dose and 5, 20 and 80 mg (R076477-eq.)/kg/month from the 2nd until the 6th administration (Study No. FK2206).

The tissue distribution of paliperidone (R076477) was studied in male and female beagle dogs in a 6-month i.m. toxicity study on an aqueous depot suspension F001 formulation of the paliperidone palmitate. The animals were dosed once a month at 2.5, 10, and 40 mg (R076477-eq.)/kg for the first dose and at 5, 20, and 80 mg (R076477-eq.)/kg from the 2nd until the 6th administration. Plasma and tissue samples were analyzed for the active drug paliperidone by a RIA-method. Peak plasma concentrations after the third dose were 56.8+ 3.0 ng/mL, 220 + 40 ng/mL, and to 912 + 218 ng/mL at 5, 20, and 80 mg/kg, respectively. Comparable mean peak plasma concentrations were observed after the sixth dose administration: 52.5+ 27.1 ng/mL, 181 + 33 ng/mL, and 638 + 166 ng/mL. Peak plasma concentrations as well as $AUC_{0\text{-}504\ h}$-values increased in general dose-proportionally. After the 6th dose administration, highest tissue to plasma concentration ratios were found for lymph nodes (119 at 5 mg eq./kg) and in the injection site muscle (25.8, 62.1, and 90.9 at 5, 20, and 80 mg/kg, respectively). Mean tissue to plasma concentration ratios of about 6.6 were found for kidney, lung and liver. Ratios amounting to approximately 1 were calculated for brain and non-injected muscle.

Based on the Sponsor's calculations, in general, tissue concentrations increased more than dose-proportionally from the 5- to the 20-mg eq./kg dose level (about 4.6 to 7.3 times), except in liver and brain where the increase was less than dose-proportional and in lymph nodes where a decrease was seen (of about 1.5 times). From the 20- to the 80-mg/kg dose level, a less than dose-proportionally to a fairly dose-proportional increase was observed, except for muscle and lymph nodes, where the increase was proportional to more than dose-proportional (about 4.6 and 18.6 times, respectively).

Mean (N=4) tissue to plasma concentrations ratios of paliperidone in beagle dogs at 744 h after the six dose administration of the aqueous depot suspension formulation of paliperidone palmitate in a six-month intramuscular chronic toxicity study is shown in the following Sponsor's figure:



3. Study title: Toxicokinetics and tissue distribution of paliperidone (9-hydroxy-risperidone, R076477) in the beagle dog in a twelve-month intermittent repeated dose intramuscular toxicity study (Exp. No. 4692) on an aqueous depot suspension formulation of paliperidone palmitate (R092670) at 5, 20 and 80 mg paliperidone-eq./kg/month for the first dose and 5, 10 and 40 mg paliperidone-eq./kg/month for the 2nd until the 12th administration (Study No. FK3024).

Note: The following summary is taken directly from the Sponsor's report with some modifications.

"The toxicokinetics and tissue distribution of paliperidone (9-hydroxy-risperidone, R076477) in the beagle dog were studied in a twelve-month intramuscular toxicity study (Exp. No. 4692) on an aqueous depot suspension formulation of paliperidone palmitate (R092670) at 5, 20 and 80 mg paliperidone-eq./kg/month for the first dose and 5, 10 and 40 mg paliperidone-eq./kg/month for the 2nd until the 12th administration. In general, for each dose level and for each dose administration the plasma concentration versus time profiles showed high interindividual variability, but were more comparable intra-individually. Over different dose levels and different administrations, maximum plasma concentrations were generally achieved within 48 h following administration. From peak time on, plasma concentrations gradually decreased. Plasma concentrations reached steady-state after the first administration. From the 5 to 20 mg/kg or to 10 mg/kg dose groups the $C_{average}$ and AUC-values increased slightly less than proportionally with the administered dose. From the 20 to 80 or 40 mg/kg dose groups the parameters increased fairly dose-proportionally. The paliperidone concentrations in tissues taken at necropsy, were subjected to a high interindividual variability. The tissue to plasma concentration ratios (T/P-ratio), however, were well comparable between all dose levels. Highest concentrations were found at the injection site muscle (mean T/P-ratio is 78). The concentrations in kidney, lymph nodes, lung and liver were on average 6 times the

corresponding plasma concentrations. Concentrations in brain and in non-injected muscle were comparable to somewhat lower than in plasma. The 2-fold increase in dose - from the 5 to 10 mg/kg dose groups – produced a more than dose-proportional increase of paliperidone concentrations in liver and lung (about 11 times). The 4-fold increase in dose - from the 10 to 40 mg/kg dose groups – produced a dose-proportional increase in tissue concentration (about 5 times)".

4. Study title: R092670: Single Dose Toxicity in Minipigs by Intramuscular Route with Various Recovery Periods (Study No. TOX 7209)

Note: The following summary is based on the summary of the Sponsor's report.

This study was designed to evaluate local toxic effects induced by a single intramuscular injection of paliperidone palmitate in male Gottingen minipigs (15 animals per sex per group) and to evaluate the reversibility of these effects over a period of 7 days, 1, 2 or 3 months (subgroups A, B, C, and D-E, respectively, representing the different days of necropsy). As macroscopic changes were still observed 3 months post dose (subgroup D), an extra recovery period of 8 weeks was included for subgroup E. In addition at each necropsy, the tissue concentration at the injection site and the concentration of paliperidone in plasma were analyzed.

Methods: Group 1 was treated with 1.5 ml placebo per injection site. Group 2 was treated with 0.38 mL paliperidone palmitate per injection site. Group 3 was treated with 1.5 ml paliperidone palmitate (100 mg/mL). Once on Day 1, two intramuscular injections were given in the *muscle biceps femoris* (bilateral: left and right) at a dose level of 0 mg/kg in Group 1, 5 mg/kg in Group 2, and 20 mg/kg in Group 3. Clinical signs were recorded daily. Injection sites were scored daily until Day 41, after which the injection sites were scored weekly. Body weights were recorded on arrival, on the day of tattooing, on re-allocation, on Day 1, and weekly thereafter until necropsy. Remains of food were estimated daily from Day -7 and until the day of necropsy for each animal. Blood samples for analysis of creatinine kinase and toxicokinetic evaluation were taken from all animals prior to termination. At termination, animals were sacrificed and a sample was taken from the left muscle biceps femoris injection site for toxicokinetics analysis of paliperidone. At the same time each intramuscular injection site with skin, underlying subcutaneous tissue and *muscle biceps femoris* (from the right site) were sampled for histopathology.

Results: No adverse clinical sims were seen in Group 1. In Group 2 on Day 15, one animal was observed standing unsteadily on its hind legs and with signs of prolapse of the rectum. In addition, two animals were obseived shaking and observed sensitive to sound and touch. In Group 3, soft faeces or diarrhoea and/or reduced appetite were observed on some of the animals at different timepoints in the period between Day 4 and Day 17 of the study. From Day 11, clinical observations as slow movements and reactions and less activity were seen in all aniinals of Group 3. Furthermore, except from animal No 44, slow reactions on sounds were seen in all animals of Group 3. Shivering, unsteadily standing or poor balance were seen in most of the animals in Group 3. In

addition on one occasion, one animal was observed hiding its head in the hay, whereas one animal was jumping around in the pen, whining and shaking, and one animal was standing unsteadily with its head in the corner of the pen, and on another occasion one animal was running around in the pen, hitting its head into the wall. In general, clinical signs were seen in Groups 2 and 3, with extending severity, incidence and duration in Group 3 from Day 11 to Day 16 in the study and further until Day 22, however, with less severity. As no clinical signs were seen in Group 1 and as clinical signs were more severe in Group 3 than in Group 2, the clinical signs were considered being related to treatment.

No reactions were observed at the injection sites (left or right side) in Group 1 at any time point during the study. In Group 2, swelling at the injection sites was observed in two animals and in Group 3 swelling was observed in six animals on a few days. Generally, the most swellings at the injection sites were seen from Day 8 to Day 15. Body weight was statistically significantly lower in Group 3 on Day 15 and on Day 29. Body weight gain was statistically significantly lower in Group 3 from Day 1-29 compared to Group 1. These findings were considered test item-related.

From Day 1 to Day 16 food remains were observed in one animal in Group 2 and in four animals in Group 3 on a few occasions. Food remains were observed during periods, where, in addition, possible test item-related adverse clinical signs, reduced body weight gain and local reaction at the injection sites w'ere observed and therefore considered being related to treatment. No significant differences were observed between the groups on the parameter creatinine kinase. The concentrations of paliperidone in the muscle at the injection site were much higher than those in plasma.

No macroscopical changes were seen in Group l. Macroscopic findings showed a white focus in all tluee injection sites in the skeletal muscle in Groups 2 and 3 in animals sacrificed on Days 8, 29 and 57, whereas in animals sacrificed on Day 92, a white focus was observed in two of the animals in the skeletal muscle in Group 3 and in one animal in Group 2. Animals sacrificed on Day 149 showed no changes in any of the injection sites. In general, no macroscopic reaction was observed in the skeletal muscle surrounding the white foci seen in most of the injection sites treated with R092670.

Microscopic findings observed in the skin of the injection sites were generally: focal miisimal scab, occasional needle canal, dermal accumulation of pigmented cells (related to the tattooing), subcutaneous accumulation of macrophages and subcutaneous granulomatous inflan°ation associated with the reaction in the skeletal muscle. The two latter changes were observed in Groups 2 and 3 in a dose-dependent matter and decreasing in severity with time.

In conclusion, a single intramuscular injection of paliperidone palmitate (R092670) injected in muscle biceps femoris (bilateral: left and right) at a concentration of 100 mg eq./ml injected with fixed doses of 0.38 ml and 1.5 ml to minipigs resulted in dose-related CNS effects and in local reactions at the injection sites in/at both dose groups. Additionally decreases in body weight and body weight gain were recorded in the high dose group.

Histopathological changes were observed at the injection sites, however, the severity of the granulomatous inflammation decreased with time and only a minimal focus was present in one site in the low dose group 149 days after the injection. Minimal interstitial fibrosis and minimal regeneration were observed in some of the other sites 149 days after injection. In addition, minimal to slight focal necrosis of the muscle fibres was present 8, 29 and 57 days after injection. This reaction is a normal response taking into accomit the amount of test item injected into the muscle. Only minimal changes were found 8, 29 and 57 days after injection in the animals treated with vehicle and no changes were found in these animals on Days 92 and 149.

The toxicokinetic evaluation showed a much higher concentration of paliperidone in the muscle at the injection site than those in plasma.

5. Study title: The determination of the solubility of R092670 in buffer, human blood and plasma (Study No. FK6790).

Note: The following summary is taken directly from the Sponsor's report.

Paliperidone palmitate nanosupension was incubated at 1.56 mg/ml (or 1 mg paliperidone-equivalent/ml) in isotonic phosphate buffer pH 7.4, human blood and plasma. After 3 and 8 h of incubation at 37 °C, dissolved paliperidone palmitate and released paliperidone were separated from undissolved paliperidone palmitate particles by centrifugation and filtration. The concentrations of dissolved paliperidone palmitate and hydrolyzed paliperidone were measured by LC-MS/MS.

The extent of paliperidone palmitate dissolution was the same in the three matrices studied; final concentrations in buffer, human blood and plasma are comparable at the end of the 8-h incubation period (43155, 47508 and 37967 ng/ml, respectively). Adding to this, the amounts of paliperidone (R076477) from ester hydrolysis only changed the total amount in blood noticeably, as this is the matrix with the higher reported hydrolysis rate (43188, 49793 and 38168 ng/ml in buffer, human blood and plasma, respectively).

The in vitro dissolution of paliperidone palmitate nanosuspension increased only as a function of time in the buffer incubation, although the increase between 3-h and 8-h time point was not statistically significant.

2.6.4.5 Metabolism

1. Study title: The in vitro hydrolysis of paliperidone palmitate ester (R092670) and the chiral inversion of Paliperidone enantiomers in hepatocytes, liver subcellular fractions, blood and plasma of the male and female rat, male dog and human, and in lymphatic fluid and muscle of dog (Study No. FK2989).

Note: The following summary is taken directly from the Sponsor's submission following evaluation of the study report by the reviewer.

"The in vitro ester hydrolysis of paliperidone palmitate (R092670), was studied in blood, plasma, hepatocyte suspensions, primary hepatocyte cultures, liver microsomes and 12,000 x g supernatants of male and female rat, male dog and man. R092670 was incubated at 15 μM concentration in the above matrices at 37 °C for various time periods. Hydrolysis products i.e., the paliperidone enantiomers, R078543 (+) and R078544 (-), were extracted and measured by a validated chiral LC/MS/MS method. % total product along with the % individual enantiomer contributions were calculated in all the samples. Ester hydrolysis was also studied at low concentration (0.15 μM) in 12,000 x g fractions, plasma and blood of above species. To document the possible chiral inversion, the individual paliperidone enantiomers were incubated at 5 μM in the above matrices for various time periods parallel to the main study and were analysed by validated chiral LC/MS/MS method. Results indicate that there are relative differences in extent of in vitro hydrolysis of paliperidone palmitate between various matrices and species. Taking the metabolism into consideration, the extent and rate rank order of ester hydrolysis in liver was rat>dog>human and in blood was rat>dog = man. Both liver and blood seem to be primarily involved in the ester hydrolysis in rats, but in dog and human, liver seems to play the primary role and blood seems to play a minor role. The ester was found to be stable in muscle and lymphatic fluid of dog. Ester hydrolysis results at low concentration (0.15 μM) were more or less similar to that observed at 15 μM. There seems to be a stereoselectivity in hydrolysis of the ester favouring more towards release of R078543 than R078544. Results of the chiral inversion experiment indicated that there was some extent of chiral inversion with R078543 to R078544 and this was more prominent in liver and almost negligible in blood/plasma. Extent of chiral inversion in liver derived matrices of human were minor, intermediate in dog and highest in rat. Chiral inversion from R078544 to R078543 was not observed in any of the species/matrices. It can be safely concluded that the paliperdione palmitate was extensively hydrolysed to release the active compounds (R078543 & R078544) in all the species taking account of contributions from both liver and blood. Based on the present in vitro findings, it is proposed that the sustained release profile of paliperidone palmitate from intramuscular depot injection will mainly depend on delivery of the ester to the systemic circulation rather than on the hydrolysis of the ester to release the active compounds (R078543 & R078544)."

2. Study title: The in-vitro hydrolysis of R092670 in selected tissue fractions of human and the identification of esterase(s) involved in the hydrolysis (Study No. FK5302).

The present study was designed (1) to determine the relative role of different human tissue fractions (liver, muscle, kidney), blood and plasma (healthy subjects and hepatic impaired patients') in the hydrolysis of paliperidone palmitate, (2) to determine the relative contribution of esterases versus non-esterases (eg: oxidoreductases, CYP 450s or other oxidative enzymes) following the hydrolysis of paliperidone palmitate in human liver and kidney sub-cellular fractions (microsomes and 12,000 x g fractions) with and without addition of a NADPH regenerating system, and (3) to determine the nature of the esterases involved in the hydrolysis following incubation of paliperidone palmitate in human liver microsomes, blood and plasma in the presence of different diagnostic esterase inhibitors [paraoxon, di-isopropyl fluorophosphate (DIFP) for serine esterases;

bis(4-nitrophenyl)- phosphate (BNPP) for carboxylesterses; eserine for cholinesterases and carboxylesterases; acetylcholine for acetylcholinesterase; benzoylcholine for pseudocholinesterse; chloral hydrate for retinylpalmitoyl hydrolase]2,3.

Methods and summary of results: (taken directly from the Sponsor's submission):
"The in vitro ester hydrolysis of paliperidone palmitate (R092670, a racemate) was studied in human liver subcellular fractions with and without addition of NADPH system at different concentrations (5- 3000 ng paliperidone eqv./mL). The hydrolysis was also examined in 12,000 x g fractions of human kidney and muscle tissue. In all samples, paliperidone palmitate was measured by a qualified achiral LC-MS/MS method and the hydrolysis products (paliperidone enantiomers, R078543 (+) and R078544 (-)) were measured by a qualified chiral LC-MS/MS method. The percent hydrolysis of paliperidone palmitate was calculated based on the sum of the released paliperidone enantiomers and the relative role of the different tissues in the hydrolysis was assigned. The hydrolysis was also investigated in plasma and blood of healthy human subjects and plasma samples of hepatic impaired patients. To determine the nature of esterases involved in the hydrolysis, paliperidone palmitate hydrolysis was examined in human liver microsomes, plasma and blood with and without addition of diagnostic esterase inhibitors [paraoxon (1 μM), di-isopropylfluorophosphate (DIFP, 1 μM) for serine esterases; bis(4-nitrophenyl)-phosphate (BNPP, 1 μM) for carboxylesterses; eserine for cholinesterase and carboxylesterase (100 μM); acetylcholine (100 μM) for acetylcholinesterase; benzoylcholine (100 μM) for pseudocholinesterse; chloral hydrate (10 μM) for retinylpalmitoyl hydrolase]. The percent inhibition by various diagnostic inhibitors was expressed against the hydrolysis observed in control incubations without inhibitor.

The ester hydrolysis of paliperidone palmitate increased with incubation time in both microsomes and 12,000 x g fractions of all matrices tested. In general at the highest concentration (3000 ng/mL) the relative hydrolysis was lower than the other concentrations (5 – 500 ng/mL). There was no difference in percent hydrolysis with and without NADPH system indicating that oxidoreductase enzymes were not involved. It appears that the extent of hydrolysis was highest (up to 55.2 %) in liver microsomes and liver 12,000 x g fractions than in any other matrices tested in this study. The extent of hydrolysis appeared to be moderate (up to 28.3 %) and similar in human muscle and human kidney 12,000 x g fractions. A limited fraction of paliperidone palmitate was hydrolyzed (up to 5.4 %) in human blood. The hydrolysis was negligible or undetectable in healthy human and hepatic impaired patient plasma samples. Nearly complete inhibition of hydrolysis was observed with DIFP in liver microsomes indicating that serine esterases were involved in the hydrolysis. Other inhibitors did show weak to moderate inhibition of hydrolysis and possible role of the respective enzymes in the hydrolysis cannot be ruled out. In blood, both serine esterase inhibitors (DIFP and paraxon) significantly inhibited the hydrolysis, which further substantiates that serine esterases are involved in the hydrolysis of paliperidone palmitate".

2.6.4.6 Excretion
See page 23 of this review.

2.6.4.7 Pharmacokinetic drug interactions

See page 23 of this review.

2.6.4.8 Other Pharmacokinetic Studies

NA

2.6.4.9 Discussion and Conclusions

Note: The following summary is taken directly from the Sponsor's submission.

"ADME studies conducted with paliperidone palmitate were designed to investigate the plasma kinetics of paliperidone and/or paliperidone palmitate in various species after i.m. administration. The objectives of these studies were to characterize the hydrolysis process of paliperidone palmitate to paliperidone and to characterize the release mechanism of paliperidone palmitate and paliperidone from the site of injection.

Paliperidone showed a high bioavailability after i.m. dosing of the prodrug. The shape of the pharmacokinetic profile of paliperidone after i.m. or i.l. administration was similar, but paliperidone plasma concentration after i.l dosing were on average 28% lower as compared to i.m. administration. An i.v. administration of paliperidone palmitate, did not produce an immediae release of paliperidone, but resulted in measurable paliperidone plasma concentrations for a period of 9-41 days.

Paliperidone palmitate concentrations were also measured in rats in a carcinogenicity study with the F013 formulation intended for marketing. The fraction of paliperidone palmitate in plasma was maximally 2.9 to 6.7 % of the paliperidone plasma concentration.

A QWBA study in which male rats received both ^{14}C-paliperidone palmitate and paliperidone ^{3}H-palmitate showed that an agglomerate of paliperidone palmitate nanoparticles formed in the muscle after i.m. injection. This agglomerate served as the depot from where the drug substance was released. The muscle was identified as a first site of hydrolysis. In the inside core of the agglomerate there was no indication of hydrolysis, whereas hydrolysis was observed in the muscle tissue surrouding the depot.

In vitro incubations showed that liver and blood (blood to a minor extent in dog and human) played a major role in the hydrolysis of paliperidone palmitate. There was stereoselectivity in hydrolysis of the ester favoring more towards release of the (+)-enantiomer (animals > humans). The extent of chiral inversion from the (+)-enantiomer to the (-)-enantiomer in liver derived matrices of human was minor. Chiral inversion from the (-)- enantiomer to the (+)-enantiomer was not observed. Serine esterases are involved in the hydrolysis of paliperidone palmitate, but a possible role of other esterases in the hydrolysis cannot be ruled out. There was no involvement of oxidoreductase enzymes (cytochrome P450 enzymes) in the hydrolysis.

Highest paliperidone concentrations were found at the injection site muscle (T/P-ratio up to 489). The T/P-ratios in kidney, lymph nodes, lung and liver were on average 6.

Concentrations in brain and in non-injected muscle were comparable to somewhat lower than in plasma.

The further metabolism and clearance of paliperidone, was documented following oral administration of paliperidone to laboratory animals and human volunteers".

2.6.4.10 Tables and figures to include comparative TK summary

NA

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

NA

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: The nonclinical toxicology program in support of paliperidone palimitate long acting injectable formulation consisted of single-dose toxicity studies in dogs, pigs, and minipigs, repeat-dose toxicity studies up to 6 months in rats, 12 months in dogs, and 3 months in minipigs. These studies addressed both local tolerance at the i.m. injection site and systemic toxicity. Moreover, several nonclinical toxicology studies were previously conducted with oral paliperidone. The NDA 22-264 for i.m. paliperidone palmitate cross-references the toxicology study reports and nonclinical summaries submitted previously under NDA 21-999 for p.o. paliperidone (INVEGA). All pivotal toxicity studies were conducted in full compliance with the OECD Good Laboratory Practice guidelines. Nonclinical toxicity studies conducted with paliperidone or paliperidone palmitate are listed in the following Sponsor's table:

SINGLE-DOSE TOXICITY

Species / **Route**		**Mouse p.o.**[b]	**Mouse i.v.**[c]	**Rat p.o.**	**Rat i.v.**
paliperidone	Strain	albino Swiss CD1	albino Swiss CD1	Wistar Wiga	Wistar Hannover
	Mode	gavage	bolus	gavage	bolus
	Dose (mg/kg)	0, 20, 40, 80	0, 10, 20, 40	0, 20, 40, 80, 160, 320	0, 10, 20, 40
	Exp. no.[d]	4892 (ref 1)	4893 (ref 2)	2651 (ref 3)	4894 (ref 4)
paliperidone palmitate		not conducted	not conducted	not conducted	not conducted

Species **Route**		**Dog** **i.m.**[e]	**Dog** **i.m.**	**Dog** **i.m.**	**Dog** **i.m.**
paliperidone		not conducted	not conducted	not conducted	not conducted
paliperidone palmitate	Strain	beagle[13]	beagle[14]	beagle[15,16]	beagle[17,18]
	Mode	bolus	bolus	bolus	bolus
	Dose (mg eq./kg)[f]	0, 2.5, 40	0, 5	0, 5	0, 5

Species **Route**		**Pig** **i.m.**	**Pig** **i.m.**	**Pig** **i.m.**	**Pig** **i.m.**
paliperidone		not conducted	not conducted	not conducted	not conducted
paliperidone palmitate	Strain	Belgian stress negative[19,20]	Belgian stress negative[21,22]	Belgian stress negative[23,24]	Belgian stress negative[25,26]
	Mode	bolus	bolus	bolus	bolus
	Dose (mg eq./kg)	0, 5, 20, 80	0, 5	0, 5	0, 5

Species **Route**		**Minipig** **i.m.**
paliperidone		not conducted
paliperidone palmitate	Strain	Göttingen[27]
	Mode	bolus
	Dose (mg eq./kg)	0, 5, 20

REPEAT-DOSE TOXICITY

Species **Route** **Duration**		**Dog** **i.m.** **1 week**	**Dog** **i.m.** **1 week**
paliperidone		not conducted	not conducted
paliperidone palmitate	Strain	beagle[33]	beagle[34]
	Mode	bolus	bolus
	Injection volume (mL)	0, 1.5 (Intralipid 10%), 1.5[g]	0, 1.5 (Intralipid 20%), 1.5[g]

Species **Route** **Duration**		**Mouse** **p.o.** **2 weeks**	**Rat** **i.v.** **2 weeks**	**Dog** **i.v.** **2 weeks**
paliperidone	Strain Mode Dose (mg/kg/day) Exp. no.	albino Swiss CD1 diet 0, 10, 20, 40, 80 TOX6404 (ref 5)	Sprague-Dawley infusion (30 minutes) 0, 0.63, 2.5, 10 TOX6192 (ref 11)	beagle infusion (30 minutes) 0, 0.31, 1.25, 5 TOX6193 (ref 14)
paliperidone palmitate		not conducted	not conducted	not conducted

Species **Route** **Duration**		**Rat** **p.o.** **1 month**	**Dog** **p.o.** **1 month**
paliperidone	Strain Mode Dose (mg/kg/day) Exp. no.	Wistar Wiga gavage 0, 0.63, 2.5, 10, 10 (RIS)[h] 2849 (ref 7)	beagle capsules 0, 0.31, 1.25, 5 2850 (ref 12)
paliperidone palmitate		not conducted	not conducted

Species **Route** **Duration**		**Mouse** **p.o.** **3 months**	**Rat** **p.o.** **3 months**	**Rat** **p.o.** **3 months**	**Rat** **i.m.** **3 months**
paliperidone	Strain Mode Dose (mg/kg/day) Exp. no.	albino Swiss CD1 gavage 0, 0.63, 2.5, 10, 10 (RIS) TOX5721 (ref 6)	Sprague-Dawley diet 0, 1.25, 5, 20 TOX6343 (ref 8)	Wistar Hannover gavage 0, 0.63, 2.5, 10, 10 (RIS) 4603 (ref 9)	not conducted
paliperidone palmitate	Strain Mode Dose (mg eq./kg/month)	not conducted	not conducted	not conducted	Sprague-Dawley[28] bolus 0, 20, 80, 160

Species Route Duration		Dog p.o. 3 months	Dog p.o. 3 months	Minipig i.m. 3 months
paliperidone	Strain Mode Dose (mg/kg/day) Mode Dose (mg/kgday) Exp. no.	beagle capsules 0, 0.31, 1.25, 5, 5 (RIS) 4604 (ref 13)	beagle ER[i] tablets 0, 30[j], 90[j] powder 90/60[j] TOX6488 (ref 15)	
Paliperidone palmitate	Strain Mode Dose (mg eq./kg/month)	not conducted	not conducted	Göttingen[39] bolus 5, 20

Species Route Duration		Rat p.o. 6 months	Rat i.m. 6 months	Rat i.m. 6 months	Dog i.m. 6 months
paliperidone	Strain Mode Dose (mg/kg/day) Exp. no.	Sprague-Dawley gavage 0, 0.63, 2.5, 10, 10 (RIS) TOX5708 (ref 10)	not conducted	not conducted	not conducted
paliperidone palmitate	Strain Mode Dose (mg eq./kg/month)	not conducted	Wistar[29,30] bolus 0, 20, 80, 160	Wistar[31,32] bolus 0, 20, 80, 160	beagle[35,36] bolus 0, 2.5 → 5, 10 → 20, 40 → 80

Species Route Duration		Dog p.o. 12 months	Dog i.m. 12 months
risperidone[k]	Strain Mode Dose (mg/kg/day) Exp. no.	beagle capsules untreated, 0.31, 1.25, 5 1789 (ref 16)	not conducted
paliperidone palmitate	Strain Mode Dose (mg eq./kg/month)	not conducted	beagle[37,38] bolus 0, 5, 20 → 10, 80 → 40

The development drug substance batches used in the nonclinical toxicity studies with paliperidone palmitate were produced by different manufacturing procedures. Early (b) (4) batches were manufactured (b) (4) according to Synthesis Method 01. Subsequent batches manufactured using the same method were (b) (4) Later, batches were manufactured according to Synthesis Method 02 using (b) (4) to produce sterile drug substance. An overview of the various paliperidone palmitate batches is provided in the following Sponsor's table:

Table 3: Paliperidone Palmitate DS Batches as Used in Nonclinical Toxicity Studies

	DS Batch Number	Study type, duration, species
Early (b) (4) DS batches	PLUY_0083_084_1 (ZR092670PL2), PLUY_0083_099_1 (ZR092670PL3), ZR092670PFA011	- 6-month rat[18] - 6-month dog[24]
	PLUY_0083_084_1 (ZR092670PL2)	- in vitro Ames reverse mutation[29]
	ZR092670PUA011	- single dose dog[1]
	MR092670PUA021	- single dose pig[10]
	ZR092670PFP03	- 3-month rat[17]
(b) (4) DS batches	ZR092670EXA001	- single dose dog[1]
	ZR092670EXA002	- single dose pig[9] - 6-month rat[20] - 12-month dog[26]
	ZR092670EXA003	- single dose dog[2] - single dose pig[10,12] - 12-month dog[26]
	ZR092670EXA005	- single dose dog[2,4] - single dose pig[12,14]
	ZR092670EXA006	- single dose dog[6]
	ZR092670EXA008	- 1-week dog[22] *
(b) (4) DS batches	ZR092670PFA041	- in vitro mouse lymphoma assay[30]
	ZR092670PFA101	- 1-week dog[23] *
	ZR092670PFA111	
	ZR092670PFA051	- carcinogenicity rat[31]
	ZR092670PFA081	- pilot embryo-fetal development rat[32]
	ZR092670PFA091	
	ZR092670PFA111	
	ZR092670PFA121	
	ZR092670PFA201	- single dose minipig[16]
	ZR092670PFA211	- carcinogenicity rat[31] - embryo-fetal development rat[33]
	ZR092670PFA461	- 3-month minipig[28]
	ZR092670PFA471	

* intermittent-dose toxicity studies conducted with Intralipid® 10% or 20%, and paliperidone palmitate as a comparator

Genetic toxicology: The potential genotoxic effects of paliperidone palmitate were studied in a bacterial reverse mutation (Ames) test with *Salmonella typhymurium* and an *in vitro* mouse lymphoma assay. These studies, as well as a full battery of genotoxicity studies with paliperidone showed no genotoxic potential of these articles. The studies with p.o. paliperidone included two *in vitro* bacterial reverse mutation (Ames) tests with *Salmonella typhimurium* (Exp. Nos. 4555 and TOX6095), two mouse lymphoma assays (Exp. Nos. 4556 and TOX6093), and an *in vivo* rat micronucleus test with p.o. dosing (Exp. No. TOX6094). These studies were submitted previously to the NDA 21-999 for paliperidone. Please see pharmacology/toxicology reviews of the NDA 21-999 for paliperidone (INVEGA) for more information. All these genetic toxicology studies were conducted in full compliance to GLP regulations.

