

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-999

PHARMACOLOGY REVIEW



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: 21-999
SERIAL NUMBER: N-0000
DATE RECEIVED BY CENTER: 11/30/2005
PRODUCT: (paliperidone) extended-release tablets
INTENDED CLINICAL POPULATION: Patients with schizophrenia
SPONSOR: Janssen, L.P.
AUTHORIZED U.S. AGENT: Johnson & Johnson Pharmaceutical Research and
Development, L.L.C., 1125 Trenton-Harbourton
Road, P.O. Box 200, Titusville, NJ 08560
DOCUMENTS REVIEWED: electronic NDA submission (pharmacology and
toxicology studies)
REVIEW DIVISION: Division of Psychiatry