An *in vitro* bacterial gene mutation test with paliperidone palmitate was performed in triplicate using *Salmonella typhimurium* strains TA1535, TA 1537, TA102, TA98, and TA100. The experiments were performed with paliperidone palmitate (early development batch) in DMSO at concentrations ranging from 5 too 500 µg/plate in the absence or presence of an Aroclor 1254-induced male rat liver S9 metabolic activation system. Due to precipitation at higher concentrations, the 5 mg/mL concentration (yielding 500 µg/plate) was selected as the top concentration. The bacterial reverse mutation test with

paliperidone palmitate did not cause any biologically significant increase of the number of revertant colonies above the solvent control incidence in strains tested. Therefore, it was concluded that paliperidone palmitate had no mutagenic properties in presence and in the absence of rat metabolic activation system up to 500 µg/plate under conditions of this study.

Paliperidone palmitate was also tested for its ability to induce forward mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells *in vitro*, both with or without the addition of an Aroclor 1254-induced male rat liver S9 metabolic activation system. The tests involved 3-hr treatment with or without S9-mix, and 24-hr treatment without S9. They were performed with paliperidone palmitate crystallized batch no. ZR092670PFA041 dissolved in acetone up to the maximum practicable concentration of 70 µg/mL. This maximum concentration, which was limited by the solubility of paliperidone palmitate in acetone, was achieved by warming at 37°C and ultrasonication. Paliperidone palmitate did not exert a biologically significant increase in mutant frequency in any of the experiments performed. Therefore, it was concluded that paliperidone palmitate had no clastogenic properties in presence and in the absence of rat metabolic activation system up to 70 µg/mL under conditions of this study.

Carcinogenicity: In the 24-month intermittent dose intramuscular carcinogenicity study in the rat**,** intramuscular administration of paliperidone palmitate for 104 weeks resulted in increased mortality in male rats at 30 (MD) and 60 (HD) mg eq. /kg/month when compared to control groups (63% and 77% of animals died, respectively, compared to 49% in saline controls and 51% in vehicle controls). In female rats, minimally higher mortality was observed at the MD. Since the increase in mortality in female rats was not dose related, it was considered to be incidental. Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in males (0/65, 0/65, 8/65, and 4/65 in the vehicle control, LD, MD, and HD, respectively, using the vehicle control and all treated groups but not using the saline control group; the incidence in this group was 1/65). Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. [It should be noted that prolactin levels were increased in male and female rats in this study]. In female rats, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors, except for the LD vs. the vehicle comparison of adenocarcinomas (15/65, 32/65, 28/65, and 29/65 in the vehicle control, LD, MD, and HD, respectively). There were no other significant test article related tumors.

Local tolerance: The single and repeat dose toxicity studies addressed local tolerance at the i.m. injection site.

2.6.6.2 Single-dose toxicity:

Single dose toxicity studies were conducted in dogs, pigs, and minipigs. The main purpose of the single dose non-GLP studies in dogs and pigs was to assess local tolerance

of various paliperidone palmitate formulations at the i.m. injection site. In addition, a GLP-compliant injection site recovery study was performed in minipigs with the F013 formulation intended for marketing. In the single dose dog and pig studies, an aqueous suspension of paliperidone palmitate (100 mg eq./mL) F013 formulation was injected in the left *musculus biceps femoris* at doses ranging from 2.5 to 40 mg eq./kg (injection volume 0.05 to 0.4 mL/kg) in dogs or from 5 to 80 mg eq./kg (injection volume 0.05 to 0.8 mL/kg) in pigs.

Toxicologically important observations in dogs dosed at 2.5 mg eq./kg included swelling and/or hardening at the injection site. In dogs dosed at 40 mg eq./kg, slight to moderate sedation was observed during the first week of dosing. Slight to severe reaction at the injection site (swelling, hardening and/or abscess formation) was noted in all these animals. A subcutaneous fibrous tissue reaction was also observed. One or two month after administration, histological changes included encapsulation of a test article, pale injection site muscle, moderate inflammatory fibro-granulomatous reaction with necrotic center, focal necrotic fibers, and thickened endomysium and perimysium. A fibrogranulomatous reaction with bleeding in the subcutis was noted in 1/8 animals dosed at 2.5 mg eq./kg and in 4/8 dogs dosed at 40 mg eq./kg. There were no changes in the vehicle control group. Toxicologically important clinical signs in the single dose studies in pigs dosed at 5 mg eq./kg included sedation and abnormal biting behavior in the first days after injection. Tremors were observed at 20 or 80 mg eq./kg. Reaction at the injection site and histopathology findings were generally similar to that observed following single dose administration to dogs (see above), including white strand formation at injection site, multifocal inflammatory histiocytic tissue reaction, subcutaneous powdery deposit, granulocytic infiltration, encapsulation of the test article, giant cells and necrotic centers within the encapsulation.

The doses of paliperidone palmitate administered to dogs in single dose studies were approximately 1.5 to 24-fold the MRHD (100 mg eq. per person). The doses of paliperidone palmitate administered to pigs in single dose studies were approximately 3 to 47-fold the MRHD.

Mean toxicokinetic parameters of paliperidone in the single dose toxicity studies in dogs and pigs following administration of paliperidone palmitate, and exposure margins compared to the human exposure at the MRHD are summarized in the following Sponsor's table:

Table 5: Mean Toxicokinetic Parameters of Paliperidone in The Single-Dose Toxicity Studies With Paliperidone Palmitate in Dogs and Pigs

Species	Dose (mg eq./kg)	C_{max} (ng/mL)	$AUC_{0\text{-}28\ days}$ (µg.hr/mL)	Exposure ratio[a]		Study number
				C_{max}	$AUC_{0\text{-}28\ days}$	
Dog	5	109-335	29-61	3.3-10	1.9-4.0	2,3,4,5,6, 2
Pig	5	18-48	7-12	0.5-1.4	0.5-0.8	9,10,11,12,13,14
	80	365	183	11	12.1	

[a] exposure ratio animal *versus* human; mean human C_{max}- and human $AUC_{0\text{-}28}$ days-values are 33.2 ng/mL and 15.1 µg.hr/mL, respectively, after 2 injections (Days 1 and 8) of paliperidone palmitate (F013, 100 mg eq./month) in the *m. deltoid* of patients with schizophrenia (Module 2.7.2.,Section 2.1.1.3.)

In the single dose minipig study, an aqueous suspension of paliperidone palmitate F013 formulation (100 mg eq./mL) was injected in the left and right *musculus biceps femoris* of male Göttingen minipigs (two bilateral injections) at fixed injection volumes of 0.38 and 1.5 mL per injection site. The injection volumes of 0.38 mL and 1.5 mL given bilaterally yielded a dose of approximately 5 and 20 mg eq./kg, respectively. At 5 mg eq./kg, shaking, standing unsteadily on hind legs, increased sensitivity to sound and touch were ocassionally observed. At higher doses, the CNS toxicity was observed including slow movements and reactions, shivering, unsteadily standing or poor balance, and other signs. Upon microscopic examination of the injection site, findings were similar to those in dogs and pigs following single dose administration.

The doses of paliperidone palmitate administered to minipigs in this study (5 and 20 mg eq./kg) were approximately 3- to 12-fold the MRHD (100 mg eq. per person) on a mg eq./kg basis.

Mean toxicokinetic parameters of paliperidone in the single dose toxicity study in minipigs following administration of paliperidone palmitate are summarized in the following Sponsor's table:

Table 7: Mean Toxicokinetic Parameters of Paliperidone in Minipigs Following a Single Bilateral I.M Injection of Paliperidone Palmitate (F013)

Parameter	Plasma		Parameter	Injection site muscle	
	0.38 mL (~ 5 mg eq./kg)	1.5 mL (~ 20 mg eq./kg)		0.38 mL (~ 5 mg eq./kg)	1.5 mL (~ 20 mg eq./kg)
T_{max} (day)	10	8.0	T_{max} (day)	10	29
C_{max} (ng/mL)	8.09	43.4	C_{max} (ng/g)	1800	5920
$AUC_{0\text{-}148\ days}$ (µg.day/mL)	0.188	0.988	$AUC_{0\text{-}148\ hr}$ (µg.day/g)	42.8	183
$AUC_{0\text{-}148\ days}$ (µg.hr/mL)[a]	4.512	23.712			

[a] calculated from the mean $AUC_{0\text{-}148\ days}$ (µg.day/mL)-value

2.6.6.3 Repeat-dose toxicity

Studies in rats:

Studies No. TOX 6266 (3 month toxicity/TK studies in rats), TOX 3848 (first 6 month toxicity/TK study in rats) and TOX4696 (second 6 month toxicity/TK study in rats) have been submitted to the IND 67,356 and reviewed by Dr. Aisar Atrakchi. Dr. Atrakchi's reviews of these studies dated November 9, 2004 and June 20, 2003 are available in the DARRTS. The summaries of these studies and conclusions taken directly from Dr. Atrakchi's review are provided below (please see full reviews for more information):

1. Study title: 3-month intermittent dose intramuscular toxicity study in the rat (Study No. TOX 6266)

Summary and Conclusions: "Paliperidone palmitate was injected once a month for 3 months for a total of 3 doses to SD male and female rats at 0, 20, 80, and 160mg/kg. The drug caused death in HDf but not in males, clinical signs were seen in all drug groups and limited to ptosis and hardened injection site in addition to sedation in mid and high dose groups. Mean wt and wt gain were reduced significantly in 80 and 160mg/kg male groups whereas a significant increase in these parameters noted in all 3 female drug groups though it was not dose related with the highest increase seen in low dose. This change in B.wt correlated with some decrease in food intake in males and a corresponding increase in female food intake. There were no consistent or clear drug related effects on hematology and clinical chemistry parameters, no drug effect on urinalysis or ophthalmology. Mean absolute and relative wts of the medial iliac lymph nodes in all 3 female drug groups and in HDm were increased significantly and corresponded to histopath changes, mean relative wt of the adrenals was slightly decreased in all 3 female drug groups but was increased in mid and high dose males and did not correlate to histopathology therefore, was not considered of toxicological significance. Target organs for toxicity included injection site, iliac lymph nodes and male and female reproductive organs, the latter was considered extension of the pharmacology of the drug in response to increase in serum prolactin.

The following drug related findings were seen:
In the low dose of 20mg/kg: clinical signs, changes in B.wt/wt gain (6% decrease), and food intake only in f, increase in serum prolactin in f only (though data highly inconsistent), powdery deposit at injection site in both sexes, mean relative wt of iliac lymph node increased only in f, unilateral inflammatory granulomatous reaction at injection site both sexes, small increase in pigmented macrophages in medial iliac lymph nodes in f only, mammary gland and female reproductive organ changes, and increase in acute but not chronic, inflammation of the dorsolateral prostate lobe of minimal to moderate degree predominantly with granulocytes.

In addition to the above changes the following were seen in 80 & 160mg/kg groups: Clinical signs (sedation in addition t ptosis), continued decrease in mean B.wt/wt gain in

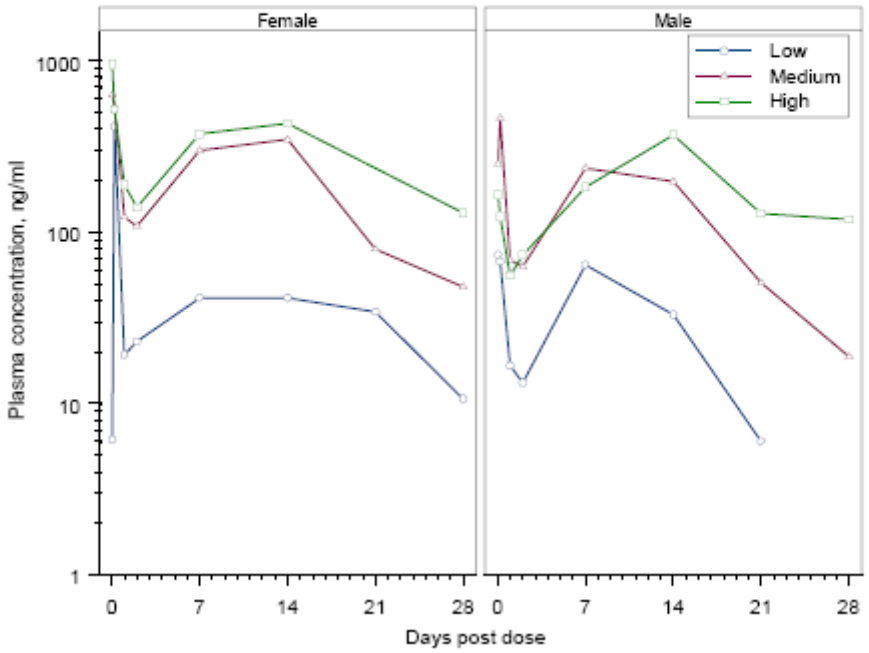
males and increase in females, food intake decreased in males both doses and increased in both female groups, and female appearance in male mammary glands.

Paliperidone showed 2 peak plasma concentrations with concentrations rapidly declining after the 1st peak this was suggested by the sponsor to be due to inadvertent partial injection into the vasculature instead of i.m. The 2nd peak was reached 1-2wks after dosing. Females showed about 35% higher paliperidone concentrations than males and exposures in both sexes generally increased proportional to dose. Mean AUC0-672hr at 20mg/kg in males after the 3rd dose was 18ug.hr/ml and in females 24ug.hr/ml; exposures at 80mg/kg in males and females were 85 and 131ug.hr/ml respectively.

Based on the findings in this study, 160mg/kg exceeded MTD in females due to death in 2 animals, the NOAEL in both sexes is 20mg/kg, 80mg/kg was tolerated in both sexes following 3 monthly injections but this dose may not be a reasonable high dose to be used for a 2 year bioassay in the rat to be injected for a total of 24 times in 24 months".

Toxicokinetics: Mean plasma concentration-time profiles of paliperidone following administration of paliperidone palmitate for 3 months in the toxicity study in rats are shown in the following Sponsor's figure:

Figure 6: Mean Plasma Concentration-Time Profiles of Paliperidone after the Third I.M. Administration of Paliperidone Palmitate (F011) in the 3-Month Repeat-Dose Toxicity Study in Rats at Dose Levels of 20 (Low), 80 (Medium) or 160 (High) mg eq./kg/month



Toxicokinetic parameters of paliperidone following administration of paliperidone palmitate for 3 months in the toxicity study in rats are shown in the following Sponsor's table (data taken from the Toxicology Written Summary of the NDA 22-264):

Table 9: Mean Toxicokinetic Parameters of Paliperidone in the 3-Month Repeat-Dose I.M. Toxicity Study With Paliperidone Palmitate (F011) in Rats

Parameter	Dose level (mg eq./kg/month)					
	20		80		160	
	Males	Females	Males	Females	Males	Females
After the 3rd injection						
$T_{max,\,1}$ (hr)	1.0	5.0	5.0	1.0	1.0	1.0
$C_{max,\,1}$ (ng/mL)	73.9	413	461	631	165	955
$T_{max,\,2}$ (hr)	168	336	168	336	336	336
$C_{max,\,2}$ (ng/mL)	64.4	41.4	236	348	369	430
$AUC_{0\text{-}28\ days}$ (µg.hr/mL)	18.0	24.3	84.9	131	125	179

Prolactin levels: Prolactin levels increased in female rats at all dose levels. Mean serum prolactin levels in the 3-month toxicity in rats are shown in the following Sponsor's table:

Table 8: Mean Serum PRL Levels (ng/mL) in the 3-Month Repeat-Dose I.M. Toxicity Study With Paliperidone Palmitate (F011) in Rats (mean ± SE)

Time point	Dose level (mg eq./kg/month)			
	0 (vehicle)	20	80	160
Males				
Day 63[a]	-	30 ± 14	60 ± 25	37 ± 8
Day 70[a]	-	32 ± 15	17 ± 6	16 ± 2
Day 77[a]	-	15 ± 3	43 ± 19	38 ± 9
Necropsy[b]	28 ± 2.3	29 ± 2.3	26 ± 2.5	29 ± 4.1
Females				
Day 63[a]	-	174 ± 33	234 ± 27	174 ± 57
Day 70[a]	-	262 ± 138	243 ± 19	262 ± 21
Day 77[a]	-	171 ± 85	99 ± 47	135 ± 28
Necropsy[b]	91 ± 19	69 ± 16	107 ± 13	124 ± 21

[a] n = 3; [b] n = 20

2. Study title: Evaluation of the subchronic toxicity potential in SPF Wistar rats (Study No. 3848; 6 month toxicity/TK study in rats)

Summary and Conclusion: "Monthly i.m. injections of R092670 to male and female Wistar rats at 20, 80, or 160 mg/kg using F1 formulation did not cause mortality and the sedation/ptosis observed in all drug groups was absent after the 2nd injection (adaptation occurred). There were some drug effect on wt and wt gain particularly in females where both parameters increased significantly in low dose at given periods relative to control and in MD from wk2 onwards but no effect in HD. Males showed only a slight reduction in mean wt on wk10 in HD. The changes in wt in females paralleled increase in food intake. No drug effect on hematology, opthalmoscopy, clinical chemistry, urinalysis or

organ wts. Target organs for toxicity included injection site, mammary glands, female genital tract and, male accessory sex organs. Injection site findings were similar to those observed in the dog and included fibrogranulomatous reaction with histiocytes and giant cells seen in perimysium and epimysium in all drug groups of both sexes with dose dependent increase in severity; changes were more severe after 6 months. In mammary glands, a female aspect with prominent secretion was found in all male drug groups. In females, alveolar development and prominent secretion seen in all drug groups plus reduced cycle activity in ovaries, uterus, and vagina indicative of pseudopregnancy. A diffuse atrophy of the epithelium of coagulating glands in males and seminal vesicles was seen in mid and high dose with no effect in low dose. Increased inflammatory infiltrate in dorsolateral part of the prostate (no effect on the ventral region). The diffuse atrophy of epithelium of the coagulating glands and seminal vesicles was not seen at 3months. A NOEL could not be determined due to injection site reaction and clinical signs".

Toxicokinetics: Toxicokinetic evaluation of paliperidone in the study No. 3848 indicated the first peak of paliperidone plasma levels within 24 hours after dosing. The plasma levels declined during the first two subsequent days. The second peak occurred within two weeks and declined again. The AUC values increased in general in proportion to the dose. Mean toxicokinetic parameters in this study are shown in the following Sponsor's table (data taken from the Toxicology Written Summary of the NDA 22-264):

Table 11: Mean Toxicokinetic Parameters of Paliperidone in the First 6-Month Repeat-Dose I.M. Toxicity Study in Rats (mean ± SD)

Parameter	Dose level (mg eq./kg/month)					
	20		80		160	
	Males	Females	Males	Females	Males	Females
After the 6th injection						
$T_{max, 1}$ (hr)	5[a]	3.7 ± 2.3	3.7 ± 2.3	3.7 ± 2.3	11.3 ± 11.0	16.3 ± 13.3
$C_{max, 1}$ (ng/mL)	26.9[a]	41.2 ± 15.2	326 ± 228	173 ± 9	541 ± 464	264 ± 97
$T_{max, 2}$ (hr)	336[a]	168 ± 0	392 ± 97	280 ± 97	224 ± 97	336 ± 0
$C_{max, 2}$ (ng/mL)	50.3[a]	63.1 ± 20.8	159 ± 10	219 ± 66	425 ± 97	419 ± 110
$AUC_{0\text{-}30\ days}$ (μg.hr/mL)	24.835[a]	35.397 ± 12.554	95.260 ± 16.171	124.479 ± 31.226	246.739 ± 48.823	231.987 ± 53.062

[a] n = 2

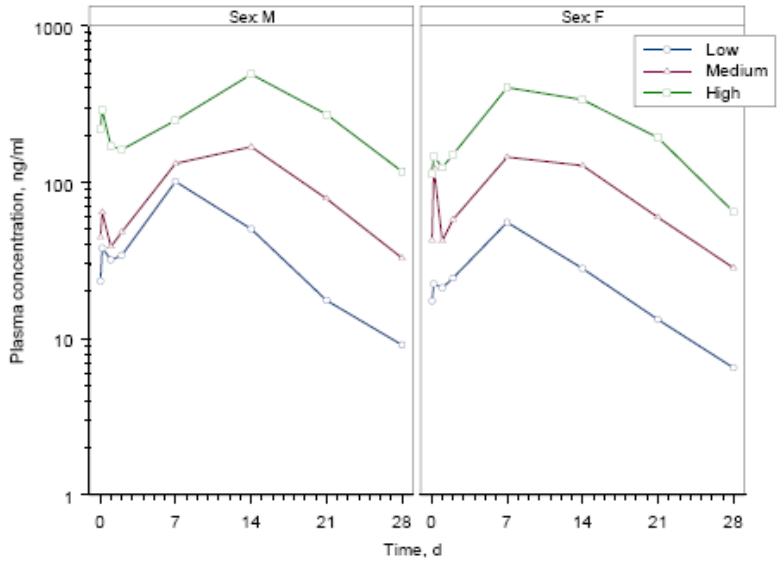
3. Study title: 6-month intermittent repeated dose intramuscular toxicity study in the Wistar rat (Study No. 4696)

Summary and Conclusion: "R092670 was injected i.m. to male and female Wistar rats once monthly for 6 months at 20, 80, and 160mg/kg using F4 formulation. There were no drug related mortalities. Drug related effects were comparable to those observed in previous studies. Clinical signs included ptosis and sedation. Mean body wt and wt gain were decreased in males with small transient increase in food intake, however, wt and wt gain were increased in females together with transient increase in food intake. There were changes in hematology and clinical chemistry parameters that reached statistical significance such as decrease in HcT, Hb, and RBCs in females and HDm, increase in MCH and MCHC in all 3 male drug groups, mean neutrophil value was significantly and

dose dependently increased in males and females at 6months, serum Ca and PI were significantly and dose dependently increased in both sexes. These changes were small and may not have a toxicological significance. Mean wt of several organs/tissues were affected and correlated with histopath findings: spleen wt was significantly and dose dependently increased in both sexes, kidney wt was significantly increased in HDm (but decreased in LDm), adrenal wt was significantly and dose dependently increased in males but relative wt decreased in females, gonads wt of females were significantly reduced in MD & HD compared to control. Gross morphological exam showed a white powdery deposit at injection site in all dose groups of both sexes and mammary gland stimulation was observed in all female drug groups and in 1 HDm. Histopathological exam revealed findings in the following organs/tissues: injection site, adrenals, kidneys, mammary glands, ovaries, prostate, seminal vesicles, spleen, testes, and pituitary. Similar to other studies, findings at injection site were those of inflammatory immunoreactive changes, in the adrenals, swollen cortical cells of zona fasiculata and reticularis were markedly increased in all male drug groups compared to control, and increased dilation of cortical renal collecting tubules in MD&HDm and in all female drug groups relative to corresponding controls. There was female appearance (alveolar development) with increased secretion significantly present in all male drug groups, similarly, alveolar development and secretion were increased in all female groups compared to vehicle control. Focal hyperplasia of alveolar epithelium was seen in MD & HDm and in all female drug groups. Reduced cyclic activity in uterus and male accessory sex organs showed low epithelium of ventral prostate, seminal vesicles, and coagulation gland. Increase in prolactin-immunoreactivie cells in males but a decrease in females, on the other hand, serum prolactin was increased in all male treated drug groups and in HDf. These changes in male and female sex/reproductive organs are extension of the pharmacology of the drug and have been observed in other studies and comparable effects also observed in other species. Based on these results, a NOEL can not be determined due to presence of injection site reactions as well other effects including histopathology at the low dose of 20mg/kg. However, 20mg/kg may be considered a NOAEL."

Toxicokinetics: Plasma concentration time profiles of paliperidone after the 6th administration of paliperidone palmitate are ahown in the following Sponsor's figure (data taken from the Toxicology Written Summary of the NDA 22-264):

Figure 7: Mean Plasma Concentration-Time Profiles of Paliperidone after the 6th I.M. Administration of Paliperidone Palmitate (F004) at 20 (Low), 80 (Medium) or 160 (High) mg eq./kg in a 6-Month Repeat-Dose Toxicity Study in Male (M) and Female (F) Rats



The mean toxicokinetic parameters in the 6 months toxicity study in rats are shown in the following Sponsor's table (data taken from the Toxicology Written Summary of the NDA 22-264):

Table 13: Mean Toxicokinetic Parameters of Paliperidone in the Second 6-Month Repeat-Dose I.M. Toxicity Study with Paliperidone Palmitate (F004) in Rats (mean ± SD)

Parameter	Dose level (mg eq./kg/month)					
	20		80		160	
	Males	Females	Males	Females	Males	Females
After the 6th injection						
$T_{max,1}$ (hr)	8.8 ± 10.3	5.0[a]	4.0 ± 2.0	5.0 ± 0.0	5.0 ± 0.0	5.0[a]
$C_{max,1}$ (ng/mL)	39.3 ± 10.0	27.2[a]	66.1 ± 30.1	124 ± 148	367 ± 348	146[a]
$T_{max,2}$ (hr)	168 ± 0.0	168 ± 0.0	294 ± 84.0	168 ± 0.0	378 ± 84.0	168[a]
$C_{max,2}$ (ng/mL)	101 ± 30.2	55.4 ± 21.3	179 ± 87.9	145 ± 55.7	492 ± 377	404[a]
$AUC_{0\text{-}28\ days}$ (μg.hr/mL)	30.339 ± 4.376	17.969 ± 6.385	68.366 ± 30.461	61.305 ± 21.672	192.668 ± 105.135	167.863[a]

[a] n = 2

Prolactin levels: Serum prolactin levels at necropsy were increased in females dosed at 160 mg eq./kg/month. Males showed a dose-dependent increase in prolactin levels at all dose levels. Mean serum prolactin levels are shown in the following Sponsor's table (data taken from the Toxicology Written Summary of the NDA 22-264):

Table 12: Mean Serum PRL Levels (ng/mL) in the Second 6-Month Repeat-Dose I.M. Toxicity Study with Paliperidone Palmitate (F004) in Rats (mean ± SE)

Dose level (mg eq./kg/month)			
0 (vehicle)	**20**	**80**	**160**
Males			
16 ± 6	35 ± 7**	93 ± 21***	112 ± 14***
Females			
83 ± 27	24 ± 6*	88 ± 13	159 ± 12**

Statistical significance: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Studies in dogs:

Studies No. 3849 (6 month toxicity/TK studies in dogs) and 4692 (12 month toxicity/TK studies in dogs) have been submitted to the IND 67,356 and reviewed by Dr. Aisar Atrakchi. Dr. Atrakchi's review of these studies dated June 20, 2003 is available in the DARRTS. The summaries of these studies and conclusions taken directly from Dr. Atrakchi's review are provided below (please see full review for further details):

1. Study title: Evaluation of the subchronic toxicity potential in beagle dogs (Study No. 3849; 6 months administration)

Summary and conclusions: "Monthly i.m. injections of paliperidone palmitate to male and female beagle dogs for 6 months did not cause mortality nor did it induce any clinical signs except for mild sedation at 80mg/kg. The sponsor stated that because of suspected severe sedation at higher doses they decided to administer 2.5, 10, and 40mg/kg as the 1st dose and from the 2nd dose onwards doses increased to 5, 20, and 80mg/kg. Drug related injection site reactions in all drug groups at both muscle sites was seen as swelling, hardness, and abscess formation. They were described histologically as encapsulated fibro-granulomatous reaction associated with intragranulomatous chronic inflammatory cell reaction and focal necrosis in the perimysium and epimysium. Site injection reactions were seen at 5mg/kg dose and up i.e. after the 2nd dose in both male and female dogs. Moreover, a powdery deposit was observed at or near injection site in all drug groups (no further detail was provided). Moderate increase in RBCs in red pulp of the spleen was observed at the 3month interim sacrifice as well as end of study wk26 and related to the α-lytic activity of the cpd. Changes in male and female reproductive organs in all drug groups were contributed to the antidopaminergic effect of the drug and those at the 3month interim to the immaturity of the dogs at that time. The plasmocytes in the medullary cords of the iliac lymph nodes were reduced in all drug groups; the toxicological significance of this finding is unclear. A NOEL could not be determined in this study due to the injection site findings however, the drug seemed to be well tolerated up to 80mg/kg dose".

Toxicokinetics: C_{max} and AUC values increased fairly dose proportionally over the three dose levels in the 6 months study in dogs. Mean toxicokinetic parameters of paliperidone are shown in the following Sponsor's table:

Table 14: Mean Toxicokinetic Parameters of Paliperidone in the 6-Month Repeat-Dose I.M. Toxicity Study in Dogs (mean ± SD)

Parameter	Dose level (mg eq./kg/month)		
	5	20	80
After the 6th injection			
T_{max} (hr)	252 ± 97	396 ± 245	252 ± 97
C_{max} (ng/mL)	52.5 ± 27.1	181 ± 33	638 ± 166
$AUC_{0\text{-}21\ days}$ (µg.hr/mL)	18.632 ± 8.859	72.810 ± 12.084	273.579 ± 70.678

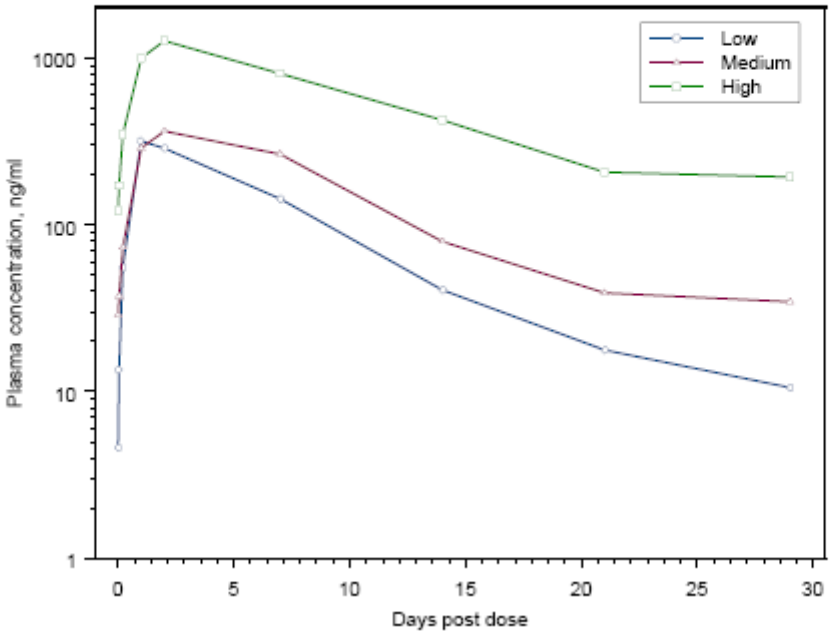
2. Study title: Twelve month intermittent repeated dose intramuscular toxicity study in the beagle dog (Study No. 4692)

Summary and conclusions: "Monthly i.m. injections of paliperidone palmitate to male and female beagle dogs for 6 months using F4 formulation, did not cause mortality but sedation occurred in all dogs of mid and high doses and 6/8 low dose group. Drug related injection site reactions comparable to those observed in the previous 6month study though using a different formulation, were observed in all drug groups but not vehicle group included: swelling, abscess, and s.c. nodules. However, these skin reactions were severe enough after the 1st injection that led to decreasing dose to 10 and 40mg/kg instead of 20 and 80mg/kg respectively. Some dogs showed claudication and edema that were contributed to injection site lesions. A finding not seen in the previous study or in other species was acute anaphylactic reaction to the polysorbate 20 in all vehicle and high dose (80- 40mg/kg) animals after each injection as well as in 3 mid dose dogs (20-10mg/kg). Signs ranged from slight (swollen eyelids), to moderate (swollen eyelids, paws and head), to severe (red spots, cyanosis, sedation, hyperpnea, and decubitus); slight vomiting also seen in vehicle and drug groups. These symptoms of anaphylaxis occurred within 1hr of dosing and lasted for few hours but dogs seemed normal by the next day. This reaction was present after each injection in the vehicle but seemed to fade with each injection in high dose dogs and was absent in the last 2 doses. There were no drug related effects on ECG, ophthalmology, or urinalysis; mean HR in 80/40mg/kg was increased significantly on wks4&12 and not significantly on wk52, at this time, heart rate was also significantly increased in the low and mid dose groups but not dose dependently. Mean B.wt was not affected by treatment however, mean wt gain was reduced during wks 1-4 in 20&80mg/kg and wks5-7 in 40mg/kg & wk5 in 10mg/kg; this wt loss ranged between -0.1 to -0.7kg; wt changes did not correspond to changes in food intake. Drug related changes in hematology and clinical chemistry were small, not dose dependent, and within the historical range. Mean serum prolactin level was significantly increased in both sexes, however due to the large variability in the data, a clear dose response relationship could not be identified. There were organ wt changes but only the decrease in spleen wt correlated with histopathology. Histopath findings in addition to those at injection site included prostate atrophy in mid and high dose, presence of brown pigmented macrophages and prominent lymphoid tissue and/or lymphoid follicles in iliac lymph nodes in all drug groups which was considered reaction to foreign material and inflammation. Slight resting appearance of uterus seen in 10 and 40mg/kg and mitotic figures within the uterine epithelium were absent in 40mg/kg group; absence of regressive and active corpora lutea in ovaries of 40mg/kg. These changes in female and male reproductive tissues/organs were related to the drug effect on prolactin. The small

increase in prolactin-immunoreactive positive cells of 40mg/kg in the adenohypophysis seemed to be present only in females. A NOEL could not be determined due to presence of injection site reactions, sedation, and other effects. It is noted however, that 40 mg/kg was well tolerated up to 1yr of monthly injections".

Toxicokinetics: Maximum plasma levels of paliperidone were generally recorded within 48 hours of paliperidone palmitate administration and later gradually decreased, as shown in the following Sponsor's figure (taken directly from the NDA 22-264 Toxicology Written Summary):

Figure 8: Mean Plasma Concentration-Time Profiles of Paliperidone after the 12th I.M. Administration of Paliperidone Palmitate (F004) at 5 (Low), 10 (Medium) or 40 (High) mg eq./kg in the 12-Month Repeat-Dose Toxicity Study in Dogs



Exposure to the paliperidone increased slightly less than dose-proportionally from the low to mid dose; it increased fairly dose-proportionally from the medium to high dose in the 12-month study in dogs. Mean toxicokinetic parameters obtained in this study are shown in the following Sponsor's table:

Table 15: Mean Toxicokinetic Parameters of Paliperidone in the 12-Month Repeat-Dose I.M. Toxicity Study With Paliperidone Palmitate (F004) in Dogs (mean ± SD)

Parameter	Dose level (mg eq./kg/month)		
	5	10	40
After the 12th injection			
T_{max} (hr)	36 ± 14	78 ± 60	114 ± 148
C_{max} (ng/mL)	378 ± 266	366 ± 92	1327 ± 858
$AUC_{0\text{-}21\ days}$ (µg.hr/mL)	57.050 ± 21.736	88.058 ± 23.378	321.319 ± 104.307
$AUC_{0\text{-}last}$ (µg.hr/mL)	59.985 ± 20.953	95.346 ± 23.330	363.433 ± 113.441

Study in minipigs:

Study title: 12-week local tolerance study of 2 paliperidone palmitate long acting injectable formulations in the minipig

Key study findings: Intramuscular administration of the F013 formulation by three consecutive injections once every 4 weeks at single 5 mg eq./kg dose resulted in slightly decreased general activity and slight tremors. The same formulation administered at 20 mg eq./kg showed slightly to moderately decreased general activity, slight tremors, excessive salivation, compulsive behavior, transient increase in white blood cells, neutrophiles, and monocytes, slight but transient decrease in red blood cell count, hemoglobin and hematocrit, and minimal decrease in plasma potassium and sodium.

Intramuscular administration of the F015 formulation at single 15 mg eq./kg dose resulted in slightly decreased general activity, slight tremors, slight increase in body weight and body weight gain. The same formulation administered at single 60 mg eq./kg dose resulted in slightly to moderately decreased general activity, slight tremors, excessive salivation, compulsive behavior, excitability, ataxia, hypotonia, chewing, slight increase in body weight and body weight gain.

Injection of both formulations resulted in similar dose-related local reactions as indicated by gross observations. The following dose-related local reactions were noted at the injection sites: (1) A dose-related inflammatory reaction with granulomata formation was observed in the high dose groups of both formulation but was more severe with F015 formulation: inflammatory reaction was graded as "marked" for the F015 formulation and minimal/slight for the F013 formulation; (2) subcutis granulomata, subcutis inflammation with large centers of amorphous material were observed only with the formulation F015; (3) Inflammation locally extending into dermis was observed only with the formulation F015; The cellular reaction pattern and the size of crystalline material seen in the inflammatory cells were different between the two formulations. Crystalline material was larger than nucleus with F015 formulation (smaller with F013 formulation); (4) macrophages, giant cells and cholesterol clefts were noted at both dose levels with F015 formulation (not with F013).

A NOAEL could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.

Study no.: TOX8249
Volume #, and page #: electronic submission
Conducting laboratory and location: Global Preclinical Development, Beerse site, Tournhoutseveg 30, 2340 Beerse, Belgium
Date of study initiation: March 12, 2007
GLP compliance: yes, except for the analysis of the pre-dose samples for hematology and clinical chemistry
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone palmitate (R092670), formulation F015: batch No. 06J17/F015, formulation F013: batch No. 06K22/F013

Methods:

Doses: formulation F015: 0, 0, 15, and 60 mg paliperidone equivalents (eq.)/kg b.w.; formulation F013: 0, 0, 5 and 20 mg paliperidone equivalents (eq.)/kg b.w.
Species/strain: Göttingen minipigs (males)
Number/sex/group or time point (main study): 3 males/group
Route, formulation, volume: Single intramuscular injection of a 12-week depot formulation (F015) or three consecutive intramuscular injections once every 4 weeks of a 4-week depot formulation (F013);
Satellite groups used for toxicokinetics or recovery: none
Age: 7.5 to 9 month on day 0
Weight: 11.4-17.4 kg on day 0
Unique study design or methodology: Paliperidone palmitate was administered to male minipigs by either a single intramuscular injection of a 12-week depot formulation (F015) at dose levels of approximately 15 and 60 mg paliperidone eq./kg b.w., or by three consecutive intramuscular injections once every 4 weeks of a 4-week depot formulation (F013) at dose levels of approximately 5 and 20 mg eq./kg b.w. Two additional groups received F015- or F013 placebo, respectively. Two control groups [saline] were also included.

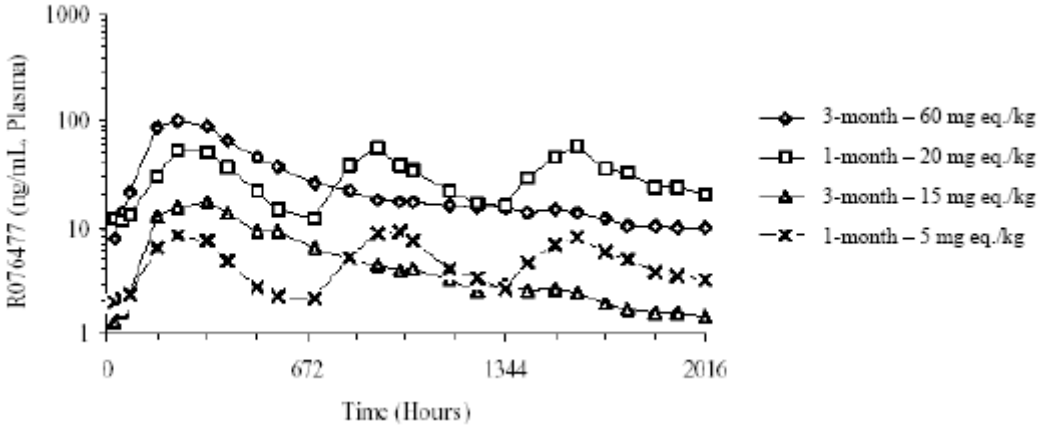
Observations, times and results:
Mortality: There was no mortality in this study.
Clinical signs: Single i.m. administration of F015 formulation at 15 mg eq./kg resulted in slightly decreased general activity and slight tremors. Single i.m. administration of F015 formulation at 60 mg eq./kg resulted in decreased general activity, slight tremors, excessive salivation, compulsive behavior, excitability, ataxia, hypotonia, and chewing. Intermittent i.m. administration of F013 formulation at 5 mg eq./kg resulted in slightly decreased general activity and slight tremors. Animals dosed with F013 formulation at 20 mg eq./kg showed slightly to moderately decreased general activity, slight tremors, excessive salivation, and compulsive behaviour.
Body weights: Single i.m. administration of F015 formulation at 15 and 60 mg eq./kg resulted in slight increase in body weight and body weight gain. There were no adverse test article related findings following administration of F013 formulation.

Food consumption: There were no adverse test article related findings following administration of F015 or F013 formulation.
Ophthalmoscopy: not conducted
EKG: not conducted
Hematology: F015 formulation: no test article-related changes. F013 formulation: a transient increase in white blood cells, neutrophils and monocytes, and slight but transient decrease in red blood cell count, hemoglobin, and hematocrit
Clinical chemistry: There were no test article related findings following single intramuscular administration of the F015 formulation. Following administration of the F013 formulation at 5 mg eq./day, minimal decrease in potassium was noted. Dosing at 20 mg eq./day resulted in minimal decrease in potassium, albumin, ALT, alkaline phosphatase, blood urea nitrogen and sodium
Urinalysis: not conducted
Gross pathology: Dose-related local reactions observed in muscles at necropsy were similar for both formulations.
Organ weights: not conducted
Histopathology: Dose-related local reactions were noted at the injection sites:

1) A dose-related inflammatory reaction with granulomata formation was observed in the high dose groups of both formulation but was more severe with F015 formulation: inflammatory reaction was graded as "marked" for the F015 formulation and minimal/slight for the F013 formulation.
2) Subcutis granulomata, subcutis inflammation with large centers of amorphous material were observed only with the formulation F015.
3) Inflammation locally extending into dermis was observed only with the formulation F015.
4) The cellular reaction pattern and the size of crystalline material seen in the inflammatory cells were different between the two formulations. Crystalline material was larger than nucleus with F015 formulation (smaller with F013 formulation).
5) Macrophages, giant cells and cholesterol clefts were noted at both dose levels with F015 formulation (not with F013).

Note: each injection site in minipigs got the volume and dose of the F015 formulation equal to that proposed for humans (at 450 mg.eq./person)

Toxicokinetics: Mean plasma concentration versus time profiles of paliperidone after dosing with the 3-month and 1-month formulation are shown in the following Sponsor's figure:



Following administration of the paliperridone palmitate 3-month formulation at 60 mg and 15 mg, paliperidone C_{max} was 64% and 71% greater than that for the 1-month formulation at 20 mg and 5 mg, respectively. According to the sponsor, the projected maximal plasma concentration (11-66 ng/mL over the proposed dose range of 75-450 mg eq.) stay within the exposure range that has been observed in the INVEGA Phase 3 program and the 1-month paliperidone palmitate program. Maximal plasma concentrations were observed around 10-14 days after dosing. T_{max} was shorter for the 3-month formulation at both dose levels when compared to the 1-month formulation. For comparison: C_{max} value obtained at 10 mg/kg paliperidone was 3717 ng/mL in the 6-month rat study. C_{max} value obtained at 5 mg/kg paliperidone was 3277 ng/mL in the 3-month dog study. AUC values increased more than dose-proportional manner for both formulations. Following administration of the paliperidone palmitate 3-month formulation at 60 mg and 15 mg, the exposure to paliperidone $AUC_{0\text{-}29day}$ was 100% and 134% greater than that than that for the 1-month formulation at 20 mg and 5 mg, respectively. Following administration of the paliperidone palmitate 3-month formulation at 60 mg and 15 mg, the exposure to paliperidone $AUC_{0\text{-}84day}$ was 3% lower and 12% greater than that than that for the 1-month formulation at 20 mg and 5 mg, respectively.

Mean pharmacokinetic parameters of paliperidone after dosing the 3-month (single dose) and 1-month formulation (3 doses) of paliperidone palmitate in minipigs is shown in the following Sponsor's table:

	3-month formulation		1-Month formulation	
Dose (mg eq./kg)	**15**	**60**	**5**	**20**
C_{max} (ng/mL)	18.5	105	10.8	64.1
T_{max} (d)	12.67	9.00	30.67	11.33
$AUC_{0\text{-}29d}$ (ng.d/mL)	297	1,649	127	823
$AUC_{0\text{-}84d}$ (ng.d/mL)	462	2,482	413	2,551
$AUC_{0\text{-}\infty}$ (ng.d/mL)	520	2,468	-	-
$t_{1/2}$ (d)	27.4[a]	47.5[a]	15.5[b]	14.7[b]
$C_{av,\tau}$ (ng/mL)	5.5	30	4.4	28
C_{max}/C_{τ}	13	11	5.0	5.4

[a] $t_{1/2,\ 29d\text{-}84d}$; [b] $t_{1/2,\ 66d\text{-}84d}$

2.6.6.4 Genetic toxicology

1. Study title: *In Vitro* Bacterial Reverse Mutation Test with *Salmonella typhimurium*

Key findings: Paliperidone palmitate did not cause any biologically significant increase of the number of revertant colonies above the solvent control incidence in the *in vitro* bacterial mutation test. Therefore, it can be concluded that paliperidone palmitate has no mutagenic properties in *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA98, and TA100 in the presence and in the absence of rat metabolic activation system up to 500 µg/plate under conditions of this study.

Study no.: TOX3985
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Research Foundation, Turnhoutseweg 30 B-2340 Beerse, Belgium
Date of study initiation: August 29, 1996
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: paliperidone palmitate (R092670); batch No.: ZR092670PL2; purity: not provided

Methods
Strains/species/cell line: *Salmonella typhimurium* strains TA1535, TA1537, TA102, TA98, and TA100
Doses used in definitive study: Paliperidone palmitate was tested at seven concentrations: 5, 10, 25, 50, 100, 250, and 500 µg/plate.
Basis of dose selection: No range finding study was done. Paliperidone palmitate was solved in DMSO at the concentration of 50 mg/mL (= 500 µg/plate) after which serial dilutions were made. However, the 50 mg paliperidone palmitate/mL DMSO formulation had to be warmed up slightly to get paliperidone palmitate into solution. After cooling to room temperature, the 50, 25, and 10 mg paliperidone palmitate/mL DMSO formulations (= 5000, 2500, and 1000 µg paliperidone palmitate/plate) precipitated. For this reason, 500 µg paliperidone palmitate/plate was selected as the top concentration for the main study.
Negative controls: A concurrent solvent control was performed. DMSO was used as solvent control for the test article.
Positive controls: Positive controls were used in the tests according to the following Sponsor's table:

Compound	CAS No.	Solvent	Without or with S9	Strains
2-nitrofluorene	607-57-8	DMSO	without	TA98
sodiumazide	26628-22-8	Water	without	TA1535,TA100
9-aminoacridine	90-45-9	DMSO	without	TA1537
2-aminoanthracene	613-13-8	DMSO	with	All strains
4-nitroquinoline-N-oxide	56-57-5	DMSO	without	TA102

Incubation and sampling times: Plates were counted after approximately 48 h of incubation at 37°C.

Results

Study validity: Each tests included 7 concentrations of paliperidone palmitate, solvent controls, and positive controls, under the same experimental conditions with or without metabolic activation (Aroclor 1254 induced male liver). All concentration levels of paliperidone palmitate, solvent controls, and positive controls were tested in triplicate. All plates were counted manually. The following criteria for positive results were used: (1) The test is valid, (2) Paliperidone palmitate produces at least a two-fold increase in the mean number of revertants with one of the strains TA98, TA102 or TA100, or a threefold increase in the mean number of revertants with one of the strains TA1535, TA1537 at one or more concentration levels, (3) a dose effect relationship is observed, and (4) these effects can be reproduced in an additional study. The tests were performed up to precipitating levels of 250 and 500 µg/plate. Decreasing concentration levels from the highest concentration level provided adequate number of data points to ensure that any possible dose-response would have been detected. The positive controls caused significant increases in the number of revertant colonies demonstrating their mutagenic activity. The number of spontaneous and solvent control revertant colonies fell within the range of laboratory historical data for all strains except TA102, for which no sufficient historical control data were available. As all of the tests satisfied the criteria for a valid test, no further testing was done.

Study outcome: In the absence and presence of metabolic activation, a dose related increase in precipitation of the test article was observed with all of the strains at concentrations of 250 and 500 paliperidone palmitate µg/plate. At concentrations 5-500 µg/plate, paliperidone palmitate did not reveal any biologically significant increase in the number of revertant colonies, either in the presence or absence of metabolic activation. Based on the lack of biologically significant increase of the number of revertants, it can be concluded that paliperidone palmitate has no mutagenic properties in *Salmonella typhimurium* strains in the presence and in the absence of rat metabolic activation system under conditions of this study.

2. Study title: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) Using the Microtitre^{R} Fluctuation Technique

Key findings: Paliperidone palmitate was not mutagenic in the mouse lymphoma L5178Y cells when tested using the microtitre fluctuation technique up to the maximum practicable concentration (70 µg/mL) under the conditions employed in this study.

Study no.: TOX6362
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: February 23, 2004
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: paliperidone palmitate (R092670), batch no. ZR092670PFA041, purity: 99.8%

Methods
Strains/species/cell line: mouse lymphoma L5178Y cells
Doses used in definitive study: In the Experiment 1 (3 hour treatment; in the absence or presence of S-9), the following six concentrations of paliperidone palmitate were tested: 10, 20, 40, 50, 60, and 70 µg/mL. In the Experiment 2 (24 hour treatment in the absence of S-9, 3 hour treatment in the presence of S-9), the following ten concentrations of paliperidone palmitate were tested in the absence of S-9: 1, 2, 4, 6, 7, 8, 9, 10, 12.5, and 15 µg/mL; In the presence of S-9, the following six concentrations were tested: 10, 20, 40, 50, 60, and 70 µg/mL.
Basis of dose selection: Test article concentrations were selected based on cytotoxicity range-finding study, in which 9 doses of paliperidone palmitate ranging from 0.293 to 70 µg/mL (limited by solubility in the primary solvent) were tested in the absence of metabolic activation following 24 hour treatment. Marked toxicity was observed at concentration of 9.375 µg/mL (that yielded 18% of relative survival) and above. In addition, 6 doses of paliperidone palmitate ranging from 2.344 to 70 µg/mL were tested in the absence or presence of metabolic activation following 3 hours treatment. Upon addition of the test article to the cultures, precipitate was observed at the highest dose tested, but no precipitate was observed following the treatment incubation period. The highest dose of 70 µg/mL yielded 47% and 103% relative survival in the absence or presence of metabolic activation, respectively.
Negative controls: solvent (acetone)
Positive controls: The positive controls used are shown in the following Sponsor's table:

Chemical	Source	Stock* concentration (µg/mL)	Final concentration (µg/mL)	S-9
4-nitroquinoline 1-oxide (NQO)	Sigma-Aldrich Chemical Co, Poole, UK	15	0.15#	-
		20	0.20#	-
benzo(a)pyrene (BP)	Sigma-Aldrich Chemical Co, Poole, UK	200	2.00	+
		300	3.00	+

* All solutions were prepared in anhydrous analytical grade dimethyl sulphoxide (DMSO). BP and NQO stock solutions were stored as frozen aliquots at –80°C in the dark.

\# For Experiment 2 - S-9 (24 hour treatment), final concentrations of NQO were 0.02 and 0.04 µg/mL, respectively.

Results

Study validity: Paliperidone palmitate was tested for its ability to induce mutations at the *tk* locus in mouse lymphoma cells. A cytotoxicity range finding assay was conducted to select concentrations for the subsequent two independent experiments. Precipitate was observed at the highest concentrations tested (70 µg/mL) in these experiments. The numbers of small and large colonies were scored for the negative and positive controls. Marked increases in the number of these colonies were observed following treatment with the positive controls. The test article was considered to be mutagenic if all the following criteria were met: (1) the assay was valid, (2) the mutant frequency at one or more doses was significantly greater than that of the negative control ($p<0.05$), (3) there was a significant dose-relationship as indicated by the linear trend analysis ($p<0.05$), and (4) the effects were reproducible. The acceptance criteria were met and the study was considered to be valid.

Study outcome: No statistically significant increases in mutant frequency were observed following treatment with paliperidone palmitate at any concentration levels tested in two independent experiments, in the absence or presence of S-9.

Genetic toxicology studies with impurities:

3. Study title: (b) (4) Reverse mutation assay "AMES test" screening method using *Salmonella typhimurium* TA100, TA98 and TA102.

Key study findings: (b) (4) induced dose-related and toxicologically significant increases in revertant colony frequency in tester strain TA100, both with and without metabolic activation. Therefore, (b) (4) was considered to be mutagenic under the conditions of this study.

Study no.: 1827/022
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: July 17, 2003

GLP compliance: no
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: (b) (4) batch No. 00409328; purity: not provided

Methods: (b) (4) was tested using the Ames plate incorporation method in *Salmonella typhimurium* strains TA98, TA100, and TA102 at nine concentrations (0.5 to 5000 µg/plate in the main experiment) in triplicate, both with and without the addition of a rat liver homogenate metabolizing system (10% liver S9 in standard co-factors). (b) (4) caused no visible reduction in the growth of the bacterial background lawn at any concentration level. No test article precipitate was observed on the plates at any of the concentrations tested. Therefore, the test article was tested up to the maximum recommended concentration level of 5000 µg/plate.

Results: All of the positive control chemicals produced increases in the frequency of revertant colonies, both with and without metabolic activation. The vehicle (dimethyl sulphoxide) control plates gave counts of revertant colonies within the normal range. Therefore, the sensitivity of the assay and the efficacy of the S9-mix were validated. Significant increases in revertant colony frequency were observed in tester strain TA100. The number of revertants (mean number of colonies per plate) was 91, 121, 235, 498, and 224 in the vehicle control, 500 µg/plate, 1500 µg/plate, 5000 µg/plate, and positive control (3 µg ENNG/plate) plates, respectively, in the assay without metabolic activation. The number of revertants (mean number of colonies per plate) was 83, 217, 491, 873, and 1255 in the vehicle control, 500 µg/plate, 1500 µg/plate, 5000 µg/plate, and positive control (1 µg 2AA/plate) plates, respectively, in the assay with metabolic activation. No significant increases in the frequency of revertant colonies were recorded for other strains used in this study.

4. Study title: (b) (4): Screening chromosome aberration test in human lymphocytes *in vitro.*

Key findings: (b) (4) induced statistically significant increase in the frequency of cells with chromosome aberrations in the absence of a liver enzyme metabolizing system after a 4-hour exposure. Therefore, (b) (4) was considered to be clastogenic in human lymphocytes *in vitro*, under conditions of this study.

Study no.: 1827/022
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: April 29, 2003
GLP compliance: no
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: (b) (4), batch No. 00409328; purity: not provided

Methods: Duplicate cultures of human lymphocytes were exposed to a series of concentrations of the test article in three exposure groups (4 hours in the presence of an

induced rat liver homogenate metabolizing system (S9) with cell harvest after a 20-hour expression period; 4-hour exposure in the absence of metabolic activation (S9) with a 20-hour expression period; and 24-hour continuous exposure in the absence of S9), as shown in the following Sponsor's table:

Group	Final concentration of (b) (4) (µg/ml)
4(20)-hour without S9	0*, 40, 80*, 120*, 160, 320*, 480, MMC 0.4*
4(20)-hour with S9	0*, 80*, 160*, 240*, 320, 480, 640, CP 10*
24-hour without S9	0*, 20*, 40*, 80*, 120, 160, 240, MMC 0.2*

* dose levels selected for metaphase analysis; MMC: mitomycin C; CP: cyclophosphamide

A minimum of three concentration levels and the concurrent vehicle and positive controls were evaluated for chromosome aberrations for each exposure group.

Results: Treatment with (b) (4) induced 56% mitotic inhibition at 320 µg/mL in the 4 (20)-hour exposure group without S9, 64% mitotic inhibition at 240 µg/mL in the 4 (20)-hour exposure group with S9, and 75% mitotic inhibition at 80 µg/mL in the 24-hour exposure group without S9. Therefore, acceptable levels of toxicity were achieved in all cases. In all treatment groups, the maximum concentrations evaluated for chromosome aberrations were selected on the basis of their toxicity. All of the vehicle control cultures had frequencies of cells with chromosome aberrations within the expected range. The positive controls induced statistically significant increases in the frequency of cells with aberrations. Therefore, the validity of the test method was confirmed. Treatment with (b) (4) induced statistically significant increases in the frequency of cells with aberrations in the absence of metabolic activation (S9) after a 4-hour exposure. The response was predominantly due to chromatid breaks observed at 160 and 320 µg/mL concentration levels. The frequency of aberrant cells was 1%, 7%, 11%, and 13% in the vehicle control, 160 µg/mL, 320 µg/mL, and positive control (mitomycin C) groups, respectively, following 4 (20)-hour treatment without metabolic activation. Treatment with (b) (4) did not induce a statistically significant increase in the numbers of polyploid cells at any dose level in any of the treatment groups.

5. Study title: (b) (4): Reverse mutation assay "AMES test" screening method using *Salmonella typhimurium* TA100, TA98 and TA102.

Key study findings: (b) (4) induced dose-related and toxicologically significant increases in revertant colony frequency in tester strain TA100, both with and without metabolic activation, and in the strains TA102 and TA98 in the presence of metabolic activation. Therefore, (b) (4) was considered to be mutagenic under the conditions of this study.

Study no.: 1827/016
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: July 17, 2003
GLP compliance: no
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: (b) (4) batch No. 00282450; purity: not provided

Methods: (b) (4) was tested using the Ames plate incorporation method in *Salmonella typhimurium* strains TA98, TA100, and TA102 at nine concentrations (0.5 to 5000 µg/plate in the main experiment) in triplicate, both with and without the addition of a rat liver homogenate metabolizing system (10% liver S9 in standard co-factors). (b) (4) caused reduction in the growth of the bacterial background lawn in all of the tester strains (except TA102 with metabolic activation) at concentration level of 1500 µg/plate. No test article precipitate was observed on the plates at any of the concentrations tested. Therefore, the test article was tested up to the maximum recommended concentration level of 5000 µg/plate.

Results: All of the positive control chemicals produced increases in the frequency of revertant colonies, both with and without metabolic activation. The vehicle (sterile water) control plates gave counts of revertant colonies within the normal range. Therefore, the sensitivity of the assay and the efficacy of the S9-mix were validated.
Significant increases in revertant colony frequency were observed in tester strain TA100. The number of revertants (mean number of colonies per plate) was 83, 285, 535, 843, 1068, and 224 in the vehicle control, 150 µg/plate, 500 µg/plate, 1500 µg/plate, 5000 µg/plate, and positive control (3 µg ENNG/plate) plates, respectively, in the assay without metabolic activation. The number of revertants (mean number of colonies per plate) was 83, 231, 606, 867, 1584, 2342, 1578, 1018, and 1255 in the vehicle control, 5 µg/plate, 15 µg/plate, 50 µg/plate, 150 µg/plate, 500 µg/plate, 1500 µg/plate, 5000 µg/plate, and positive control (3 µg ENNG/plate) plates, respectively, in the assay with metabolic activation. The increases in the frequency of revertant colonies were also recorded for other strains used in this study at the upper concentrations of the test article in the presence of metabolic activation only.

6. Study title: (b) (4): Screening chromosome aberration test in human lymphocytes *in vitro.*

Key findings: (b) (4) induced statistically significant increase in the frequency of cells with chromosome aberrations in the absence of a liver enzyme metabolizing system after a 4-hour exposure. Therefore, (b) (4) was considered to be clastogenic in human lymphocytes *in vitro*, under conditions of this study.

Study no.: 1827/017
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)

Date of study initiation: April 29, 2003
GLP compliance: no
QA reports: yes ( ) no (x)

Drug, lot #, and % purity: (b) (4) batch No. 00393669; purity: not provided

Methods: Duplicate cultures of human lymphocytes were exposed to a series of concentrations of the test article in three exposure groups: 4 hours in the presence of metabolic activation (an induced rat liver metabolizing system S9) with cell harvest after a 20-hour expression period; 4-hour exposure in the absence of metabolic activation with a 20-hour expression period; and 24-hour continuous exposure in the absence of metabolic activation, as shown in the following Sponsor's table:

Group	Final concentration of (b) (4) (µg/ml)
4(20)-hour without S9	0*, 37.5, 75*, 150*, 200*, 250, 300, MMC 0.4*
4(20)-hour with S9	0*, 1.18, 2.35, 4.7*, 9.4*, 18.75*, 37.5, , CP 10*
24-hour without S9	0*, 5, 10, 20, 40*, 60*, 80*, MMC 0.2*

* dose levels selected for metaphase analysis; MMC: mitomycin C; CP: cyclophosphamide

A minimum of three concentration levels and the concurrent vehicle and positive controls were evaluated for chromosome aberrations for each exposure group.

Results: Treatment with (b) (4) induced 54% mitotic inhibition at 200 µg/mL in the 4 (20)-hour exposure group without S9, 58% mitotic inhibition at 18.75 µg/mL in the 4 (20)-hour exposure group with S9, and 53% mitotic inhibition at 80 µg/mL in the 24-hour exposure group without S9. Therefore, acceptable levels of toxicity were achieved in all cases. In all treatment groups, the maximum concentrations evaluated for chromosome aberrations were selected on the basis of their toxicity. All of the vehicle control cultures had frequencies of cells with chromosome aberrations within the expected range. The positive controls induced statistically significant increases in the frequency of cells with aberrations. Therefore, the validity of the test method was confirmed. Treatment with (b) (4) induced statistically significant increases in the frequency of cells with aberrations in the presence of metabolic activation (S9) after a 4-hour exposure. The response was predominantly due to chromatid breaks, chromatid exchanges, and chromosome breaks observed at 9.4 and 18.75 µg/mL concentration levels. The frequency of aberrant cells (without gaps) was 1%, 20%, 14%, and 16% in the vehicle control, 9.4 µg/mL, 18.75 µg/mL, and positive control (cyclophosphamide) groups, respectively, following 4 (20)-hour treatment with metabolic activation. Treatment with (b) (4) did not induce a statistically significant increase in the numbers of polyploid cells at any dose level in any of the treatment groups.

2.6.6.5 Carcinogenicity

Study title: 24-month intermittent dose intramuscular carcinogenicity study in the rat

Key study findings: Intramuscular administration of paliperidone palmitate for 104 weeks resulted in increased mortality in male rats at 30 (MD) and 60 (HD) mg eq. /kg b.w./month when compared to control groups (63% and 77% of animals died, respectively, compared to 49% in saline controls and 51% in vehicle controls). In female

rats, minimally higher mortality was observed at the MD. Since the increase in mortality in female rats was not dose related, it was considered to be incidental. Dosing with paliperidone resulted in narrowing of the palpebral fissure in both sexes at all dose levels throughout the study. An increased incidence of small skin lesions located on subcutaneous tissue masses was observed in female rats at all dose levels and in MD and HD males. At terminal sacrifice, body weight in HD males was 9% and 11% less than that of the saline and vehicle control groups, respectively. In HD females, body weight was 11% and 13% less than that of the saline and vehicle control groups, respectively. Therefore, the MTD was achieved in this study. There were no toxicologically significant changes in food consumption. A fibrohistiocytic inflammatory reaction was observed at the injection site mainly in HD and MD male and female rats. A prominent granulocytic reaction resulting in abscess formation was observed occasionally in HD animals of both sexes. Prolactin mediated effects were seen in both sexes, manifested by the slightly increased incidences of swollen pituitaries in both sexes and mammary gland secretion in males as well as the slightly lower incidence of cysts in the uterus in females. Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in male rats using the vehicle control and all treated groups but not using the saline control group. Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. The increased incidences of combined mammary gland tumors in male rats may be related to increased prolactin levels observed in male rats in this study. Prolactin levels were increased also in female rats. However, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors in female rats, except for the LD vs. the vehicle comparison of adenocarcinomas.

Adequacy of the carcinogenicity study and appropriateness of the test model:

In general, the Agency requires studies in two rodent species for the carcinogenicity assessment. However, injected i.m. paliperidone palmitate is hydrolized to paliperidone. Marketed oral paliperidone (INVEGA) is the major active metabolite of marketed risperidone (RISPERDAL). Carcinogenicity studies with risperidone in rats and mice were conducted and previously reviewed by the Agency. Therefore, the Division agreed that only one species study (rat) was sufficient for the assessment of the carcinogenic potential of paliperidone palmitate.

The study was conducted according to standard procedures to assess the carcinogenic potential of the test article. Rats (Sprague-Dawley) were selected based on recommendations of applicable guidelines and available historical control data for this species in the Sponsor's laboratory conducting the study. Rats were treated with paliperidone palmitate *via* intramuscular injection for 104 weeks at dosages accepted by the Agency's Executive CAC on November 9, 2004. The intramuscular route was selected since this is the intended route of human exposure to paliperidone palmitate. Paliperidone palmitate was formulated in an aqueous suspension composed of polysorbate 20, cytric acid monohydrate, disodium dihydrogen phosphate, and NAOH.

One control group was administered this aqueous suspension and the second control group received saline. An adequate number of animals (65/group) was used. Treatment with paliperidone palmitate produced evidence of toxicity in male rats decreasing survival from Week 92 in the MD group and from Week 72 in the HD group, when compared to the control groups. Statistical analysis showed highly statistically significant dose response relationship for mortality in male rats. No test article-related increases in mortality were seen in female rats. At terminal sacrifice, body weight in HD males was 9% and 11% less than that of the saline and vehicle control groups, respectively. In HD females, body weight was 11% and 13% less than that of the saline and vehicle control groups, respectively. Therefore, the MTD was achieved in this study. Exposures to the test article (paliperidone palmitate) as well as paliperidone were demonstrated in this study with no overlap of AUC values of the different dose groups at each time point measured. A complete histopathological examination was performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the study. It is concluded that this carcinogenicity study is adequate.

Evaluation of tumor findings:

Statistical evaluation of the incidence of tumors was conducted by the reviewing mathematical statistician Dr. Atiar Rahman.

Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in males (0/65, 0/65, 8/65, and 4/65 in the vehicle control, LD, MD, and HD, respectively, using the vehicle control and all treated groups but not using the saline control group; the incidence in this group was 1/65). Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. [It should be noted that prolactin levels were increased in male and female rats in this study].

In female rats, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors, except for the LD vs. the vehicle comparison of adenocarcinomas (15/65, 32/65, 28/65, and 29/65 in the vehicle control, LD, MD, and HD, respectively).

The incidences of pancreatic islet cell tumors (islet cell adenomas and islet cell carcinomas) were slightly increased but not dose related in males at all dose levels when compared to the vehicle control group (islet cells adenomas: 10/65, 6/65, 15/65, 16/65, and 12/65 in the saline control, vehicle control, LD, MD, and HD, respectively; islet cells carcinomas: 2/65, 3/65, 0/65, 2/65, and 2/65 in the saline control, vehicle control, LD, MD, and HD, respectively; combined pancreatic islet cell tumors: 12/65, 9/65, 15/65, 18/65, and 14/65 in the saline control, vehicle control, LD, MD, and HD, respectively). These increases were not statistically significant according to CDER criteria.

Based on CDER criteria of adjustment for multiple testing of trends, the incidences of hepatocellular adenoma in male rats (0/65, 1/65, 1/65, and 3/65 in the vehicle control, LD, MD, and HD, respectively) were statistically significant using the vehicle control and all treated groups (but not using the saline control group). However, the pairwise comparisons of the vehicle control with the LD, MD, or HD groups for the incidence of hepatocellular adenoma were not statistically significant. There was no increase in carcinomas in that tissue. The incidence of hepatocellular adenomas in male rats in the saline control group (3/65) was equal to that in HD males. Therefore, the increase in hepatocellular adenomas in HD male rats is not considered drug related.

Study no.: TOX6726
Volume #, and page #: electronic submission
Conducting laboratory and location: Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: November 25, 2004
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone palmitate (R092670); batch No. 04J11/F013 and No. 05E26/F13D;
CAC concurrence: yes (November 9, 2004)

Methods

Doses: 10, 30, and 60 mg paliperidone eq./kg b.w./month (LD, MD, and HD, respectively)

Basis of dose selection: The dose selection for the present study was based upon the MTD determined in a previously conducted 3-month intramuscular toxicity study with paliperidone palmitate in Sprague-Dawley rats and a 6-month intramuscular toxicity study with paliperidone palmitate in Wistar rats. In both studies, the dose levels administered were 20, 80, and 160 mg paliperidone eq./kg b.w./month. The top dose of 60 mg eq./kg/month was selected for the carcinogenicity study in male rats based on dose limiting toxicities observed at dose levels of 80 and 160 mg eq./kg/month. These toxicities consisted of a decrease in body weight gain in the 3-month intramuscular toxicity study greater than 10% and an injection site necrosis in the 6-month intramuscular toxicity study. The top dose of 60 mg eq./kg/month was selected for the carcinogenicity study in female rats based on the following observations: (1) treatment-related mortality caused by injection site damage was occasionally seen at 160 mg eq./kg/month in the 3-month study, and (2) injection site necrosis was observed at doses greater than or equal to 20 mg eq./kg/month in the 6-month intramuscular toxicity study. The number of animals showing injection site necrosis and a degree of trauma observed at 80 and 160 mg eq./kg/month was expected to decrease survival in the carcinogenicity study. The top dose level of 60 mg eq./kg/month (i.e., 360 mg eq./m^2/month) in male and female rats is approximately 3.9-fold higher than the maximum recommended human dose for paliperidone palmitate on a mg/m^2 basis (i.e., 150 mg eq./4 weeks or 92.5 mg eq./m^2/4 weeks).

Species/strain: rat/Sprague-Dawley Crl:CD®
Number/sex/group (main study): 65
Route, formulation, volume: intramuscular (*m. biceps femoris*); aqueous suspension containing polysorbate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, citiric acid monohydrate, sodium hydroxide, polyethylene glycol 4000, and water; volume: 2 x 0.3 (0.6), 2 x 0.3 (0.6), 0.1, 2 x 0.15 (0.3), and 2 x 0.3 (0.6) mL/kg b.w./month per injection site administered bilaterally
Frequency of dosing: once a month (once every 4 weeks)
Satellite groups used for toxicokinetics: 6/sex/group
Age: approximately 5 to 6 weeks on Day 0
Animal housing: Rats were housed individually in wire-mesh cages.
Restriction paradigm for dietary restriction studies: NA
Drug stability/homogeneity: Test article formulations of batch No. 04J11/F013 were analyzed on a 3 monthly basis. Batch No. 05E26/F13D was only analyzed once during the study instead of on a 3-monthly basis because the shelf life of the test article formulations was 24 months, based on available stability data.
Dual controls employed: saline control group (0.9% NaCl w/v) and vehicle control group (aqueous suspension not loaded with paliperidone palmitate),
Interim sacrifices: none
Deviations from original study protocol: none

Observations, times, and results:

Mortality: All animals were observed at least once a day for moribund state or mortality. No differences in mortality were observed between male and female rats of the saline control and vehicle control groups. Mortality rate was slightly increased in MD males from Week 92 and in HD males from Week 72 of the treatment when compared with the saline control or vehicle control groups. Male mortality data at the end of 24-month treatment period are shown in the following table:

Dose Group (mg eq./kg/month)	Saline Control	Vehicle Control	Low (10)	Medium (30)	High (60)
No. of males that died or were sacrificed moribund/No. of animals (% animals that died)	32/65 (49.2%)	33/65 (50.8%)	32/65 (49.2%)	41/65 (63.1%)	50/65 (76.9%)

The statistical analysis of mortality data in male rats showed a highly statistically significant dose-response relationship. The intercurrent mortality data for male rats (Table 1A), results of the test for dose response relationship and homogeneity of survivals of male rats (Table 2A), and Kaplan-Meier survival curves for male rats (Figure 1A) taken directly from Dr. Rahman's statistical review are shown below:

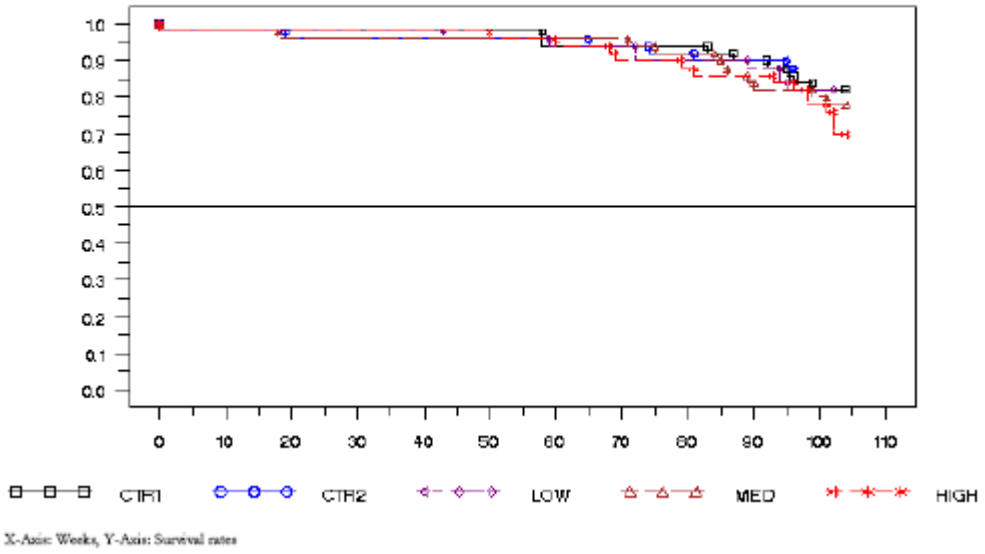
Table 1A: Intercurrent Mortality Rate
Male Rats

Week	NEGATIVE CONT No. of Death	Cum. %	VEHICLE CONT No. of Death	Cum. %	LOW No. of Death	Cum. %	MEDIUM No. of Death	Cum. %	HIGH No. of Death	Cum. %
0-52	3	4.6	4	6.2	2	3.1	1	1.5	1	1.5
53-78	6	13.8	4	12.3	6	12.3	6	10.8	15	24.6
79-91	6	23.1	12	30.8	9	26.2	13	30.8	12	43.1
92-104	16	47.7	13	50.8	15	49.2	21	63.1	21	75.4
Term. Sac.	34	52.3	32	49.2	33	50.8	24	36.9	16	24.6

Table 2A: Intercurrent Mortality Comparison
Male Rats

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.0002	0.0005
Homogeneity	0.0047	0.0121

Figure 1A: Kaplan-Meier Survival Functions for Male Rats
Male Rats



X-Axis: Weeks, Y-Axis: Survival rates

In female rats, minimally higher mortality was observed at the MD (71% of animals died compared to 63% in the vehicle control group). Since this increase was not dose related, it is considered to be incidental. Female mortality data at the end of 24-month treatment period are shown in the following table:

Dose Group (mg eq./kg/month)	Control (0)	Vehicle (00)	Low (10)	Medium (30)	High (60)
No. of females that died or	35/65	41/65	45/65	46/65	42/65

were sacrificed moribund/ No. of animals (% animals that died)	(53.8%)	(63.1%)	(69.2%)	(70.8%)	(64.6%)

There was no statistically significant dose-response relationship among treatment groups or difference between treatment groups in mortality in female rats. The intercurrent mortality data for female rats (Table 1B), results of the test for dose response relationship and homogeneity of survivals of female rats (Table 2B), and Kaplan-Meier survival curves for female rats (Figure 1B) taken directly from Dr. Rahman's statistical review are shown below:

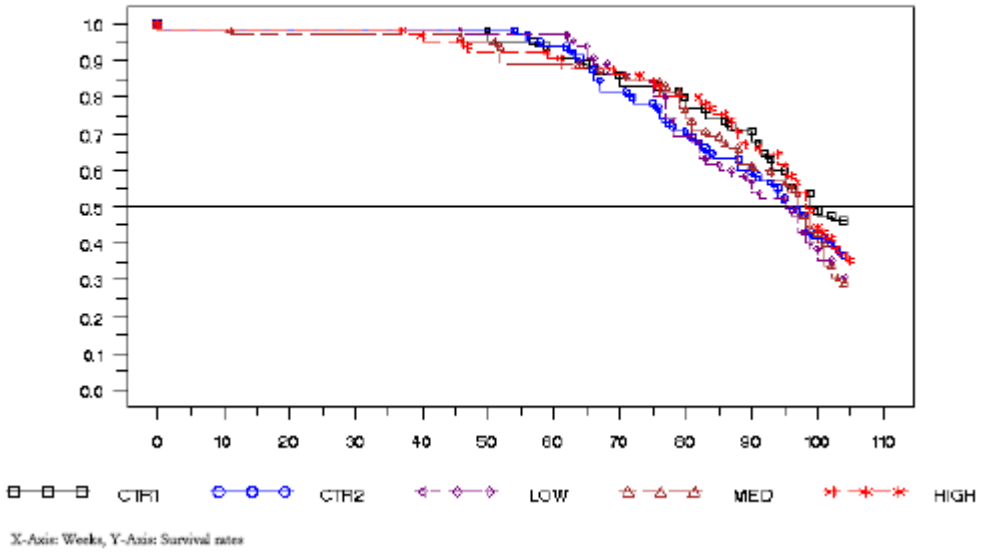
Table 1B: Intercurrent Mortality Rate
Female Rats

	NEGATIVE C		VEHICLE CO		LOW		MEDIUM		HIGH	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0-52	1	1.5	.	.	1	1.5	4	6.2	4	6.2
53-78	10	16.9	18	27.7	16	26.2	7	16.9	7	16.9
79-91	10	32.3	9	41.5	13	46.2	14	38.5	11	33.8
92-104	14	53.8	14	63.1	15	69.2	21	70.8	19	63.1
Term. Sac.	30	46.2	24	36.9	20	30.8	19	29.2	24	36.9

Table 2B: Intercurrent Mortality Comparison
Female Rats

Test	P-Value Cox	P-Value Kruskal-Wallis
Dose Response	0.8586	0.8393
Homogeneity	0.4391	0.5554

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Female Rats



X-Axis: Weeks, Y-Axis: Survival rates

Clinical signs: Animals were observed for clinical signs at least once a day. An extensive examination was performed weekly to detect new masses and to give them a score. The time of onset, location, dimensions, appearance, and progression of each visible or palpable mass were recorded after palpation. The discovered masses were checked and scored daily. Dosing with paliperidone resulted in narrowing of the palpebral fissure in both sexes at all dose levels throughout the study. Narrowing of the palpebral fissure lasted for one day in LD animals of both sexes (occasionally was observed during 2 to 10 days) and generally was present on the days of dosing or in the first week or 2 weeks after dosing (lasting for one or more days) in MD and HD animals of both sexes. This effect was slightly more pronounced and the frequency was higher at the HD compared to the MD. An increased incidence of presence of long nails and local swelling (noticed mainly in the hind foot) was observed in male rats at all dose levels. This finding correlated histologically with granulomatous chronic inflammation but not with the intramuscular injection of the test article. The focal swelling and long nails were generally present in the second year of the study, with the occurrence higher towards the end of the study. According to the Sponsor, these observations may be related to the marginally lower activity resulting from the sedative pharmacological effect of the test article in combination with the wire mesh housing conditions. An increased incidence of small skin lesions located on subcutaneous tissue masses was observed in female rats at all dose levels and in MD and HD males. Additionally, a slightly higher incidence of chromodacryorrhea was observed in MD and HD female rats.

The following table shows the incidence of test article related clinical observations per dosage group:

	Males (N=65)					**Female** (N=65)				
	Saline Contr.	Vehic. Contr.	10 mg eq/day	30 mg eq/day	60 mg eq/day	Saline Contr.	Vehic. Contr.	10 mg eq/day	30 mg eq/day	60 mg eq/day
Cold extremities	0	1	2	7	10 **	1	3	8	5	8
Subcutaneous tissue mass	30	31	34	37	42	43	42	44	45	45
Cutaneous tissue mass	10	5	9	8	8	2	0	4	2	3
Focal swelling	14	11	23*	39***	39***	9	6	8	7	16*
Narrowing of palpebral fissure	3	9	19	62***	63***	10	4	28***	61***	65***
Exophthalmia	0	0	0	1	0	0	1	2	5	8*
Chromodacryorrhea	10	14	8	16	17	26	26	30	34	41*
Long nails	10	8	20*	28***	22**	2	2	2	8	1
Broken nails	9	14	10	10	8	0	2	2	8	7
Trimmed/cut abnormal nails	2	1	7	14***	10**	0	0	0	0	0
Skin irritation	7	6	4	7	12	6	7	10	10	18*
Skin lesions	32	24	35	44***	51***	9	10	19	21*	20

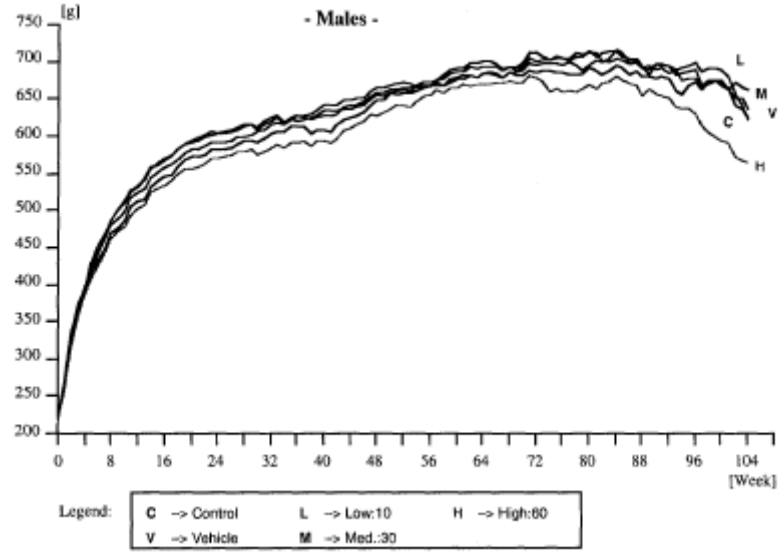
(Significance level computed by the Sponsor with Fisher Exact probability test; two tailed: * $p < .05$, ** $p < .01$, *** $p < .001$ versus the vehicle control group).

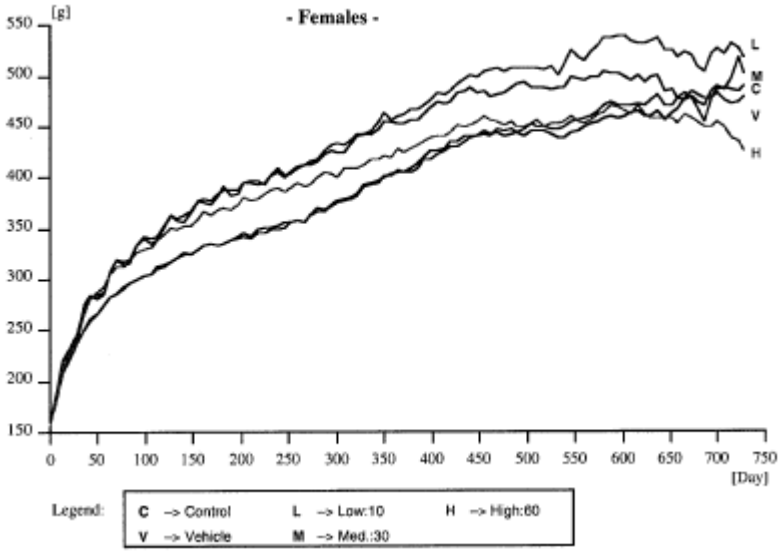
Ophthalmology: An ophthalmic examination of conjunctiva, sclera, cornea, iris, lens, and fundus was performed prior to start of dosing (Day-3), at Weeks 26, 52, and 104 of dosing using a slit lamp biomicroscope on the first twenty surviving animals of each sex in the HD group and both control groups of the main toxicity study. There were no treatment-related ocular findings in males and females examined.

Body weights: Body weights of all animals from the main toxicity study were recorded prior to treatment, on Day 0, and at weekly intervals. Terminal body weights were recorded on the day of necropsy for determination of relative organ weights. Body weight was also recorded in any rat sacrificed moribund during the study. In males, treatment at the LD did affect body weight. Dosing at the MD resulted in minimally lower body weight gain and body weight during the first 9.5 months of the study and later resulted in minimal increase in body weight gain as well as body weight (by 6 and 4% when compared to the saline and vehicle control groups, respectively). Dosing at the HD resulted in moderately lower body weight and body weight gain during the first 10 months and during the last 2 months of the study. At termination, body weight was 9% and 11% less than that of the saline and vehicle control groups, respectively.

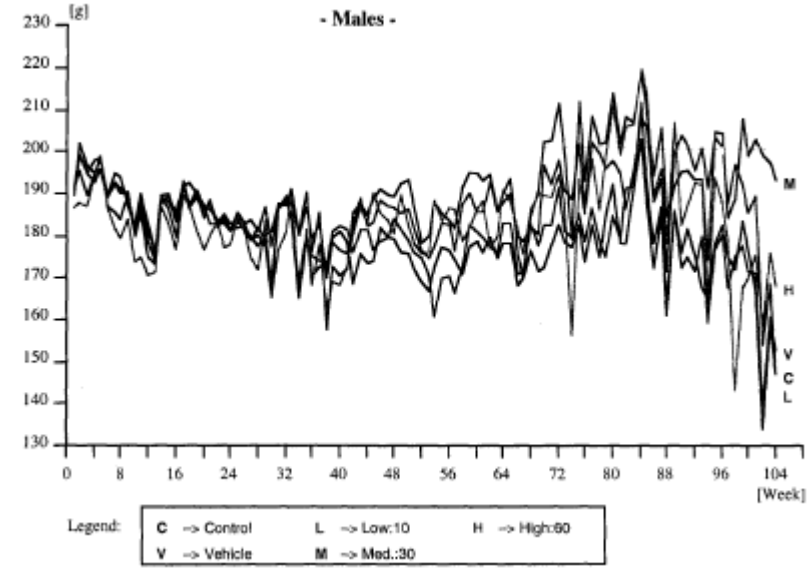
In females, treatment at the LD slightly to moderately increased body weight gain and body weight throughout the study when compared to both controls. Dosing at the MD resulted also in slightly to moderately higher body weight gain and body weight up to 11 weeks before the end of the study. At the end of the study, body weight at MD was comparable to both controls. Dosing at the HD resulted in moderately higher body weight and body weight gain during the first half of the study. At termination, body weight was 11 and 13% less than that of the saline and vehicle control groups, respectively.

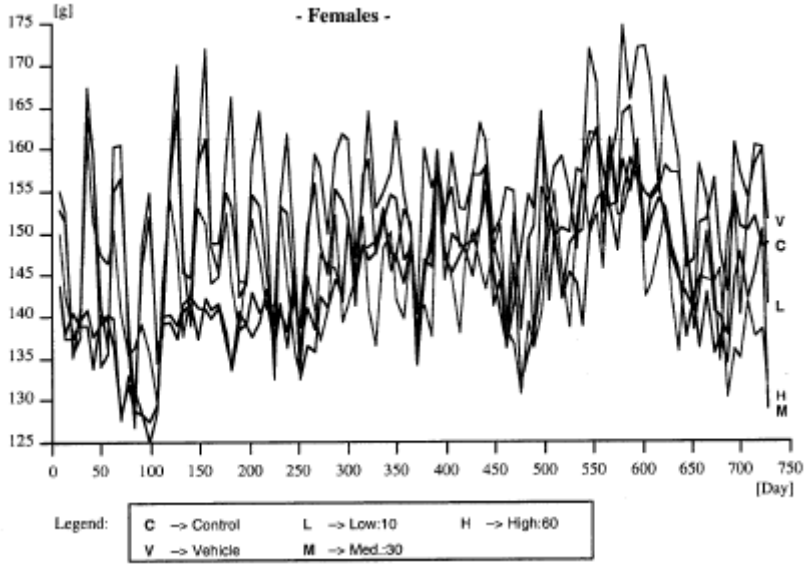
The sponsor's figures illustrating changes in body weight of the animals over the course of the carcinogenicity study are shown below:





Food consumption: Food consumption was determined at weekly intervals. Dosing at 10 mg eq./kg b.w./month for 104 weeks resulted in a minimally higher (by 2.3 and 5.5%, respectively, compared to the vehicle control group) total food consumption in male and female rats. Dosing at 30 mg eq./kg b.w./month resulted also in a minimally higher (by 4.6 and 3.0%, respectively, compared to the vehicle control groups) total food consumption in male and female rats. Total food consumption of both sexes dosed at 60 mg eq./kg b.w./month did not differ from vehicle dosed male and female rats. There were no relevant differences in mean weekly and total food consumption between rats of the saline and vehicle dosed control groups. The sponsor's figures illustrating changes in food consumption of the animals over the course of the carcinogenicity study are shown below:





Clinical pathology: Hematology, clinical chemistry, and urinalysis examinations were performed in the first 20 surviving rats/sex/group of the main toxicity study at 12 month of dosing and on all surviving rats of the main toxicity study after 24 month of dosing. Endocrinology was performed in all rats of the toxicokinetic study part. The laboratory investigations were also carried out in moribund animals whenever possible. The following hematology parameters were assessed: white blood cell count, red blood cell count, hemoglobin, hematocrit, red blood cell indices (mean cell volume, mean cell

hemoglobin, mean cell hemoglobin concentration), reticulocytes, thrombocyte count, normoblasts, differential white blood cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), blast cells, promyelocytes, myelocytes, metamyelocytes, and juvenile forms. The following clinical chemistry parameters were assessed: sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, albumin, glucose, cholesterol, triglycerides, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and gamma glutamyl transferase. The following urinalysis parameters were assessed: specific gravity, pH, volume, proteins, glucose, ketones, occult blood, color, clarity, and sediment.

Hematology: Dosing paliperidone palmitate to female rats at 10 mg eq./kg b.w./month during 104 weeks did not lead to any relevant changes in hematology parameters. In males, transient and slight increases in neutrophils and monocytes, minimal decreases in hematocrit and hemoglobin, a slight decrease in the number of red blood cells and lymphocytes, and marginal increases in mean cell volume, mean cell hemoglobin and thrombocytes were observed. Dosing at 30 mg eq./kg b.w./month resulted in the same changes in males as after dosing at 10 mg eq./kg/month. In females dosed at 30 mg eq./kg b.w./month, slight decreases in red blood cells, hematocrit and hemoglobin, and a marginal increase in thrombocytes were observed, as well as transient and minimal increases in reticulocytes and a slight and transient increase in monocytes. Dosing at 60 mg eq./kg/month, resulted in similar effects as after dosing at 30 mg eq./kg body weight/month, except for the changes in hematocrit and lymphocytes in males, which were slightly more pronounced. Additionally in females, a slight and transient increase in neutrophils was present.

Clinical chemistry: Dosing paliperidone palmitate to male and female rats at 10 mg eq. /kg/month lead to slight decreases in potassium and glucose, transient and minimal decreases in urea nitrogen in males, transient and minimal increases in potassium and chloride, and transient and minimal decreases in albumin and total bilirubin in females. At a dose of 30 mg eq./kg/month, the same differences were seen as noted after dosing at 10 mg eq./kg/month, except for the decrease in urea nitrogen, which was slightly more pronounced. In addition, a marginal and transient decrease in inorganic phosphate was measured in male rats. Dosing at 60 mg eq./kg/month resulted in the same changes as observed after dosing at 30 mg eq./kg/month. In males, a slight decrease in total bilirubin was also seen.

Urinalysis: No significant urinary effects were observed in female rats dosed for 104 weeks with paliperidone palmitate up to 60 mg eq./kg/month. Dosing at 10 mg eq./kg/month to male rats for 104 weeks resulted in a minimally lower pH and a minimally higher score for ketones. At a dose of 30 or 60 mg eq./kg/month, the same changes were present as observed after dosing males at 10 mg eq./kg/month, together with a minimal increase in squamous epithelial cell score.

Gross pathology: Dosing paliperidone palmitate at 10 mg eq./kg/month resulted in deposit often present at the injection site(s) in both sexes. Additionally, a slightly higher incidence of swollen spleen was seen in males, indicating stimulation of hematopoiesis.

A slightly higher incidence of swollen popliteal lymph nodes was noted in both sexes. According to the Sponsor, this was caused by the administration of the test article formulation and probably also influenced by the lesions in the hind foot. A slightly higher incidence of swollen medial iliac lymph nodes was also present in males. Prolactin mediated effects were seen in both sexes, manifested by the slightly increased incidences of swollen pituitaries in both sexes and mammary gland secretion in males as well as the slightly lower incidence of cysts in the uterus in females. Dosing rats with paliperidone palmitate at a dose of 30 mg eq./kg b.w. /month showed similar or slightly more pronounced observations as present at 10 mg eq./kg b.w./month. In addition in males, a slightly higher incidence of swollen extremities was seen. The deposit at the injection site(s) was observed in most of the male and female rats. The increases of deposit in the injection site(s) and injuries at the hind legs resulted in a slightly increased presence of swollen popliteal and medial iliac lymph nodes in males, while in females only the incidence of swollen popliteal lymph nodes was increased. A slightly higher incidence of swollen spleen was also seen in males. Dosing at 60 mg eq./kg b.w./month resulted in the same gross pathological changes were seen as after dosing at 30 mg eq./kg b.w./month. In addition to these changes, abscesses at the administration site(s) were present in a few males and females.

The incidences of relevant gross pathology observations are shown in the following Sponsor's table:

sex		MALES					FEMALES				
group symbol		C	V	L	M	H	C	V	L	M	H
number		65	65	65	65	65	65	65	65	65	65
extremities	swollen	4	2	3	8	10					
injection site(s), IM	deposit abscess	0 0	0 0	34 0	50 0	57 6	0 0	0 0	33 1	57 0	58 6
lymph nodes, medial iliac	swollen	11	14	21	37	23					
lymph nodes, popliteal	swollen	17	14	21	32	33	7	7	16	12	15
mammary gland	enlarged secretion mass	7 4 4	10 5 2	11 11 4	27 24 10	28 22 7					
pituitary gland	swollen	3	5	18	24	26	12	8	17	24	18
prostate	focus/area discolored	5	3	3	7	14					
spleen	swollen	3	3	9	13	12					
testes	small soft	4 14	5 13	7 12	9 16	13 24					
uterus	cyst						5	6	1	0	0

Organ weights: The following organs were weighed: adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus, and thyroid glands (including parathyroid glands). Dosing male rats at 10 or 30 mg eq./kg b.w./month or female rats up

to 60 mg eq./kg b.w./month did not result in significant effects. Dosing of male rats 60 mg eq./kg b.w./month resulted in a slight decrease in testicular weigh.

Histopathology: The following tissues were preserved at necropsy and examined histologically: injection sites (intramuscular), adrenal glands, aorta, bone marrow (femur), bone marrow (sternum), bone (sternum), bone (stifle), brain, cervix, clitoral gland(s), coagulating glands, epididymides, esophagus, exorbital lacrimal glands, eyes, Harderian glands, heart, kidneys, large intestine (cecum), large intestine (colon), large intestine (rectum), larynx, liver, lungs, lymph nodes (medial iliac), lymph node(s) (mesenteric), lymph nodes (popliteal), mammary gland(s), nose, optic nerve(s), ovaries, oviducts, pancreas, peripheral nerves (sciatic), Peyer's patches, pituitary gland, preputial gland(s), prostate, salivary gland (mandibular, parotid and sublingual), seminal vesicles, skeletal muscle (quadriceps), skin, small intestine (duodenum), small intestine (ileum), small intestine (jejunum), spinal cord (cervical), spinal cord (lumbar), spinal cord (thoracic), spleen, stomach, testes, thymus, thyroid glands (including parathyroid glands), tongue, trachea, ureter(s), urinary bladder, uterus, vagina, and all tissues showing gross lesion

Non-neoplastic: Toxicologically important non neoplastic findings are shown in the following Sponsor's tables:

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
EXTREMITIES	No.Examined	18	20	25	42	42
– Inflammation chronic granulomatous		14	12	25	39	36
	Grade 1	4	7	13	14	6
	Grade 2	8	5	7	10	17
	Grade 3	2	–	5	15	13

Sex		Females				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
EXTREMITIES	No.Examined	5	2	3	11	14
– Inflammation chronic granulomatous		3	2	1	4	10
	Grade 1	–	–	–	2	6
	Grade 2	3	1	1	1	3
	Grade 3	–	1	–	1	1

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
COAGULATING GLANDS	No.Examined	65	63	65	63	65
- Atrophy		10	12	7	7	2
	Grade 1	7	5	3	6	2
	Grade 2	2	6	2	-	-
	Grade 3	1	1	2	1	-
- Distention		1	1	1	4	4
	Grade 1	1	1	1	4	4
PROSTATE	No.Examined	65	62	65	64	65
- Inflammation exudative		55	55	53	55	60
	Grade 1	32	23	28	27	18
	Grade 2	19	27	24	25	40
	Grade 3	4	5	1	3	2
SEMINAL VESICLES	No.Examined	65	63	65	64	65
- Distention		4	4	2	17	12
	Grade 1	4	4	1	17	11
	Grade 2	-	-	1	-	1
- Inflammation chronic		3	5	4	10	21
	Grade 1	3	4	2	10	19
	Grade 2	-	1	2	-	2
- Inspissated secrete		6	5	6	19	38
	Grade 1	6	4	6	19	37
	Grade 2	-	1	-	-	1
TESTES	No.Examined	65	65	65	65	65
- Atrophy		14	8	13	18	25
	Grade 1	3	2	4	6	7
	Grade 2	3	3	7	7	5
	Grade 3	8	3	2	5	13

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
MAMMARY GLAND(S)	No.Examined	65	64	64	65	65
- Fibrosis		2	8	12	20	19
	Grade 1	2	6	12	20	15
	Grade 2	-	2	-	-	4
- Galactocele(s)		4	8	18	20	22
	Grade 1	4	8	16	13	17
	Grade 2	-	-	2	7	4
	Grade 3	-	-	-	-	1
- Glandular development		21	23	40	52	49
	Grade 1	21	23	40	48	44
	Grade 2	-	-	-	3	5
	Grade 3	-	-	-	1	-
- Hyperplasia		3	4	10	20	11
	Grade 1	3	4	10	19	8
	Grade 2	-	-	-	1	3
- Secrete		19	18	35	51	49
	Grade 1	17	12	19	31	37
	Grade 2	2	6	16	20	11
	Grade 3	-	-	-	-	1
- Secrete concrements		13	18	32	46	40
	Grade 1	13	14	28	39	31
	Grade 2	-	4	4	7	9
Sex		Females				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
MAMMARY GLAND(S)	No.Examined	65	65	65	65	65
- Glandular development		65	63	64	64	65
	Grade 1	37	34	23	14	26
	Grade 2	27	27	35	40	33
	Grade 3	1	2	6	10	6
- Hyperplasia		26	21	30	39	39
	Grade 1	22	16	19	21	23
	Grade 2	4	5	9	12	13
	Grade 3	-	-	2	6	3

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Females				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
VAGINA	No.Examined	65	65	65	65	65
- Mucification		35	41	49	48	44
	Grade 1	20	27	27	33	25
	Grade 2	15	13	19	15	19
	Grade 3	-	1	3	-	-

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
PITUITARY GLAND	No.Examined	65	65	65	65	65
- Hyperplasia (multi)focal		16	19	43	39	42
	Grade 1	10	10	19	12	16
	Grade 2	5	8	21	24	22
	Grade 3	1	1	3	3	4
- Hyperplasia diffuse		-	-	21	28	45
	Grade 1	-	-	20	23	38
	Grade 2	-	-	1	5	7

Sex		Females				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
PITUITARY GLAND	No.Examined	64	65	65	65	65
- Hyperplasia diffuse		3	10	26	34	32
	Grade 1	3	10	25	30	26
	Grade 2	-	-	1	4	6

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (K0), Incl. Deaths

Sex		Males				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
INJECTION SITE(S),IM	No.Examined	65	64	64	64	65
- Abscess(es)		-	-	-	-	5
	Grade 2	-	-	-	-	3
	Grade 3	-	-	-	-	2
- Fibrohist./granuloma		2	4	35	51	56
	Grade 1	1	3	19	28	9
	Grade 2	1	1	16	23	46
	Grade 3	-	-	-	-	1
LYMPH N MED ILIAC	No.Examined	58	61	58	62	59
- Plasmacytosis		33	34	43	46	44
	Grade 1	26	26	25	18	20
	Grade 2	6	8	15	21	20
	Grade 3	1	-	3	7	4
LYMPH NN POPLITEAL	No.Examined	64	62	63	64	64
- Plasmacytosis		27	26	33	46	49
	Grade 1	19	20	17	21	27
	Grade 2	8	5	14	20	18
	Grade 3	-	1	2	5	4
Sex		Females				
Dose Group		C	V	L	M	H
No. Animals per Dose Group		65	65	65	65	65
INJECTION SITE(S),IM	No.Examined	63	65	63	63	64
- Abscess(es)		-	-	-	-	16
	Grade 1	-	-	-	-	2
	Grade 2	-	-	-	-	12
	Grade 3	-	-	-	-	2
- Fibrohist./granuloma		-	3	36	52	58
	Grade 1	-	3	23	22	19
	Grade 2	-	-	13	29	35
	Grade 3	-	-	-	1	4
LYMPH N MED ILIAC	No.Examined	63	60	61	63	58
- Plasmacytosis		37	28	35	44	37
	Grade 1	32	22	21	32	26
	Grade 2	5	6	14	12	10
	Grade 3	-	-	-	-	1
LYMPH NN POPLITEAL	No.Examined	64	63	61	62	64
- Plasmacytosis		31	24	25	30	31
	Grade 1	30	23	18	23	24
	Grade 2	1	1	7	7	7

Neoplastic:

According to the statistical review, the following tumor types showed p-values less than or equal to 0.05 either for dose response relationship and/or pairwise comparisons of control and treated male and female groups:

Male Rats Using Negative Control and All Treatment Groups

Organ Name	Tumor Name	Cont N=65	Low N=65	Med N=65	High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
MAMMARY GLAND(S	ALL TUMORS	1	0	8	4	0.020	0.500	0.014	0.139
SKIN	SQUA_CELL+KERATO	3	5	3	8	0.043	0.358	0.633	0.062
	SQ_CAR+KERATO+PAPILL	2	5	3	8	0.016	0.135	0.472	0.014

Male Rats Using Vehicle Control and All Treatment Groups

Organ Name	Tumor Name	Cont N=65	Low N=65	Med N=65	High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LIVER	Adenoma hepatocellul	0	1	1	3	0.033*	0.505	0.495	0.099
MAMMARY GLAND(S	ALL TUMORS	0	0	8	4	0.008*	1.000	0.003#	0.045#
PANCREAS	ALL TUMORS	9	15	18	14	0.111	0.133	0.047	0.108
	Adenoma islet cell,	6	15	16	12	0.115	0.027	0.017	0.060
	ISLET_ADEN+CARC	9	15	18	14	0.111	0.133	0.047	0.108
PARATHYROID GLA	Adenoma, single, sma	3	2	0	0	0.018	0.491	0.125	0.146

Female Rats Using Negative Control and Using All Treatment Groups

Organ Name	Tumor Name	Cont N=65	Low N=65	Med N=65	High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
MAMMARY GLAND(S	ALL CARCINOMA	21	32	28	29	0.165	0.028	0.107	0.076
	Adenocarcinoma, sing	18	28	28	27	0.095	0.034	0.034	0.051
PITUITARY GLAND	Adenoma, different p	54	42	36	42	0.067	0.078	0.009	0.057

Female Rats Using Vehicle Control and Using All Treatment Groups

Organ Name	Tumor Name	Cont N=65	Low N=65	Med N=65	High N=65	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL GLANDS	Pheochromocytoma ben	1	1	6	3	0.135	0.747	0.032	0.333
MAMMARY GLAND(S	ALL CARCINOMAS	15	32	28	29	0.074	0.004#	0.023	0.015
	Adenocarcinoma, sing	14	28	28	27	0.064	0.014	0.014	0.021
PITUITARY GLAND	Adenoma	50	42	36	42	0.138	0.194	0.035	0.153
UTERUS	Polyp endometrial st	6	0	0	2	0.105	0.014	0.012	0.114

Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in males (0/65, 0/65, 8/65, and 4/65 in the vehicle control, LD, MD, and HD, respectively, using the vehicle control and all treated groups but not using the saline control group; the incidence in this group was 1/65). Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. [It should be noted that prolactin levels were increased in male and female rats in this study].

In female rats, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors, except for the low dose vs. the vehicle comparison of adenocarcinomas (15/65, 32/65, 28/65, and 29/65 in the vehicle control, LD, MD, and HD, respectively).

Based on CDER criteria of adjustment for multiple testing of trends, the incidences of hepatocellular adenoma in male rats (0/65, 1/65, 1/65, and 3/65 in the vehicle control, LD, MD, and HD, respectively) were statistically significant using the vehicle control and all treated groups (but not using the saline control group). However, the pairwise comparisons of the vehicle control with the LD, MD, or HD groups for the incidence of hepatocellular adenoma were not statistically significant. There was no increase in carcinomas in that tissue. The incidence of hepatocellular adenomas in male rats in the saline control group (3/65) was equal to that in HD males. Therefore, the increase in hepatocellular adenomas in HD male rats is not considered drug related.

The incidences of pancreatic islet cell tumors (islet cell adenomas and islet cell carcinomas) were slightly increased but not dose related in males at all dose levels when compared to the vehicle control group (islet cells adenomas: 10/65, 6/65, 15/65, 16/65, and 12/65 in the saline control, vehicle control, LD, MD, and HD, respectively; islet cells carcinomas: 2/65, 3/65, 0/65, 2/65, and 2/65 in the saline control, vehicle control, LD, MD, and HD, respectively; combined pancreatic islet cell tumors: 12/65, 9/65, 15/65, 18/65, and 14/65 in the saline control, vehicle control, LD, MD, and HD, respectively). The following table summarizes the incidence of pancreatic islet cell tumors:

	Males					**Female**				
	Untr. Contr.	Vehic. Contr.	10 mg eq/day	30 mg eq/day	60 mg eq/day	Untr. Contr.	Vehic. Contr.	10 mg eq/day	30 mg eq/day	60 mg eq/day
Number animals examined	65	65	65	65	65	64	65	65	64	64
Islet cells adenomas	10	6	15	16	12	3	3	2	5	5
Islet cells carcinomas	2	3	-	2	2	-	-	-	1	-
All pancreatic islet cell tumors	12	9	15	18	14	3	3	2	6	5
All pancreatic islet cell tumors (%)	18%	14%	23%	28%	22%	5%	5%	3%	9%	8%

These increases were not statistically significant according to CDER criteria.

[Note: The incidence of pancreatic islet cell adenomas was also increased in oral risperidone carcinogenicity study in rats (NDA 20-272) and i.m. risperidone study in rats (NDA 21-346). The incidence of pancreatic islet cells neoplasms in oral risperidone carcinogenicity study is shown in the following table:

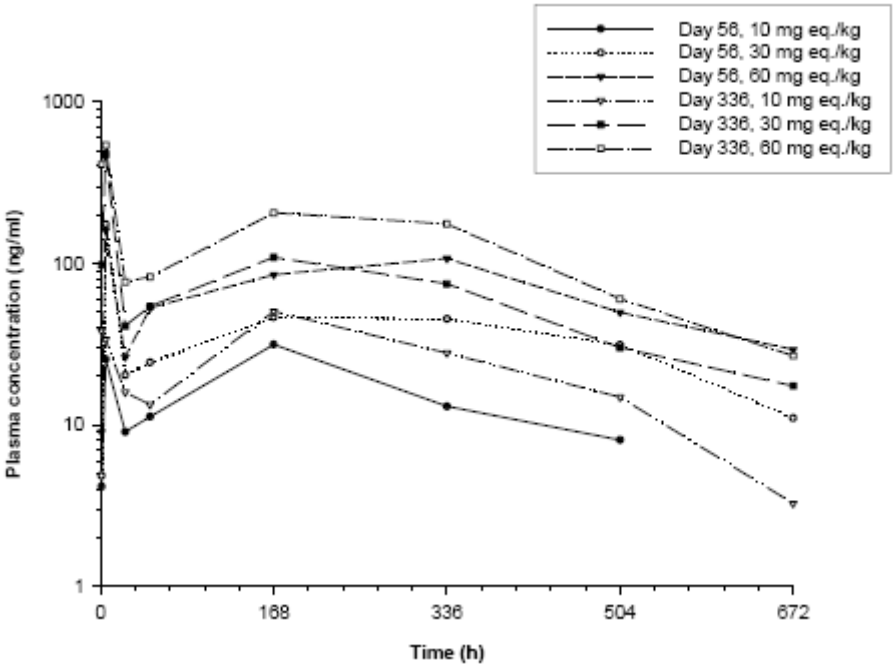
	Males				**Female**			
	Control	LD	MD	HD	Control	LD	MD	HD
Number animals examined	49	49	49	49	50	50	50	50
All pancreatic islet cell tumors (adenomas)	9	9	14	14	3	4	4	3
All pancreatic islet cell tumors (%)	18%	18%	29%	29%	6%	8%	8%	6%]

Toxicokinetics: Blood samples were collected from the satellite group animals: (1) from the first 3 male and female rats from both saline and vehicle control groups before administration of the first dose and after the 3rd injection (Day 56 of dosing) at 168, 336, and 672 h after administration; (2) from the first 3 male and female rats at 1, 24, 168, and 504 h post-dose and from the last 3 male and female rats of the paliperidone palmitate dosed-animals at 5, 48, 336, and 672 h post-dose after the 3rd injection (Day 56 of dosing) and after the 13th injection (Day 336 of dosing). Toxicokinetic data of paliperidone (the $C_{max\ 2}$ levels and $AUC_{0\text{-}672h}$ values) after the 3rd and after the 13th injection are shown in the following Sponsor's table:

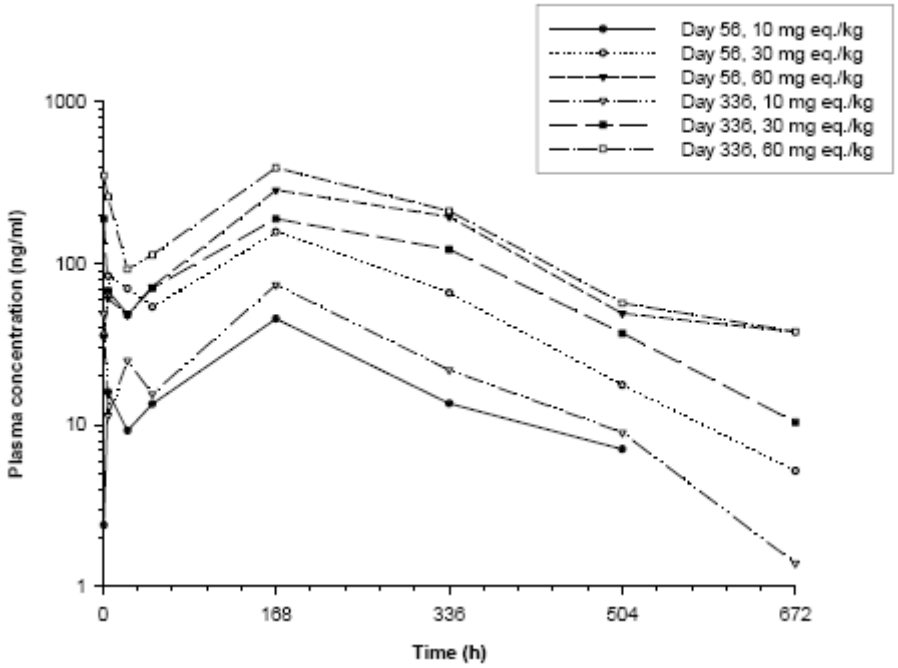
	Dose	10 mg/kg/month		30 mg/kg/month		60 mg/kg/month	
	Injection	3rd	13th	3rd	13th	3rd	13th
C_{max2}	Male	31.4	50.3	46.4	109	107	205
	Female	45.5	73.8	157	189	285	391
$AUC_{0\text{-}672h}$	Male	9460	15900	23800	42800	46100	82500
	Female	11100	16600	41300	59900	89000	114000

C_{max}: ng/mL; $AUC_{0\text{-}672h}$: ng h/mL

Plasma concentrations of paliperidone (ng/mL) versus time profile in males (mean N=3 data) is shown in the following sponsor's figure:



Plasma concentrations of paliperidone (ng/mL) versus time profile in females (mean N=3 data) is shown in the following Sponsor's figure:



Treatment with paliperidone palmitate resulted in a first peak ($C_{max\ 1}$) in the paliperidone plasma concentration within one day (1-5 h) after treatment, followed by a rapid drop in

plasma levels. Later paliperidone levels increased reaching a second maximum ($C_{max\ 2}$) paliperidone plasma concentration at 7 days (168 h) after treatment. C_{max} and AUC values in general increased dose proportionally in both sexes and were higher on Day 336 than on Day 56.

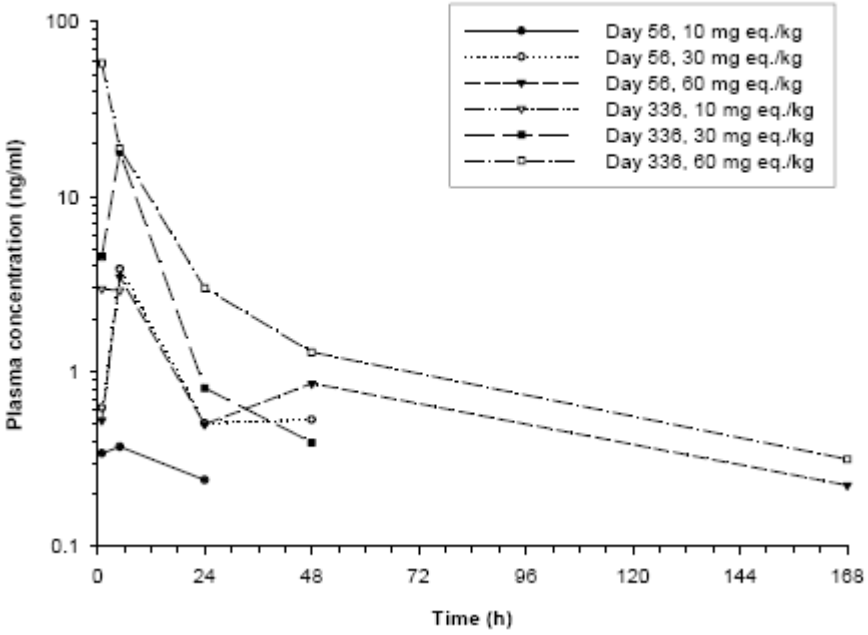
Toxicokinetic data of paliperidone palmitate (the $C_{max\ 2}$ levels and $AUC_{0\text{-}672h}$ values) after the 3rd and 13th injections are shown in the following Sponsor's table:

	Dose	10 mg/kg/month		30 mg/kg/month		60 mg/kg/month	
	Injection	3rd	13th	3rd	13th	3rd	13th
C_{max}	Male	0.372	2.97	3.86	18.0	3.49	57.7
	Female	0.392	4.17	1.56	16.8	1.65	27.3
$AUC_{0\text{-}24h}$	Male	7.32	13.2[1]	40.7	152	37.5	333
	Female	1.27[1]	13.5	13.4	57.8	17.9	103

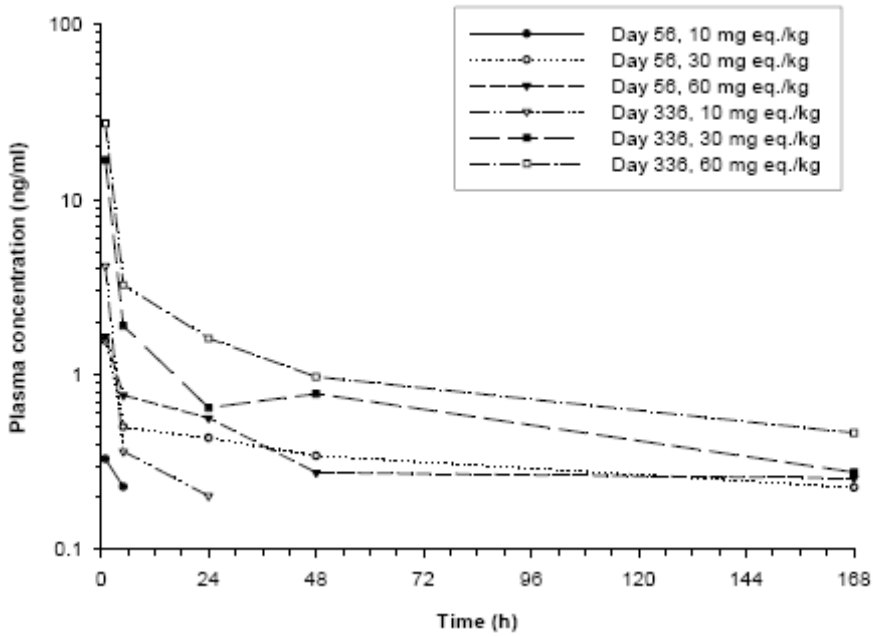
[1] $AUC_{0\text{-}8h}$

C_{max}: ng/mL; $AUC_{0\text{-}672h}$: ng h/mL

Plasma concentrations of paliperidone palmitate (ng/mL) versus time profile in males (mean N=3 data) is shown in the following Sponsor's figure:



Plasma concentrations of paliperidone palmitate (ng/mL) versus time profile in females (mean N=3 data) is shown in the following Sponsor's figure:



2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Fertility and early embryonic development studies were not conducted with paliperidone palmitate. These studies were bridged to those conducted previously with p.o. paliperidone under NDA 21-999. P.o. paliperidone was tested in male and female fertility studies in rats (Studies No.: TOX6967 and TOX6348, respectively). The summaries and conclusions of these studies are provided below. Please see pharmacology/toxicology review of the NDA 21-999 for further details.

1. Study title: Male Fertility Study in the Rat

Study no.: TOX6967 (RR1052)
Volume #, and page #: electronic submission to the NDA 21-999
Conducting laboratory and location: (b) (4)
Date of study initiation: February 9, 2005
GLP compliance: yes (UK GLP, OECD GLP)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: paliperidone, lot ZR076477EIA041, purity: 99.2%

Methods

Doses: 0, 0.16, 0.63, and 2.5 mg/kg/day
The dose selection for this study was based on information from previously conducted toxicity studies with oral paliperidone. In a 3-month repeated dose toxicity study in Wistar rats and a 6-month oral toxicity study in Sprague-Dawley

rats, paliperidone was administered at dose levels of 0.63, 2.5, and 10 mg/kg/day. Dose-related sedation and decreases in body weight and body weight gain were observed in males in these studies. The reviewer noted that body weight and body weight gain of males dosed with paliperidone at 2.5 mg/kg/day for 6 month were only moderately lower compared to the control group (90% and 84% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with paliperidone at 2.5 mg/kg/day were slightly increased compared to control group (112% and 123% of control mean value, respectively, on Day 182 of the study). At all levels, males showed prolactin-mediated inflammation of the dorso-lateral prostate. In addition, an increased accumulation of red blood cells in the splenic red pulp at 10 mg/kg/day was observed. Therefore, in opinion of the reviewer, there was no clear justification for selecting such a low top dose for fertility study based on previous toxicity studies in rats. However, the dose selection was also based on the results of two oral fertility studies conducted in Wistar rats with risperidone. In the first study, there were many toxic effects at 5 mg/kg/day (decreased body weight and body weight gain, marked decrease in the copulation rate, and increase in the pre-coital interval) and some at lower doses. In the second study males showed a decrease in body weight and body weight gain at 2.5 mg/kg/day. Other parameters remained unchanged. According to the Sponsor, testing higher doses of paliperidone in male fertility study was deemed not feasible due to prolactin-mediated decrease in mating behavior resulting in a marked reduction of the copulation rate as demonstrated at 5 mg/kg/day in a combined male and female fertility study in rats with risperidone conducted to support marketing of Risperdal.

Species/strain: SPF rats/Sprague Dawley Crl:CD (SD) BR
Number/sex/group: 24 males/group
Route, formulation, volume: oral (gavage), aqueous solution with tartaric acid and NaOH, volume: 10 mL/kg body weight.
Satellite groups used for toxicokinetics: none
Study design: In this male fertility study, rats were dosed orally with paliperidone for 63 days prior to mating, during the mating, and until termination in Week 13. Female rats were not dosed. Females with confirmed (by vaginal smears) evidence of mating were separated from the male and killed on Day 14 of gestation.
Parameters and endpoints evaluated: mortality, clinical observations, body weight, food consumption and utilization, organ weights (testes, epididymides), gross pathology, mating and fertility (vaginal smears to determine when mating had occurred), and uterine examinations (number of corpora lutea, live fetuses, early and late intra-uterine deaths). As there was no evidence of treatment-related effect on fertility, sperm analysis was not conducted.

Summary and conclusions: The objective of this study was to investigate potential effects of paliperidone administered p.o. at 0, 0.16, 0.63, and 2.5 mg/kg/day on male fertility. There were no test article related findings at dose level of 0.16 mg/kg/day. In rats dosed at 0.63 mg/kg/day, clinical observations of subdued or decreased activity were

noted from Week 1 to 5. Partially closed eyes were recorded from Week 2 to 13. Epididymides weights were lower by 6% than those of controls. In rats dosed at 2.5 mg/kg/day, clinical observations were similar to those at 0.63 mg/kg, and were recorded from Week 1 to 13 (subdued behavior or decreased activity) and Week 2 to 13 (both eyes partially closed). Body weights were moderately decreased (up to 6% lower than control). Food utilization was slightly reduced in Weeks 5 to 9 and overall. Epididymides weights were lower by 7% than those of controls. Finding in epididymides at the MD and HD were clearly not associated with any functional impairment and therefore not considered to be toxicologically significant. There were no effects on precoital interval. There were no effects on male fertility at any of the dose levels tested. There were no other test article related changes. The high dose of 2.5 mg/kg/day was the NOAEL for fertility in male rats.

2. Study title: Oral Female Fertility Study in the Rat

Study no.: TOX6348
Volume #, and page #: electronic submission to the NDA 21-999
Conducting laboratory and location: Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: February 3, 2004
GLP compliance: Yes (OECD)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone, lot ZR076477EIA041, purity 99.6%

Methods

Doses: 0, 0.16, 0.63, and 2.5 mg/kg/day
The dose selection for this study was based on information from previously conducted 3-month repeated dose toxicity study in Wistar rats and a 6-month oral toxicity study in Sprague Dawley rats, as well as based on the results of two oral fertility studies performed in Wistar rats with risperidone (see the review of Male Fertility Study in the Rat for further details)
Species/strain: SPF rats/Sprague Dawley (Crl:CD (SD) rats)
Number/sex/group: 24 females/group
Route, formulation, volume: oral (gavage), aqueous solution with tartaric acid and NaOH, volume: 10 mL/kg body weight.
Satellite groups used for toxicokinetics: none
Study design: Female rats were dosed orally with paliperidone for 14 days prior to mating, during the mating with undosed males and up to Day 7 of pregnancy. Female rats were sacrificed on Day 14 of pregnancy for evaluation of pregnancy status and determination of the fertility rate.
Parameters and endpoints evaluated: mortality, clinical observations, body weight, body weight gain, food consumption, weight of gravid uterus, gross pathology, fertility rate, copulation rate, pre-coital interval, number of corpora lutea of pregnancy, number of implantations, number of resorptions, number of embryos, pre- and postimplantation loss.

Summary and conclusions: The objective of this study was to investigate any potential effects of paliperidone administered p.o. at 0, 0.16, 0.63, and 2.5 mg/kg/day on female fertility and reproductive performance. There were no test article related findings at dose level of 0.16 mg/kg/day. Maternal toxicity was slight in females receiving 0.63 mg/kg/day as evidenced by ptosis, slightly decreased body weight gain during pregnancy, and decreased maternal corrected weight gain. During the preparing period, increased body weight gain and food consumption were noted. The pre-coital interval was increased from 3 (control) to 11 days, likely due to reduced estrus cycle activity. Pseudopregnancy or consecutive pseudopregnancies were observed by vagina cytology in all females administered paliperidone. These pseudopregnancies are considered as a consequence of prolactin mediated effects. Copulation, fertility rates, and pregnancy parameters remained unaffected by treatment with paliperidone. In females receiving 2.5 mg/kg/day, ptosis, lacrimation, increases in body weight gain and food consumption during the first week of treatment, and a slight reduction in food intake were noted. Moreover, the corrected maternal weight gain was decreased at 2.5 mg/kg/day. These findings indicate that the selected high dose was adequate. The pre-coital interval was increased from 3 (control) to 10 days. Adverse effects on fertility and reproductive capacities at 2.5 mg/kg/day were evidenced by increase in pre- and postimplantation loss (23% versus 14% in control group and 14% versus 8% in control group, respectively) resulting in decreases in the numbers of implantations (-13%) and live fetuses (-16%) as expressed per pregnant female, and lower weights of the gravid uterus. The dose of 0.16 mg/kg was the NOAEL for fertility and reproductive capacity for female rats based on increased percoital interval (11 versus 3 days) and decreased corrected maternal weight (-20%) at 0.63 mg/kg/day.

Embryofetal development

Paliperidone administered orally was tested in embryofetal development toxicity studies in rats (Study no. TOX6194) and rabbits (Study no. JRF4708) submitted to the NDA 21-999 (please see pharmacology/toxicology review of the NDA 21-999 for further details). Embryofetal developmental study in rabbits was not conducted with paliperidone palmitate. Paliperidone palmitate administered intramuscularly was tested in rats in the embryofetal development dose-range finding study (Study no. TOX7169) and definitive study (Study no. TOX7170). The reviews of these studies are provided below.

1. Study title: Pilot Developmental Toxicity Study in Sprague-Dawley Rat after Single Intramuscular Dosing with Paliperidone Palmitate.

Summary and conclusions: Intramuscular administration of paliperidone palmitate at doses of 0, 20, 80, and 160 mg eq./kg b.w. in the pilot study resulted in ptosis in 6/8 rats of the MD and HD groups during a short period (Days 9-13 of pregnancy) overlapping with the anticipated period of main exposure. The mean maternal body weight gain was reduced in comparison with the control group by 35% and 55% in the MD and HD groups, respectively, during Days 6-9 of pregnancy. The corrected mean maternal weight gain was reduced by 30%. Food consumption was reduced in MD and HD animals in comparison with the control group during from Day 14 to Day 20 of pregnancy by 11%.

There were no test article-related effects on pregnancy parameters including the numbers of corpora lutea, implantations, live fetuses, and pre- and postimplantation loss. A slight reduction (by 6%) in fetal weight was observed in the HD group. There were no test article-related effects on sex ratio or external malformations.

Study no.: TOX7169
Volume #, and page #: electronic submission to the NDA 22-264
Conducting laboratory and location: Global Preclinical Development, Beerse site, Turnhoutseweg 30, B-2340 Beerse, Belgium
Date of study initiation: June 14, 2008
GLP compliance: no
QA reports: yes ( ) no (x)
Drug, lot #, and % purity: paliperidone palmitate (R092670); lot 04J11/F013; purity: not provided

Methods

Doses: 0, 20, 80, and 160 mg eq./kg b.w. (dosages for the individual groups were achieved by varying the dose volumes)
Species/strain: rat/Sprague-Dawley (approximately 11-12 weeks of age on Day 0 of pregnancy; weight range 218 – 262 g)
Number/sex/group: 8 pregnant females/group
Route, formulation, volume: intramuscular (bolus in the *m. biceps femoris*; hindleg); aqueous suspension containing 156 mg/mL paliperidone palmitate (equivalent of 100 mg paliperidone/mL) and polysorbate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, cytric acid monohydrate, sodium hydroxide, polyethylene glycol, and water; volume: 2x0.08, 1x0.02, 2x0.04, 2x0.08 mL/100 g b.w./day in the vehicle, LD, MD, and HD groups, respectively.
Satellite groups used for toxicokinetics: none
Study design: All mated females received a single intramuscular bolus administration of paliperidone palmitate on Day 3 of presumed pregnancy. The vehicle group received the vehicle according to the same regimen as the HD group. The females were killed on Day 21 of pregnancy and a necropsy was performed during which the females and fetuses were examined.
Parameters and endpoints evaluated: Females: mortality, clinical signs of toxicity, body weight gain, corrected maternal weight gain, food consumption, weight of gravid uterus, and gross pathology. Litter: number of live and dead fetuses per litter, mean litter size, number of early, late and total resorptions, number of implantations, number of corpora lutea, pre- and postimplantation loss, weight of live fetuses, and external fetal observations.

Results

Mortality (dams): All animals were observed at least once a day for mortality. There were no unscheduled deaths in this study.

Clinical signs (dams): All animals were observed at least once a day for clinical signs. Ptosis was noticed in 6/8 rats of the MD and HD during a short period of pregnancy (Days 9-13) overlapping with the anticipated period of main exposure.
Body weight (dams): Body weight group mean values were calculated for the following periods of pregnancy: Days 0 to 2, 3 to 5, 6 to 9, 10 to 13, 14 to 17, and 18 to 20. The mean maternal body weight gain was reduced in MD and HD animals in comparison with the vehicle group from Day 3 to Day 13 of pregnancy. The decrease was statistically significant during Days 6-9 of pregnancy, with body weight gain decreased by 35% and 55% in the MD and HD groups, respectively, when compared to controls. The corrected mean maternal weight gain was reduced by 30% of the control value in both MD and HD animals.
Food consumption (dams): Food consumption group mean values were calculated for the following periods of pregnancy: Days 0-5, 6-9, 10-13, 14-17, and 18-20. Food consumption was reduced in MD and HD animals in comparison with the vehicle group during Days 14-20 by 11%.
Toxicokinetics: Not conducted. According to the Sponsor, based on results of previous studies, it was expected that the critical period of organogenesis (i.e. Days 6 through 17 of gestation) would correspond with Day 3 through Day 13 after administration and would largely overlap with the anticipated period of main exposure.
Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): There were no gross pathological lesions in maternal animals at necropsy. There were no test article-related statistically significant effects on pregnancy parameters including the number of corpora lutea, number of implantations per pregnant female, number of live fetuses, mean litter size, and pre-and post-implantation loss (although pre-implantation loss decreased in the MD and HD groups by 42% and 34%, respectively, post-implantation loss increased by 122% in the HD group, when compared to controls.
Offspring (malformations, variations, etc.): A slight reduction in fetal weight (by 6%) was observed in the HD group relative to control. There were no significant test article-related effects on sex ratio. The number of fetuses examined for external malformations was 101, 117, 112, and 108 in the control, LD, MD, and HD, respectively. There were no external malformations in any group except one HD fetus with kinky tail. Summarized results are shown in the following Sponsor's table:

Observation		Vehicle 0 mg/kg	Low 20 mg/kg	Medium 80 mg/kg	High 160 mg/kg
ADULT RAT DATA					
Number of dosed females		8	8	8	8
Number of pregnant females/ terminally sacrificed	(2)	7/8	8/8	7/8	8/8
Number of dead or sacrificed females/ dosed females	(1)	0/8	0/8	0/8	0/8
Body weight gain (d0 - d2)	(3)	17	16	15	14
Body weight gain (d3 - d5)	(3)	15	11	11	11
Body weight gain (d6 - d9)	(3)	20	18	13 *	9 *
Body weight gain (d10 - d13)	(3)	23	31	24	16
Body weight gain (d14 - d17)	(3)	56	57	59	53
Body weight gain (d18 - d20)	(3)	53	55	49	47
Weight gravid uterus	(3)	105.0	106.7	111.9	91.6
Corrected mean maternal weight gain	(3)	62.3	64.1	44.0 *	43.5 **
Food consumption (d0 - d5)	(3)	159	155	154	152
Food consumption (d6 - d9)	(3)	121	120	116	117
Food consumption (d10 - d13)	(3)	119	128	112	104
Food consumption (d14 - d17)	(3)	131	133	121 *	118 **
Food consumption (d18 - d20)	(3)	97	96	82 **	84 **
LITTER DATA					
Number of live fetuses/pregnant female	(3)	14.4	14.6	16.0	13.5
Number of dead fetuses/pregnant female	(3)	0.00	0.00	0.00	0.00
Mean litter size	(3)	14.4	14.6	16.0	13.5
Number of early resorptions/pregnant female	(3)	0.57	1.12	0.57	1.25
Number of late resorptions/pregnant female	(3)	0.00	0.00	0.00	0.00
Total number of resorptions/pregnant female	(3)	0.57	1.12	0.57	1.25
Pre-implantation loss (%)	(3)	10.78	11.81	6.23	7.08
Post-implantation loss (%)	(3)	4.13	7.90	3.47	9.15
Number of implantations/pregnant female	(3)	15.0	15.8	16.6	14.8
Number of corpora lutea of pregnancy/pregnant female	(3)	16.7	17.6	17.7	15.9
Weight of live fetuses	(3)	5.4	5.4	5.2	5.1
Sex ratio (% male fetuses)	(3)	43.5	57.4	48.4	48.9
Incidence of malformed fetuses	(1)	0/101	0/117	0/112	0/108

Significances computed by Fisher Exact Test
(1) Right tail probability (Mid P Value)
(2) Left tail probability (Mid P Value)
(3) Significances computed by Mann-Whitney U test (two tailed)
Note : all weights are in gram

* : $p < 0.05$ ** : $p < 0.01$ *** : $p < 0.001$

Reference group = Vehicle
TerS12Reporter : Version 3.4.2

2. Study title: Intramuscular Developmental Toxicity Study of R092670 in the Rat

Summary and conclusions: In the embryofetal developmental study of paliperidone palmitate administered intramuscularly as a bolus on Day 3 of pregnancy, there were 22/24, 22/24, 23/24, and 24/24 pregnant female rats in the vehicle control and groups

dosed at 20, 80, and 160 mg eq./kg. All animals survived until scheduled sacrifice. Ptosis was observed on the day of dosing in all groups and between Day 4 and 21 of pregnancy at the MD and HD. Body weight gain was decreased by 43% between Days 6 and 9 of pregnancy in MD animals. Body weight loss was observed between Days 6 and 17 of pregnancy in HD animals. However, by the end of the study body weight gain was increased in the HD animals over the vehicle group. The corrected mean maternal weight gain was slightly reduced in the MD group and markedly reduced in the HD group. Food consumption was markedly decreased from Day 8 until Day 17 of pregnancy in the HD group. There were no relevant changes in implantations, number of corpora lutea, pre- and post implantation loss, number of live and dead fetuses, mean litter size, early and late resorptions, and fetal sex ratio. Delayed ossification, including incomplete ossification of the hyoid and sternum bones, absent sternum bones and centra of cervical vertebrae, and reduced ossification of the metatarsal bones was observed in all groups. These findings were most pronounced in the HD group. There were no malformations in the vehicle control group. There were no external malformations in any dose group. The incidence of malformed fetuses in the paliperidone palmitate treatment groups was 2/285, 1/284, and 2/275 at the LD, MD, and HD, respectively. In view of the isolated nature, these malformations are considered accidental. Therefore, paliperidone palmitate was not teratogenic under conditions of this study.

Peak plasma concentrations of paliperidone were observed on Days 10 and 11 indicating that an exposure was achieved during the period of organogenesis (Days 6 to 17 of gestation) with C_{max} and $AUC_{0\text{-}18}$ days values of 655 ng/mL and 153000 ng·h/mL, respectively. These exposures were approximately 20- and 10- fold higher than the mean C_{max} (33.2 ng/mL) and mean $AUC_{0\text{-}28\ days}$ – value (15132 ng·h/mL), respectively, after two injections of paliperidone palmitate into deltiod muscle (Days 1 and 8) in humans at the MRHD.

Study no.: TOX7170
Volume #, and page #: electronic submission to the NDA 22-264.
Conducting laboratory and location: Global Preclinical Development, Beerse site, Turnhoutseweg 30, B-2340 Beerse, Belgium
Date of study initiation: December 06, 2005
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: paliperidone palmitate (R092670); batch 05E26/F013D; purity: not provided
Methods

Doses: 0, 20, 80, and 160 mg eq./kg b.w. (dosages for the individual groups were achieved by varying the dose volumes)
Species/strain: rat/Sprague-Dawley (approximately 10-11 weeks of age on Day 0 of pregnancy; weight range 224 – 282 g)
Number/sex/group: 24 time-mated females
Route, formulation, volume, and infusion rate: route: intramuscular (bolus in the *m. biceps femoris*; single dose on day 3 of presumed pregnancy); formulation: an injectable aqueous suspension with polyethylene glycol at a constant

concentration of 156 mg/mL, equivalent with 100 mg paliperidone/mL. The ingredients of the suspensions were: 156 mg paliperidone palmitate, polysorbate 20 parenteral (b) (4)), citric acid monohydrate parenteral (b) (4) disodium hydrogen phosphate anhydrous parenteral (b) (4)), sodium dihydrogen phosphate monohydrate parenteral (b) (4)), sodium hydroxide all use (b) (4)), polyethylene glycol 4000 parenteral (b) (4) and water for injections q.s. ad ((b) (4) mL); volume: 2x0.08, 1x0.02, 2x0.04, 2x0.08 mL/100 g b.w./day; vehicle solution contained the following ingredients: polysorbate 20 parenteral ((b) (4) citric acid monohydrate parenteral ((b) (4)), disodium hydrogen phosphate anhydrous parenteral (b) (4)), sodium dihydrogen phosphate monohydrate parenteral ((b) (4)), sodium hydroxide all use (b) (4)), polyethylene glycol 4000 parenteral (b) (4)), and water for injections 1.s. ad ((b) (4)

Satellite groups used for toxicokinetics: 21 satellite females (3 control females and 6 females per test article dose group)

Study design: The purpose of this study was to assess the potential toxicity of paliperidone palmitate and its active metabolite paliperidone on pregnant rats and embryo-fetal development when administered intramuscularly as a bolus on Day 3 of presumed pregnancy. The intramuscular route is the intended route of human exposure to the test article. Consequently, based on the results of the 6-month toxicity study in Wistar rats, it was expected that the critical period of organogenesis (i.e. Days 6 through 17 of gestation corresponding with Day 3 through Day 13 after administration) would largely overlap with the period of main exposure. Animals were killed and necropsy was conducted on Day 21 of pregnancy.

Parameters and endpoints evaluated: females: mortality, clinical observations, body weight gain and corrected maternal weight gain, food consumption, weight of gravid uterus, gross pathology, and toxicokinetics; litter: number of live and dead fetuses per litter, mean litter size, number of early, late, and total resorptions, number of implantations, number of corpora lutea of pregnancy, pre- and post-implantation loss, weight of live fetuses, sex ratio of live fetuses, and fetal observations (external, soft tissue, skeletal). Half of the live fetuses in each litter were processed for skeletal examination and the other half was placed in Bouin's fixative for visceral examination. The thoracic and abdominal cavities of ± half of each litter were reserved for skeletal examination. Following evisceration, the fetuses were further processed for skeletal examination. Clearing and staining of the skeletons was done with Alizarin red. The Bouin's fixed fetuses were examined, after free-hand serial sectioning, using the Wilson technique. Malformation, minor abnormalities, and variants were recorded.

Results:

Mortality (dams): All animals of the main study were observed at least once a day for mortality. There were no unscheduled deaths or premature sacrifices in any of the groups of the main toxicity study.

Clinical signs (dams): All animals of the main study were observed at least once a day for clinical signs, abnormal behavior, or unusual appearance. Ptosis was observed on the day of dosing in 0/24, 2/24, 6/24, and 7/24 animals in the control, LD, MD, and HD groups,

respectively. Ptosis was also observed in 5/24 and 15/24 animals in the MD and HD groups, respectively, between Day 4 and 21 of pregnancy. Waste of food and red vaginal discharge was observed in 5/24 and 20/24 animals in the HD group. According to the Sponsor, red vaginal discharge of unknown etiology was observed predominantly around Day 14 of pregnancy; this effect had no negative impact on the pregnancy.

Body weight (dams): Female rats were weighed prior to dosing and on Days 6, 10, 14, 18, and 21. Body weight gain data were reported to the following periods of pregnancy: Days 0-2, 3-5, 6-9, 10-13, 14-17, and 18-20. Corrected maternal weight gain was calculated as the weight change (Day 21 minus Day 6) minus gravid uterus weight. There were no significant effects on body weight gain in LD animals. Body weight gain was decreased by 43% between Days 6 and 9 of pregnancy in MD animals. Body weight loss (up to -6 g) was observed between Days 6 and 17 of pregnancy in HD animals. However, by the end of the study body weight gain was increased in the HD animals over the vehicle group. The corrected mean maternal weight gain was slightly reduced (by 16% of controls) in the MD group and markedly reduced (by 53% of controls) in the HD group. These data are shown in the following table:

Body weight gain [a]	vehicle	20 mg eq./kg	80 mg eq./kg	160 mg eq./kg
Days 3-5	13 g	11 g	11 g	6 g ***
Days 6-9	21 g	18 g	9 g ***	- 4 g ***
Days 10-13	24 g	24 g	22 g	- 6 g ***
Days 14-17	47 g	56 g	52 g	69 g *
Gravid uterus weight [a]	88.0 g	94.5 g	89.0 g	81.6 g
Corrected mean maternal weight gain [a, b]	60.1 g	60.5 g	50.7 g	28.3 g ***

[a] statistical analysis method used: Mann-Whitney U Test
[b] corrected mean maternal body weight gain = body weight minus weight gravid uterus minus body weight at Day 6
* - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

Food consumption (dams): Food consumption was reported for the following periods of pregnancy: Days 0 to 2, Days 3 to 7, Days 8 to 12, Days 13 to 17, and Days 18 to 20. Food consumption was marginally increased in the animals dosed at the LD and MD from Day 3 to Day 7 and marginally decreased in the animals dosed at the MD from Day 8 to Day 12 of pregnancy. At the HD, food consumption was markedly decreased from Day 8 until Day 17 of pregnancy. These data are shown in the following table:

Food consumption [a, b]	vehicle	20 mg eq./kg	80 mg eq./kg	160 mg eq./kg
Days 3-7	133 g	1.07 g *	1.06 g	0.99 g
Days 8-12	145 g	1.03 g	0.92 g *	0.67 g ***
Days 13-17	155 g	1.01 g	0.97 g	0.87 g ***

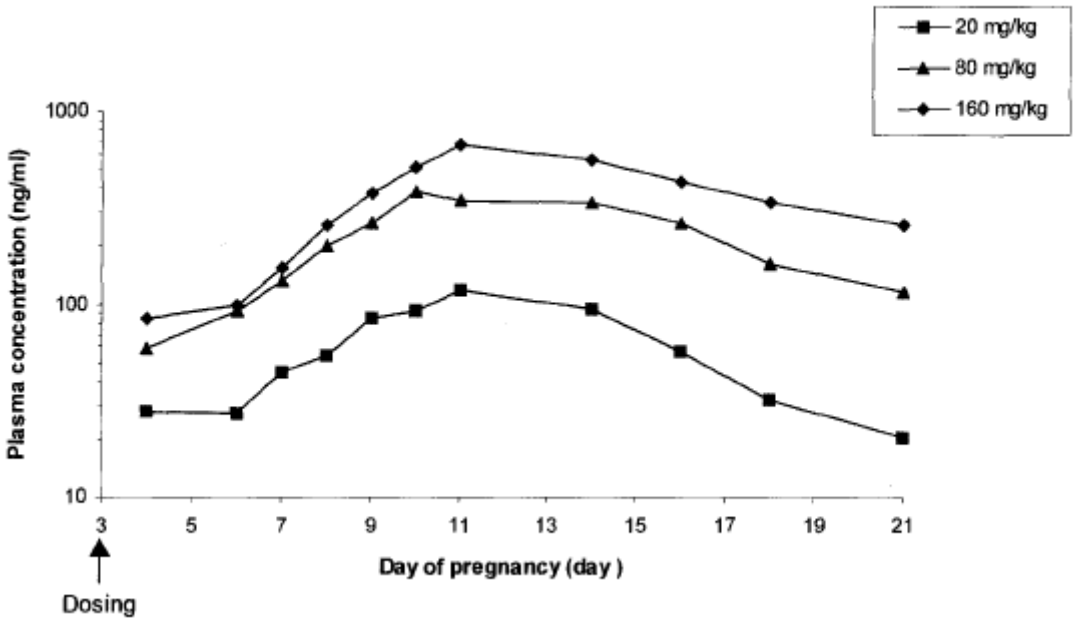
[a] Statistical analysis method used: Mann-Whitney U Test
[b] For controls, group mean are shown. For treated groups, findings are expressed as multiples of control.
* - $p<0.05$, ** - $p<0.01$, *** - $p<0.001$

Toxicokinetics: Blood samples (0.5 ml on EDTA) were taken from the satellite rats by puncture of the orbital venous plexus. Blood samples from the vehicle group were taken

at 168, 312, and 432 h after dosing. Blood samples from the paliperidone palmitate treatment groups were taken from the first three female satellite animals at 24, 96, 144, and 192 h after dosing and from the last three female satellite animals at 72, 120, and 168 h after dosing. In addition, blood samples were taken from all female satellite animals at 264, 312, 360, and 432 h after dosing. Peak plasma concentrations of paliperidone were observed on Days 10 and 11 indicating that an exposure was achieved during the period of organogenesis (Days 6 to 17 of gestation). The increase in C_{max} and AUC values was generally proportional to the dose. These data are shown in the following table and Sponsor's figure:

Toxicokinetic parameters[a]	vehicle	20 mg eq./kg	80 mg eq./kg	160 mg eq./kg
No. of animals	3	6	6	6
$AUC_{0\text{-}inf}$ (ng·h/mL)[b]	-	27100	108000	153000
C_{max} (ng/mL)	-	118	381	665
T_{max} (h)	-	192	168	192
$T_{1/2}$ (264-432 h)	-	75	105	148
AUC ratio			3.6	1.7
C_{max} ratio			3.2	1.7

[a] for toxicokinetics satellite animals were used
[b] at 160 mg eq./kg, $AUC_{0\text{-}432\ h}$ was calculated



Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): There were no significant test article-related changes in the mean number of live fetuses per pregnant female, mean litter size, number of corpora lutea, number of implantations per pregnant female, preimplantation loss, postimplantation loss, weight and sex ratio of fetuses. These data are shown below:

C-section data [a]	vehicle	20 mg eq./kg	80 mg eq./kg	160 mg eq./kg
mean No. of live fetuses/pregnant female	12.0	13.0	12.3	11.5
mean litter size	12.0	13.0	12.3	11.5
mean No. of corpora lutea	16.5	17.5	16.5	16.0
mean No. of implantations	12.9	14.9	13.8	13.0
mean % preimplantation loss	16.61	14.84	17.10	19.97
mean % postimplantation loss	15.25	12.98	11.69	18.14
mean weight of live fetuses	5.4	5.2	5.3	5.3
sex ratio (% male fetuses)	48.4	42.3	54.5	49.7

[a] statistical analysis method used: Fisher Exact Test and Mann-Whitney U test; all weights are in gram

Offspring (malformations, variations, etc.): The number of fetuses examined by sectioning was 127, 136, 136, and 130 in the control, LD, MD, and HD, respectively. The number of fetuses examined skeletally was 137, 149, 148, and 145 in the control, LD, MD, and HD, respectively. There were no malformations in the vehicle control group. The incidence of malformed fetuses in the paliperidone palmitate treatment groups was 2/285, 1/284, and 2/275 at the LD, MD, and HD, respectively. At the LD, there were two malformed fetuses from two liters. Fetus No. 14 (litter L44) showed polydactyly. Findings in fetus No. 11 (litter L46) included no tail or anus, absent one ureter and kidney, protrusion of the tongue, hydrops, omphalocele, adyctyly, and a spina bifida occulate. At the MD, there was one malformed fetus No. 1 (litter M82) showed dysplasia of the thoracic vertebrae and series of other abnormalities. At the HD, there were two malformed fetuses. Fetus No. 4 (litter H91) exhibited limb hyperextension. Fetus No. 4 (litter H112) was lacking several vertebra (lumbar, sacral, and caudal) and showed atresia and kyphosis. In addition, an increased incidence of wavy ribs and one pair of rudimentary 14th rib(s) were observed in all dosed groups. However, there was no clear dose-relationship for these findings. Reduced and retarded ossification of skeleton manifested differently in different bones was observed, including incomplete ossification of the hyoid and sternum bones, absent sternum bones and centra of cervical vertebrae, and reduced ossification of the metatarsal bones was observed in all groups. A summary of noteworthy findings is shown in the following Sponsor's table:

Report Title: Intramuscular Developmental Toxicity Study in the Rat **Test Article: R092670**

Daily Dose (mg eq./kg)	00 (Vehicle)	20	80	160
Noteworthy Findings (Continued)				
Litters: Mean litter size[a]	12.0	13.0	12.3	11.5
Mean No. Live Fetuses[b]	12.0	13.0	12.3	11.5
Mean No. Early Resorptions[b]	0.59	1.59 *	1.39 *	1.42
Mean No. Late Resorptions[b]	0.05	0.23	0.04	0.08
Mean No. Total Resorptions[b]	0.64	1.82 *	1.43 *	1.50
Total No. Dead Fetuses[b]	0	2	0	0
Mean % Postimplantation Loss[b]	15.25	12.98	11.69	18.14
Mean Fetal Body Weight (g)[b]	5.4	5.2	5.3	5.3
Fetal Sex Ratios[b]	48.4	42.3	54.5	49.7
Fetal Anomalies:[a]				
Gross External	-	-	-	-
Visceral Anomalies	-	-	-	-
Skeletal Anomalies[c]				
Ribs: one rudimentary 14th rib				
No. Fetuses (%)[d]	10 (7.49)	23 (15.14) *	15 (10.13)	19 (13.52)
No. Litters (%)	8 (40.00)	11 (50.00)	12 (52.17)	11 (50.00)
Ribs: rudimentary 14th pair				
No. Fetuses (%)[d]	4 (2.96)	11 (9.63) *	17 (11.00) **	11 (6.67) *
No. Litters (%)	3 (15.00)	6 (27.27)	9 (39.13) *	7 (31.82)
Sternum bone(s): incomplete ossification				
No. Fetuses (%)[d]	0 (0.00)	4 (6.82) *	8 (5.38) **	4 (2.35) *
No. Litters (%)	0 (0.00)	3 (13.64)	3 (13.04)	3 (13.64)

[a] Statistical analysis method used: Fisher Exact probability test.
[b] Statistical analysis method used: Mann-Whitney U test.
[c] Skeletal examinations were conducted in 50% of fetuses.
[d] Mean % fetuses affected per litter.

- No noteworthy findings
* - p<0.05, ** - p<0.01, *** - p<0.001

(Continued)

Report Title: Intramuscular Developmental Toxicity Study in the Ratt **Test Article:** R092670

Daily Dose (mg eq./kg)	00 (Vehicle)	20	80	160
Litters (Continued):				
Fetal Anomalies (continued):[a]				
Skeletal Anomalies (continued)[b]				
Sternum bone(s): absent				
No. Fetuses (%)[c]	0 (0.00)	1 (0.48)	1 (0.62)	4 (2.44) *
No. Litters (%)	0 (0.00)	1 (4.55)	1 (4.35)	4 (18.18) *
Ribs: wavy				
No. Fetuses (%)[c]	6 (3.77)	9 (5.51)	18 (12.87) **	6 (3.76)
No. Litters (%)	4 (20.00)	6 (27.27)	9 (39.13)	5 (22.73)
Hyoid: incomplete ossification				
No. Fetuses (%)[c]	10 (6.57)	16 (9.48)	21 (12.47) *	8 (5.28)
No. Litters (%)	7 (35.00)	5 (22.73)	7 (30.43)	7 (31.82)
Cervical vertebra(e): center absent				
No. Fetuses (%)[c]	64 (52.14)	84 (59.73)	85 (61.62) *	83 (61.63) *
No. Litters (%)	19 (95.00)	21 (95.45)	23 (100.00)	22 (100.00)
Reduced ossification of metatarsal bones				
No. Fetuses (%)[c]	5 (8.21)	14 (13.12) *	24 (16.29) ***	12 (8.49)
No. Litters (%)	3 (15.00)	7 (31.82)	8 (34.78)	6 (27.27)
Total affected fetuses (as above)				
No. Fetuses (%)[c]	82 (64.33)	106 (72.82)	109 (75.94)	105 (75.35)
No. Litters (%)	20 (100.00)	22 (100.00)	23 (100.00)	22 (100.00)

[a] Statistical analysis method used: Fisher Exact probability test.
[b] Skeletal examinations were conducted in 50% of fetuses.
[c] Mean % fetuses affected per litter.

* - p<0.05, ** - p<0.01, *** - p<0.001

Prenatal and postnatal development

Prenatal and postnatal development study was not conducted with paliperidone palmitate. This study was bridged to the study conducted previously with p.o. paliperidone under the NDA 21-999 as a Phase IV commitment (Study no.: TOX8342). The summary of this study is provided below. Please see pharmacology/toxicology review No. 2 of the NDA 21-999 for further details.

Background: Prenatal and postnatal developmental effects of orally (p.o) administered paliperidone were initially assessed in the first prenatal and postnatal developmental toxicity study in the rat (Study No. TOX6737) submitted to the NDA 21-999. Doses used

in this study were 0, 0.08, 0.31, and 1.25 mg/kg/day. Maternal treatment with paliperidone resulted in clinical signs of partially closed eyes with decreased activity during the gestation period. Decreased activity was observed also during the beginning of lactation. Body weight gain was slightly lower at the highest dose following the first day of dosing during gestation. However, after 7 days of dosing, mean body weight gains were similar to controls. There were no other test-article related findings. The MTD was not achieved in this study. The NOAEL for maternal treatment with p.o. paliperidone was 1.25 mg/kg/day, the highest dose administered. The same dose was the NOAEL for pup development, fertility, mating performance, or gestation of the F1 generation. Therefore, the dose selection was questionable for this study.

Based on the dose-range finding study, the pharmacology/toxicology reviewer concluded there was no reason to decrease the top dose of 2.5 mg/kg/day (the highest dose in the dose-range study) to the dose of 1.25 mg/kg/day in the first pivotal study because the dose of 2.5 mg/kg/day was not an MTD based on maternal parameters, for example maternal body weights. At 2.5 mg/kg/day in the dose range-finding study, group mean maternal body weight and body weight gain were only slightly decreased (-6% and -8%, respectively).

In conclusion, the dose selection for the first prenatal and postnatal developmental toxicity study of p.o. paliperidone conducted in the rat was inadequate. The pharmacology/toxicology reviewer recommended that the prenatal and postnatal developmental study be repeated using higher doses and submitted during Phase IV of drug development.

The sponsor conducted the second prenatal and postnatal developmental study using higher doses of p.o. paliperidone as recommended by the Agency. The following document is the summary and conclusions taken directly from the review of final study report submitted to the NDA 21-999 as well as to IND 65,850, IND (b) (4), IND 67,356, IND (b) (4), and IND 76,952 on January 25, 2008 (received by CDER on January 28, 2008).

Study title: Oral (Gavage) Pre- and Postnatal Developmental Toxicity Study in the Rat.

Summary and conclusions: In the second prenatal and postnatal developmental toxicity study, paliperidone was administered p.o to mated female rats at 0, 2.5, and 10 mg/kg b.w./day (control, LD, and HD groups, respectively) from Day 6 of gestation throughout lactation to investigate the effects on embryonic, fetal, and postnatal development, including behavior and reproductive performance of F1 generation, which was allowed to mature untreated. Although paliperidone was administered p.o. only at two dose levels, the study is considered acceptable because effects of lower paliperidone p.o. dosages had been evaluated in the first prenatal and postnatal developmental toxicity study in rats.

Marked clinical signs of partially closed eyes and decreased activity were observed in LD and HD females with a clear dosage-relationship in severity and duration. Piloerection and labored breathing were observed during the initial dosing period (from Day 6 to Day

13 of gestation) in majority of LD and HD females. Food consumption was unaffected during the gestation period but decreased during the lactation period in both test article-treated groups relative to controls. Body weight gain was markedly decreased between Days 6 and 8 of gestation and between Days 1 and 4 of lactation in LD females. Body weight loss was observed in HD females during Days 6 and 7 of gestation. Body weight gain was decreased from Day 6 to Day 9 of gestation and between Days 1 and 4 of lactation in HD females. The duration of pregnancy was slightly increased in a dose related manner in test article treated females. Although pregnancy length was increased, there was no effect on parturition. There were no test article related effects on the number or sex of litter at birth, or maternal necropsy parameters. Dose-related reduction in survival of pups to Day 4 of age was observed in both treatment groups. In the LD group, half the litters had at least one dead pup and one litter was dead by Day 4 of lactation. In the HD group, thirteen litters had lost one or more pups and six litters were dead by Day 4 of age. Observations in pups that died early included the absence of milk in the stomach, pallor, and cold body. Survival of pups from Day 4 to Day 21 of lactation was unaffected. Body weight was decreased on Day 14 of age in LD and HD pups of both sexes and on Day 21 of age in HD females. A slight delay in sexual development was noted in HD F1 females as indicated by mean day of vaginal opening. The percentage of litters with ears open, eyes open, righting reflex, startle response, and pupillary light reflex was not affected by the treatment with the test article. There were no test article-related mortalities, clinical observations, changes in body weight, behavioral development or reproduction in the F1 generation post-weaning that were considered by the Sponsor related to F0 maternal treatment. F2 generation was not assessed. In conclusion, the MTD for maternal treatment was achieved in this study based on decreased body weights in pregnant F0 females. Therefore, the study is considered adequate. The NOAEL for maternal treatment, pup survival between Days 1 and 4 of lactation, and pup development after maternal treatment is considered to be below the LD of 2.5 mg/kg/day. The NOAEL for behavioral development, fertility, or mating performance of F1 generation is considered to be the HD of 10 mg/kg/day.

Study no.: TOX8342
Volume #, and page #: electronic submission
Conducting laboratory and location: (b) (4)
Date of study initiation: June 4, 2007
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: paliperidone (R076477) or 9-hydroxy-risperidone; batch ZR076477EIA341; purity: 100%

Methods

Doses: 0, 2.5 (LD), and 10 (HD) mg/kg b.w./day
Species/strain: rat/Sprague-Dawley (8-11 weeks of age; body weights: 185.9-252.3 g)
Number/sex/group: 22 time-mated female rats/group

Route, formulation, volume: route: oral (gavage); formulation: solution (water, tartaric acid and NaOH 1M up to pH = 5 ± 0.1); volume: 5 mL/kg b.w.
Satellite groups used for toxicokinetics: none
Study design: Paliperidone was administered p.o. to mated female rats from Day 6 of gestation throughout lactation to Day 20 of lactation. Necropsy was conducted on maternal females on Day 21 of lactation. Embryonic, fetal, and postnatal development was evaluated. One week after the start of weaning, the F1 generation (20 male and 20 female pups per group) was randomly selected, including at least one from each of the weaned litters. The selected F1 generation was allowed to mature untreated. The effects on growth, development, behavior, and reproductive performance of F1 generation were assessed.
Parameters and endpoints evaluated: Maternal: mortality (observed twice daily), clinical observations (daily), body weights (reported on Days 6, 7, 8, 9, 12, 15, and 20 of gestation and Days 1, 4, 7, 10, 14, and 21 of lactation), food consumption (recorded from Days 6 to 8, 9 to 11, 12 to 14, and 15 to 20 of gestation and over Days 1 to 3, 4 to 6, 7 to 9, and 10 to 14 of lactation), parturition, major organs macroscopically at necropsy, and lactation observations. F1: litter size and sex, clinical observations (daily), body weight (recorded on Days 1, 4, 7, 14, and 21 of lactation), litter development (the number of pups in each litter with ears open on Day 3, eyes open on Day 15, the acquisition of the righting reflex on Day 5, startle response on Day 15, and pupillary light reflex on Day 21), pup development and behavioral assessment post weaning (locomotor activity using a rotarod at approximately 28 days of age; auditory function using Preyer reflex assessed at approximately 36 days of age; learning and memory potential using Morris Water Maze at approximately 48 days of age), sexual development (balanopreputial separation in males, vaginal perforation in females), and reproductive ability (selected F1 animals were reared untreated and paired at 10 weeks of age; the stage of the estrus cycle and the presence of sperm were recorded; all mated females were subjected to necropsy on Day 13 of gestation; in addition to the general necropsy, the following observations were made: pregnancy status, number of corpora lutea, and early or late resorptions). Necropsy was conducted on all pups sacrificed or found dead during lactation and unselected pups after weaning.

2.6.6.6 **Local tolerance**

Local tolerance at the i.m. injection site was studied in the context of the single-dose i.m. toxicity studies in dogs, pigs and minipigs, the repeat-dose i.m. toxicity studies in rats, dogs and minipigs, and the i.m. carcinogenicity study with paliperidone palmitate in rats. The results therefore are discussed in the aforementioned sections.

2.6.6.8 Special toxicology studies

Immunotoxicity:

No immunotoxicity study with i.m. injected paliperidone palmitate was conducted. This study was bridged to a previously conducted 28-day study with p.o. paliperidone, where

the primary T-cell dependent antibody response to sheep red blood cells was measured in a splenic plaque-forming cell assay. This study did not reveal any treatment-related change in immune function up to the highest dose of 10 mg paliperidone/kg/day tested (Study. no. TOX6965). Please see the pharmacology/toxicology review of the NDA 21-999 for p.o. paliperidone for more information.

Drug substance and drug product impurities:

1. Synthesis impurities:

The following (b) (4) impurities are present in paliperidone palmitate drug substance: paliperidone, (b) (4)

Paliperidone originates mainly from hydrolysis of paliperidone palmitate and is controlled in the final paliperidone palmitate drug substance as specified impurity with limit of not more than (b) (4)%. The impurity paliperidone is the active drug released form paliperidone palmitate and is qualified in the toxicity studies conducted with paliperidone palmitate and with paliperidone.

The impurities (b) (4) are (b) (4)

Figure 10: Chemical Structures of Paliperidone Palmitate (R092670) and the Impurities

(b) (4)

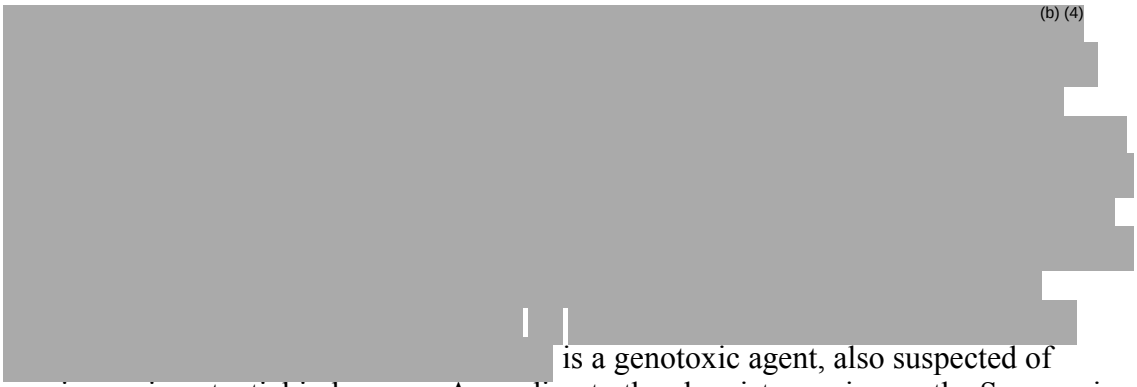
(b) (4)

They are controlled as specified impurities in the final paliperidone palmitate drug substance with a limit of no more than (b) (4) %. According to the Sponsor, these impurities are toxicologically qualified at concentrations of (b) (4) %, (b) (4) %, (b) (4) %, (b) (4) %, and (b) (4) %, respectively, based on 12-month paliperidone palmitate toxicity study conducted in dogs. No genotoxicity or reproductive toxicology studies have been conducted with these impurities. All five impurities are (b) (4) Moreover, these impurities do not contain structural alerts indicative for genotoxic potential. Therefore, they are considered to be non-genotoxic compounds. Moreover, the molecular weight of paliperidone is 426.49 whereas the molecular weight of each the (b) (4) impurities (b) (4)) is less than 50% of molecular weight of the (b) (4) , and (b) (4) impurities. Therefore, they do not require qualification since their level is less than required qualification threshold of 0.15%.

2. Alkylating agents (b) (4) and (b) (4)

Two genotoxic impurities (b) (4)) are present in the (b) (4) of paliperidone palmitate. Both (b) (4) and (b) (4) showed genotoxic properties in an *in vitro* Ames bacterial reverse mutation test and an *in vitro* chromosome aberration assay in human lymphocytes. Previous batches have contained impurities (b) (4) and (b) (4) up to levels of (b) (4) , respectively. According to the Sponsor, these values are well below the concentration limit of (b) (4) calculated on the basis of the MRHD of 100 mg eq. of paliperidone palmitate per person given as a monthly i.m. injection (corresponding with 100 mg eq./28 days or approximately (b) (4) eq./person/day), and the Threshold of Toxicological Concern (TTC) of 1.5 µg/person/day. However, this reviewer concluded that the acceptance criteria for these two impurities in the drug substance should be equal to or less than (b) (4) because this value should be calculated based on monthly (not daily) dose. The Sponsor was informed about these recommendations.

3. Genotoxic and carcinogenic degradants in paliperidone palmitate drug product:



is a genotoxic agent, also suspected of carcinogenic potential in humans. According to the chemistry reviewer, the Sponsor is scheduled to test for (b) (4) at the 24 month and 36 month pull points for the

registration batches. In the action letter, the Sponsor was asked to include a test and an acceptance limit for (b) (4) in the drug product specification.

2.6.6.9 Discussion and Conclusions

General toxicology: The nonclinical toxicology program in support of paliperidone palimitate intramuscular formulation consisted of single-dose toxicity studies in dogs, pigs, and minipigs, repeat-dose toxicity studies in rats (3 months and two 6 months studies), dogs (6 months and 12 months studies), and minipigs (3 months study). These studies addressed both local tolerance at the i.m. injection site and systemic toxicity. Moreover, several nonclinical toxicology studies were previously conducted with p.o. paliperidone. The NDA 22-264 for i.m. paliperidone palmitate cross-references the toxicology study reports and nonclinical summaries submitted previously under NDA 21-999 for p.o. paliperidone (INVEGA). All pivotal toxicity studies were conducted in full compliance with the OECD Good Laboratory Practice guidelines.

Rats: In the 3 months and two 6 months repeat-dose toxicity studies in rats, paliperidone palimitate was injected i.m. once monthly at 0, 20 (LD), 80 (MD), and 160 mg eq./kg (HD). Test article related mortalities occurred only in two HD females in the 3 months study; all animals survived in the 6 months studies. The following description is based on observations in the 6 months study in rats (Study No. 4696). However, in general, test article related effects were comparable in all studies. Clinical signs included ptosis and sedation at all dose levels. Body weight and body weight gain decreased in males and increased in females, with the greatest increases in the LD group. Changes in food consumption in general paralleled changes in body weights in both sexes. Test article related changes in hematology and clinical chemistry parameters that reached statistical significance included decrease in hematocrit, hemoglobin, and red blood cells count in females and HD males, increase in MCH and MCHC in all male groups, increase in mean neutrophil value in males and females, and increase in serum calcium and inorganic phosphorus in both sexes when compared to controls. These changes were small and may not have a toxicological significance. Mean weight of several organs/tissues were affected and correlated with histopathology findings: spleen weight was significantly and dose dependently increased in both sexes, kidney weight was significantly increased in HD males (but decreased in LD males), absolute adrenal weight was significantly and dose dependently increased in males but relative weight decreased in females, gonads weight of females were significantly reduced in the MD and HD groups compared to control. Gross morphological exam showed a white powdery deposit at injection site in all dose groups of both sexes. Mammary gland stimulation was observed in all female drug groups and occasionally in males. Histopathological exam revealed findings in the following organs/tissues: injection site, adrenals, kidneys, mammary glands, ovaries, prostate, seminal vesicles, spleen, testes, and pituitary. Similar to other studies, findings at injection site were those of inflammatory immunoreactive changes. In the adrenals, swollen cortical cells of *zona fasiculata* and *reticularis* were markedly increased in all male drug groups compared to control. Increased dilation of cortical renal collecting tubules was observed in high dose males and females, and in all female drug groups

relative to corresponding controls. There was female appearance (alveolar development) with increased secretion present in mammary glands in all male drug groups; similarly, alveolar development and secretion were increased in mammary glands of all female groups compared to controls. Focal hyperplasia of alveolar epithelium of mammary glands was seen in MD and HD males and in all female test article groups. Reduced cyclic activity was noted in the uterus. Male accessory sex organs showed low epithelium of ventral prostate, seminal vesicles, and coagulation gland. Increase in prolactin-immunoreactivie cells was observed in males. However, a decrease in these cell was seen in females. Serum prolactin was increased in all male test article treated groups and in HD females. The MTD was achieved in all repeat-dose toxicity studies in rats. Based on these results, the NOEL could not be determined due to presence of injection site reactions as well as other effects including histopathology at the LD of 20 mg eq./kg. However, 20 mg eq./kg may be considered the NOAEL.

Dogs: In the 6 months and 12 months repeat-dose toxicity studies in dogs, paliperidone palimitate was injected i.m. once monthly at 0, 5 (LD), 20 (MD), and 80 mg eq./kg (HD). However, the test article related injection site reactions led to decreasing the doses of 20 and 80 mg eq./kg to 10 and 40 mg eq./kg. The pivotal 12 months repeat-dose toxicity studyis described below. However, in general, test article related effects were comparable in all studies in dogs. The monthly injections were administered in the *m. semimembranosus/ m. semitendinosus* of both hind legs using a 21 G needle to 4 male and 4 female dogs per group. From the second dose onwards, the injections were given in the *m. biceps femoris* of both hind legs, because the *m. semitendinosus/ m. semimembranosus* were not healed yet.

Transient sedation was noted dose-dependently in all test article dosed groups. An acute, transient anaphylactic reaction (i.e., swollen eyelids, head and paws, red spots, sedation, decubitus, cyanosis and hyperpnea), probably related to the polysorbate 20 present in the vehicle, was seen in all animals of the vehicle and high dose group after each injection. Some medium-dosed animals also had a slight anaphylactic reaction (i.e., swollen eyelids and/or sedation) after the first dose of 20 mg eq./kg/month. Slight decreases in body weight and food consumption were noted after single doses of 20 or 80 mg eq./kg/month. There were no treatment-related effects on ECG, heart rate, ophthalmoscopy, and urinalysis. Systolic and diastolic blood pressure were decreased in the HD group. Drug related changes in hematology and clinical chemistry were small, not dose dependent, and within the historical control range. Serum prolactin levels were increased in all dosed groups. Peak levels were mostly reached between 7 and 14 days after dosing, showing no clear-dose response relationship due to high variability. In the HD group the relative weights of the testes and ovaries were decreased, while the relative weight of the prostate was decreased at the MD and HD. The relative weight of the spleen was increased at the HD. This finding correlated with histopathology of the spleen (see below). A dose-related reaction was noted at all dose levels in the injection site as evidenced by hardening, swelling, abscess formation, subcutaneous nodules, and skin lesions. Adhesions to the skin, white subcutaneous deposit, and nodules in the subcutis were noted as well. Slightly hardened iliac lymph nodes were observed macroscopically

in a few animals of the LD and HD groups; this finding is likely related to the injection site changes.

The following description of the injection site findings at the microscopic level is taken directly form the Sponsor's toxicology summary: "The vehicle-dosed group exhibited only slight focal muscular degeneration with slight focally thickened endomysium. These findings were slightly to prominently increased in the test article-dosed groups. Perimysially located encapsulated histiocytic granulomas with necrotic center and granulocytic infiltration were prominent in all test article-dosed groups. These granulomas showed aspects of chronic inflammation and fibrosis. Volume- and dose-related differences were not found. Occasionally comparable inflammatory fibro-granulomatous reactions in the skin (subcutis) were seen near the injection site at all dose levels. In the iliac lymph nodes, particularly in high-dosed animals, pigmented macrophages were marginally to slightly more prominent than in vehicle control animals, as a reaction to the foreign material and the inflammation at the injection sites". Additional histopathology findings included prostate atrophy in MD and HD males, slight resting appearance of the uterus and the absence of mitotic figures within the uterine epithelium at the high dose, resting appearance of the ovaries, slightly increased number of prolactin-immuno reactive cells in the pituitary gland of HD females. These findings are likely prolactin-mediated. The splenic red pulp of high-dosed animals showed an increased accumulation of red blood cells due to the a-lytic properties of the active drug. A NOAEL could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.

Minipigs: In the 12 weeks local tolerance study of two paliperidone palmitate long acting injectable formulations in the minipig, intramuscular administration of the to be marketed F013 formulation of paliperidone palmitate by three consecutive injections once every 4 weeks at single 5 mg eq./kg dose (LD) resulted in slightly decreased general activity and slight tremors. The same formulation administered at 20 mg eq./kg (HD) showed slightly to moderately decreased general activity, slight tremors, excessive salivation, compulsive behavior, transient increase in white blood cells, neutrophiles, and monocytes, slight but transient decrease in red blood cell count, hemoglobin and hematocrit, and minimal decrease in plasma potassium and sodium. The following dose-related local reactions were noted at the injection sites: a dose-related minimal/slight inflammatory reaction with granulomata formation was observed in the HD groups, and a crystalline material was seen in the inflammatory cells. A NOAEL could not be established in this study mainly due to the fact that injection site lesions already occurred at the lowest dose level.

Genetic toxicology: The potential genotoxic effects of paliperidone palmitate were studied in an *in vitro* bacterial reverse mutation (Ames) test with *Salmonella typhymurium* and an *in vitro* mouse lymphoma assay. The *in vitro* bacterial reverse mutation assay with paliperidone palmitate was performed using *Salmonella typhimurium* strains TA1535, TA 1537, TA102, TA98, and TA100. The experiments were performed with paliperidone palmitate in DMSO at concentrations ranging from 5 too 500 µg/plate in the absence or presence of an Aroclor 1254-induced male rat liver S9 metabolic activation system. Paliperidone palmitate was also tested for its ability to induce forward

mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells *in vitro*, both with or without the addition of the Aroclor 1254-induced male rat liver S9 metabolic activation system. No genotoxic potential was identified in studies conducted with paliperidone palmitate. Moreover, a full battery of genotoxicity studies was previously conducted with p.o. paliperidone. These studies were submitted previously to the NDA 21-999 for p.o. paliperidone (please see pharmacology/toxicology reviews of the NDA 21-999 for more information. The studies with p.o. paliperidone included two *in vitro* bacterial reverse mutation (Ames) tests with *Salmonella typhimurium* (Exp. Nos. 4555 and TOX6095), two mouse lymphoma assays (Exp. Nos. 4556 and TOX6093), and an *in vivo* rat micronucleus test with p.o. dosing (Exp. No. TOX6094). Genotoxicity studies with p.o. paliperidone showed no genotoxic potential. All these genetic toxicology studies were conducted in full compliance to GLP regulations.

Carcinogenicity: Carcinogenic potential of paliperidone palmitate was evaluated in the 24-month intermittent dose intramuscular carcinogenicity study in the rat. In general, the Agency requires studies in two rodent species for the carcinogenicity assessment. However, injected i.m. paliperidone palmitate is hydrolized to paliperidone. Marketed oral paliperidone (INVEGA) is the major active metabolite of marketed risperidone (RISPERDAL). Carcinogenicity studies with risperidone in rats and mice were conducted and previously reviewed by the Agency. Therefore, the Division agreed that only one species study (rat) was sufficient for the assessment of the carcinogenic potential of paliperidone palmitate. A carcinogenicity study in mice has not beeen conducted with paliperidone palmitate.

Intramuscular administration of paliperidone palmitate for 104 weeks at dosages of 0, 10 (LD), 30 (MD), and 60 (HD) resulted in increased mortality in male rats at 30 and 60 mg eq./kg b.w./month when compared to control groups (63% and 77% of animals died, respectively, compared to 49% in saline controls and 51% in vehicle controls). In female rats, minimally higher mortality was observed at the MD. Since the increase in mortality in female rats was not dose related, it was considered to be incidental. Dosing with paliperidone palmitate resulted in narrowing of the palpebral fissure in both sexes at all dose levels throughout the study. An increased incidence of small skin lesions located on subcutaneous tissue masses was observed in female rats at all dose levels and in MD and HD males. At terminal sacrifice, body weight in HD males was 9% and 11% less than that of the saline and vehicle control groups, respectively. In HD females, body weight was 11% and 13% less than that of the saline and vehicle control groups, respectively; therefore, the MTD was achieved in this study. There were no toxicologically significant changes in food consumption. A fibrohistiocytic inflammatory reaction was observed at the injection site mainly in HD and MD male and female rats. A prominent granulocytic reaction resulting in abscess formation was observed occasionally in HD animals of both sexes. Prolactin mediated effects were seen in both sexes, manifested by the slightly increased incidences of swollen pituitaries in both sexes and mammary gland secretion in males as well as the slightly lower incidence of cysts in the uterus in females. Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, and adenocarcinomas) in male rats using the vehicle control and all treated groups but not using the saline control group. Moreover, the

pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. The increased incidences of combined mammary gland tumors in male rats may be related to increased prolactin levels observed in male rats in this study. Prolactin levels were increased also in female rats. However, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors in female rats, except for the LD vs. the vehicle comparison of adenocarcinomas. However, the reviewer considers these indings to be of toxicological significance. There were no other test article related tumors.

Reproductive and developmental toxicology: Fertility and early embryonic development studies were not conducted with paliperidone palmitate. These studies were bridged to those conducted previously with p.o. paliperidone under NDA 21-999. Oral paliperidone was tested in male and female fertility studies in rats (Studies No.: TOX6967 and TOX6348, respectively). The summaries and conclusions of these studies are provided below. Please see pharmacology/toxicology review of the NDA 21-999 for further details.

The objective of the male fertility study was to investigate potential effects of paliperidone administered p.o. at 0, 0.16 (LD), 0.63 (MD), and 2.5 mg/kg/day (HD) on male fertility. There were no test article related findings at the LD. In rats dosed at the MD, clinical observations of subdued or decreased activity were noted from Week 1 to 5. Partially closed eyes were recorded from Week 2 to 13. Epididymides weights were lower by 6% than those of controls. In rats dosed at the HD, clinical observations were similar to those at the MD, and were recorded from Week 1 to 13 (subdued behavior or decreased activity) and Week 2 to 13 (both eyes partially closed). Body weights were moderately decreased (up to 6% lower than control). Food utilization was slightly reduced in Weeks 5 to 9 and 1 to 9. Epididymides weights were lower by 7% than those of controls. Findings in epididymides at the MD and HD were clearly not associated with any functional impairment and therefore not considered to be toxicologically significant. There were no effects on precoital interval. There were no effects on male fertility at any of the dose levels tested. There were no other test article related changes. The HD of 2.5 mg/kg/day was the NOAEL for fertility in male rats.

The objective of the female fertility study was to investigate any potential effects of paliperidone administered p.o. at 0, 0.16 (LD), 0.63 (MD), and 2.5 mg/kg/day (HD) on female fertility and reproductive performance. There were no test article related findings at the LD. Maternal toxicity was moderate in females receiving the MD as evidenced by ptosis, slightly decreased body weight gain during pregnancy, and decreased maternal corrected weight gain (defined as the maternal body weight on Day 14 of pregnancy minus body weight on Day 0 minus gravid uterus weight). During the preparing period, increased body weight gain and food consumption were noted. The pre-coital interval was increased from 3 (control) to 11 days, likely due to reduced estrus cycle activity. Pseudopregnancies were noted based on vagina cytology in all females administered paliperidone. These pseudopregnancies are considered as a consequence of prolactin

mediated effects. Copulation, fertility rates, and pregnancy parameters remained unaffected by treatment with paliperidone. In females receiving the HD, ptosis, lacrimation, increases in body weight gain and food consumption during the first week of treatment, and a slight reduction in food intake were noted. Moreover, the corrected maternal weight gain was decreased at the HD. These findings indicate that the selected HD was the MTD. The pre-coital interval was increased from 3 (control) to 10 days. Adverse effects on fertility and reproductive capacities at the HD were evidenced by increase in pre- and postimplantation loss (23% versus 14% in control group and 14% versus 8% in control group, respectively) resulting in decreases in the numbers of implantations (-13%) and live fetuses (-16%) as expressed per pregnant female, and lower weights of the gravid uterus. The LD of 0.16 mg/kg was the NOAEL for fertility and reproductive capacity for female rats based on incereased percoital interval (11 versus 3 days) and decreased corrected maternal weight (-20%) at 0.63 mg/kg/day.

Paliperidone administered orally was tested in embryofetal development toxicity studies in rats (Study no. TOX6194) and rabbits (Study no. JRF4708) submitted to the NDA 21-999 (please see pharmacology/toxicology review of the NDA 21-999 for further details). Embryofetal developmental study in rabbits was not conducted with paliperidone palmitate. Paliperidone palmitate administered intramuscularly was tested in rats in the embryofetal development dose-range finding pilot study (Study no. TOX7169) and definitive study (Study no. TOX7170). The summaries and conclusions of these studies are provided below.

In the pilot developmental toxicity study in rats, intramuscular administration of paliperidone palmitate at doses of 0, 20 (LD), 80 (MD), and 160 mg eq./kg b.w. (HD) resulted in ptosis in 6/8 rats of the MD and HD groups during a short period (pregnancy Days 9-13) overlapping with the anticipated period of main exposure. The mean maternal body weight gain was reduced in comparison with the control group by 35% and 55% in the MD and HD groups, respectively, during pregnancy Days 6-9. The corrected mean maternal weight gain was reduced by 30%. Food consumption was reduced by 11% in MD and HD animals in comparison with the control group during from pregnancy Day 14 to Day 20. There were no test article-related effects on pregnancy parameters including the numbers of corpora lutea, implantations, live fetuses, and pre- and postimplantation loss. A slight reduction (by 6%) in fetal weight was observed in the HD group. There were no test article-related effects on sex ratio or external malformations.

In the definitive embryofetal developmental study of paliperidone palmitate administered intramuscularly as a bolus on Day 3 of pregnancy, there were 22/24, 22/24, 23/24, and 24/24 pregnant female rats in the vehicle control and groups dosed at 0, 20 (LD), 80 (MD), and 160 mg eq./kg (HD), respectively. All animals survived until scheduled sacrifice. Ptosis was observed on the day of dosing in all groups and between pregnancy Day 4 and 21 at the MD and HD. Body weight gain was decreased by 43% between pregnancy Days 6 and 9 in MD animals. Body weight loss was observed between pregnancy Days 6 and 17 in HD animals. However, by the end of the study body weight gain was increased in the HD animals over the vehicle group. The corrected mean maternal weight gain was slightly reduced in the MD group and markedly reduced in the

HD group. Food consumption was markedly decreased from Day 8 until Day 17 of pregnancy in the HD group. There were no relevant changes in implantations, number of corpora lutea, pre- and post implantation loss, number of live and dead fetuses, mean litter size, early and late resorptions, and fetal sex ratio. Delayed ossification, including incomplete ossification of the hyoid and sternum bones, absent sternum bones and centra of cervical vertebrae, and reduced ossification of the metatarsal bones was observed in all groups. These findings were most pronounced in the HD group. There were no external malformations in any dose group. The incidence of malformed fetuses in the paliperidone palmitate treatment groups was 2/285, 1/284, and 2/275 at the LD, MD, and HD, respectively. In view of the isolated nature, these malformations are considered incidental. Therefore, paliperidone palmitate was not teratogenic under conditions of this study.

Peak plasma concentrations of paliperidone were observed on Days 10 and 11 indicating that an exposure was achieved during the period of organogenesis (pregnancy Days 6 to 17) with C_{max} and AUC_{0-18} days values of 655 ng/mL and 153000 ng·h/mL, respectively. These exposures were approximately 20- and 10- fold higher than the mean C_{max} (33.2 ng/mL) and mean $AUC_{0-28\ days}$ – value (15132 ng·h/mL), respectively, after two injections of paliperidone palmitate into deltiod muscle (Days 1 and 8) in humans at the MRHD.

Prenatal and postnatal development study was not conducted with paliperidone palmitate. This study was bridged to the study conducted previously with p.o. paliperidone under the NDA 21-999 as a Phase IV commitment (Study no.: TOX8342). The summary of this study is provided below. Please see pharmacology/toxicology review No. 2 of the NDA 21-999 for further details.

Prenatal and postnatal developmental effects of orally administered paliperidone were initially assessed in the first prenatal and postnatal developmental toxicity study in the rat (Study No. TOX6737) submitted to the NDA 21-999. Doses used in this study were 0, 0.08 (LD), 0.31 (MD), and 1.25 mg/kg/day (HD). Maternal treatment with paliperidone resulted in clinical signs of partially closed eyes with decreased activity during the gestation period. Decreased activity was observed also during the beginning of lactation. Body weight gain was slightly lower at the highest dose following the first day of dosing during gestation. However, after 7 days of dosing, mean body weight gains were similar to controls. There were no other test-article related findings. The MTD was not achieved in this study. The NOAEL for maternal treatment with p.o. paliperidone was 1.25 mg/kg/day, the highest dose administered. The same dose was the NOAEL for pup development, fertility, mating performance, or gestation of the F1 generation. Therefore, the dose selection was questionable for this study.

Based on the dose-range finding study, this reviewer concluded there was no reason to decrease the top dose of 2.5 mg/kg/day (the highest dose in the dose-range study) to the dose of 1.25 mg/kg/day in the first pivotal study because the dose of 2.5 mg/kg/day was not an MTD. At 2.5 mg/kg/day in the dose range-finding study, group mean maternal body weight and body weight gain were only slightly decreased (-6% and -8%, respectively).

In conclusion, the dose selection for the first prenatal and postnatal developmental toxicity study of p.o. paliperidone conducted in the rat was inadequate. This reviewer recommended that the prenatal and postnatal developmental study be repeated using higher doses and submitted during Phase IV of drug development.

The Sponsor conducted the second prenatal and postnatal developmental study using higher doses of p.o. paliperidone as recommended by the Agency. The following document is the summary and conclusions taken directly from the review of final study report submitted to the NDA 21-999 as well as to IND 65,850, IND (b) (4), IND 67,356, IND (b) (4) and IND 76,952 on January 25, 2008 (received by CDER on January 28, 2008).

In the second prenatal and postnatal developmental toxicity study, paliperidone was administered p.o to mated female rats at 0, 2.5 (LD), and 10 mg/kg b.w./day (HD) from Day 6 of gestation throughout lactation to investigate the effects on embryonic, fetal, and postnatal development, including behavior and reproductive performance of F1 generation, which was allowed to mature untreated. Although paliperidone was administered p.o. only at two dose levels, the study is considered acceptable because effects of lower paliperidone p.o. dosages had been evaluated in the first prenatal and postnatal developmental toxicity study in rats.

Marked clinical signs of partially closed eyes and decreased activity were observed in LD and HD females with a clear dose-relationship in severity and duration. Piloerection and labored breathing were observed during the initial dosing period (from gestation Day 6 to Day 13) in majority of LD and HD females. Food consumption was unaffected during the gestation period but decreased during the lactation period in both test article- treated groups relative to controls. Body weight gain was markedly decreased between Days 6 and 8 of gestation and between Days 1 and 4 of lactation in LD females. Body weight loss was observed in HD females during Days 6 and 7 of gestation. Body weight gain was decreased from Day 6 to Day 9 of gestation and between Days 1 and 4 of lactation in HD females. The duration of pregnancy was slightly increased in a dose related manner in test article treated females. Although pregnancy length was increased, there was no effect on parturition. There were no test article related effects on the number or sex of litter at birth, or maternal necropsy parameters. Dose-related reduction in survival of pups to Day 4 of age was observed in both treatment groups. In the LD group, half the litters had at least one dead pup and one litter was dead by Day 4 of lactation. In the HD group, thirteen litters had lost one or more pups and six litters were dead by Day 4 of age. Observations in pups that died early included the absence of milk in the stomach, pallor, and cold body. Survival of pups from Day 4 to Day 21 of lactation was unaffected. Body weight was decreased on Day 14 of age in LD and HD pups of both sexes and on Day 21 of age in HD females. A slight delay in sexual development was noted in HD F1 females as indicated by mean day of vaginal opening (1.2 days longer than the controls). The percentage of litters with ears open, eyes open, righting reflex, startle response, and pupillary light reflex was not affected by the treatment with the test article. There were no test article-related mortalities, clinical observations, changes in

body weight, behavioral development or reproduction in the F1 generation post-weaning that were considered by the Sponsor related to F0 maternal treatment. F2 generation was not assessed. In conclusion, the MTD for maternal treatment was achieved in this study based on decreased body weights in pregnant F0 females. Therefore, the study is considered adequate. The NOAEL for maternal treatment, pup survival between Days 1 and 4 of lactation, and pup development after maternal treatment is considered to be below the LD of 2.5 mg/kg/day. The NOAEL for behavioral development, fertility, or mating performance of F1 generation is considered to be the HD of 10 mg/kg/day.

2.6.6.10 Tables and Figures

NA

2.6.7 TOXICOLOGY TABULATED SUMMARY

NA

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: see Executive Summary on page 3 of this review for information.

Unresolved toxicology issues (if any): see below

Recommendations: The preclinical studies submitted in support of the NDA for paliperidone palmitate are sufficient to recommend approval of the application from a pharmacology/toxicology perspective provided the Sponsor sets a specification limiting the dose of each of the genotoxic impurities (b) (4) and (b) (4) to no more than (b) (4) µg per injection (b) (4)). We note that the Sponsor is reproducibly capable of producing "crude" batches of paliperidone palmitate with undetectable (< 1 ppm) levels of both impurities. Therefore, the Sponsor should, as the first principle, control both impurities at levels as low as reasonably practicable (please see page 15 of the Executive Summary for further information regarding impurities).

Suggested labeling: see page 3 of the review

Signatures (optional):

Reviewer Signature: Elzbieta Chalecka-Franaszek, Ph.D.

Supervisor Signature____signed electronically_____Concurrence Yes _ x__ No ___

APPENDIX/ATTACHMENTS

Executive CAC
Date of Meeting: November 9, 2004

Committee: Abby Jacobs, Ph.D., HFD-024, Acting Chair
Joseph Contrera, Ph.D., HFD-901, Member
Karen Davis-Bruno, Ph.D., HFD-510, Alternate Member
Barry Rosloff, Ph.D., HFD-120, Team Leader
Aisar Atrakchi, Ph.D., Presenting Reviewer

Author of Draft: Aisar Atrakchi, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in Dr. Atrakchi's review.

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND# 67,356
Drug Name: R092670
Sponsor: Johnson & Johnson
Beerse, Belgium

Background:
Paliperidone palmitate, R092670, is the ester of paliperidone formulated as an i.m. aqueous depot formulation to be injected to schizophrenic patients once a month at the maximum recommended human dose of 150mg. Paliperidone is the 9-hydroxy derivative of the marketed antipsychotic risperidone. Pharmacologically, paliperidone is an antagonist primarily at the $5HT_2$ and DA_2 receptors and also antagonizes α1, α2 and, H1 receptors. Rat and mouse oral carcinogenicity studies have been conducted for risperidone as part of the requirements for marketing application. Johnson & Johnson is also developing paliperidone OROS® oral dosage, the Agency and the sponsor agreed that carcinogenicity studies are not required for the oral paliperidone. Because oral administration can not adequately assess the potential local effects following long term i.m. injections, the Agency and the Sponsor agreed that a single species (rat), i.m. carcinogenicity study should be conducted with paliperidone palmitate. In this submission the sponsor proposes doses for the rat carcinogenicity study based on results from 3 month rat dose range finding study with i.m. injections of paliperidone palmitate.

Rat Carcinogenicity Study Protocol and Dose Selection:
Paliperidone palmitate was injected once per month into the biceps femoris of male and female SD rats at 0, 20, 80, and 160mg/kg for a total of 3 doses. Drug related mortality occurred in high dose female group but no deaths occurred in males. Clinical signs were observed in both sexes of all drug groups, they were limited to ptosis and hardened injection site in addition to sedation in mid and high dose groups. Mean body weight and weight gain were reduced significantly in 80 and 160mg/kg male groups whereas a significant but not dose dependent increase in these parameters noted in all 3 female drug groups. Changes in body weights correlated with only minimal decrease in food intake in males and a small increase in females. There were no consistent or clear drug related effects on hematology, clinical chemistry, urinalysis or ophthalmology. The only drug related effect on organ weight that correlated with histopathology was a significant increase in mean weights of the medial iliac lymph nodes in all 3 female drug groups and high dose male group. Target organs for toxicity included injection site, iliac lymph nodes and effects on male and female reproductive organs. The latter findings were considered extension of the pharmacology of the drug in response to increase in serum prolactin. The injection site findings included inflammatory granulomatous reactions mainly histiocytic with central presence of debris, in some cases the pathology extended to surrounding

tissues such as skeletal muscle and sciatic nerves. One of the deaths in high dosed female was partially contributed to injection site pathology. Drug-induced effects at injection site have been previously observed in another animal species, the dog, as well as in another rat strain the Wistar, when the drug was injected for 6 month in the latter. In the iliac lymph nodes, paliperidone palmitate caused dose related but relatively small increase in pigmented macrophages in both sexes. Paliperidone plasma concentration and exposure generally increased proportional to dose with females showing higher levels than males. There were 2 peaks following injection, the first appearing after 5hr of dosing and the 2nd peak between 7-14d after dosing. There does not seem to be drug accumulation with repeated dosing.

Executive CAC Recommendations and Conclusions:

Rat:

* The Committee concurred with the sponsor's proposed doses of 0, 0, 10, 30, and 60 mg/kg/month for both sexes to be injected i.m. into the biceps femoris at alternating sites in low dose and both sides for mid and high doses. This was based on results from the 3 month study where death occurred in females dosed 160mg/kg, reduced body weight and body weight gain in males dosed ≥80mg/kg, and injection site reactions in both sexes of all dose groups including the low dose of 20mg/kg.

* The Committee recommends the satellite TK animals be fasted overnight before blood collection.

* The Committee does not recommend using main study animals for clinical chemistry measurements. In addition, except for measurement of prolactin levels, the committee does not believe there is a need for clinical chemistry analyses in the carcinogenicity study since this was done in previous toxicity studies in the rat. Prolactin levels however, can be determined using the TK satellite animals.

* Using the above argument, the Committee also does not believe there is need to determine urinalysis in the carcinogenicity study.

Abigail Jacobs, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD-120
/B. Rosloff, HFD-120
/A. Atrakchi, HFD-120
/S. Hardeman, HFD-120
/A. Seifried, HFD-024

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Joe Contrera
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Executive CAC
Date of Meeting: June 10, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Aisar Atrakchi, Ph.D., DPP, Team Leader
Elzbieta Chalecka-Franaszek, Ph.D., DPP, Presenting Reviewer

Author of Draft: Elzbieta Chalecka-Franaszek, Ph.D., DPP

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-264
Drug Name: paliperidone palmitate
Sponsor: Ortho-McNeil-Janssen Pharmaceuticals Inc.; Agent: Johnson & Johnson Pharmaceutical R & D, L.L.C., 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560

Background:

In general, the Agency requires studies in two rodent species for the carcinogenicity assessment. However, injected i.m. paliperidone palmitate is hydrolyzed to paliperidone. Marketed oral paliperidone (INVEGA) is the major active metabolite of marketed risperidone (RISPERDAL). Carcinogenicity studies with risperidone in rats and mice were conducted and previously reviewed by the Agency. Therefore, the Division agreed that only one species study (rat) was sufficient for the assessment of the carcinogenic potential of paliperidone palmitate.

Rat Carcinogenicity Study:

The study was conducted according to standard procedures to assess the carcinogenic potential of the test article. Rats were treated with paliperidone palmitate *via* intramuscular injection for 104 weeks at dosages accepted by the Agency's Executive CAC on November 9, 2004. The intramuscular route was selected since this is the intended route of human exposure to paliperidone palmitate. Paliperidone was formulated in an aqueous suspension composed of polysorbate 20, citric acid monohydrate, disodium hydrogen phosphate, sodium dihydrogen phosphate and, NaOH. One control group was administered this aqueous suspension and the second control group received saline. An adequate number of animals (65/group) was used. At terminal sacrifice body weight in HD males was 9% and 11% less than that of the saline and vehicle control groups, respectively. In HD females, body weight was 11% and 13% less than that of the saline and vehicle control groups, respectively. A complete histopathological examination was

performed on all animals from all groups found dead, killed moribund, or sacrificed during or at the end of the study.

Tumor findings:

Statistically significant positive trends were seen in the incidences of combined mammary gland tumors (adenomas, fibroadenomas, adenocarcinomas) in males (0/65, 0/65, 8/65, and 4/65 in the vehicle control, LD, MD, and HD, respectively, using the vehicle control and all treated groups but not using the saline control group; the incidence in this group was 1/65). Moreover, the pairwise comparisons of vehicle control with MD or HD groups for the incidence of all mammary gland tumors combined in male rats were also statistically significant. [It should be noted that prolactin levels were increased in male and female rats in this study].

In female rats, neither the trend nor the pairwise comparisons for adenocarcinomas or adenocarcinomas and fibroadenomas combined were statistically significant according to CDER criteria for common tumors, except for the low dose vs. the vehicle comparison of adenocarcinomas (15/65, 32/65, 28/65, and 29/65 in the vehicle control, LD, MD, and HD, respectively).

The incidences of pancreatic islet cell tumors (islet cell adenomas and islet cell carcinomas) were slightly increased, but not dose related in males at all dose levels when compared to the vehicle control group (islet cells adenomas: 10/65, 6/65, 15/65, 16/65, and 12/65 in the saline control, vehicle control, LD, MD, and HD, respectively; islet cells carcinomas: 2/65, 3/65, 0/65, 2/65, and 2/65 in the saline control, vehicle control, LD, MD, and HD, respectively; combined pancreatic islet cell tumors: 12/65, 9/65, 15/65, 18/65, and 14/65 in the saline control, vehicle control, LD, MD, and HD, respectively). These increases were not statistically significant according to CDER criteria.

Based on CDER criteria of adjustment for multiple testing of trends, the incidences of hepatocellular adenoma in male rats (0/65, 1/65, 1/65, and 3/65 in the vehicle control, LD, MD, and HD, respectively) were statistically significant using the vehicle control and all treated groups (but not using the saline control group). However, the pairwise comparisons of the vehicle control with the LD, MD, or HD groups for the incidence of hepatocellular adenoma were not statistically significant. There was no increase in carcinomas in that tissue. The incidence of hepatocellular adenomas in male rats in the saline control group (3/65) was equal to that in HD males. Therefore, the increase in hepatocellular adenomas in HD male rats is not considered drug related.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee agreed that the study was acceptable noting prior FDA concurrence with the doses.

- The Committee found that the study was positive for mammary tumors (combined adenomas, fibroadenomas, and adenocarcinomas) in male rats.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/Division File, DPP
/Aisar Atrakchi, Ph.D., Team Leader, DPP
/Elzbieta Chalecka-Franaszek, Ph.D., Reviewer, DPP
/Kimberly Updegraff, R. Ph. Project Manager, DPP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
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/s/

Elzbieta Chalecka-Franaszek
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PHARMACOLOGIST

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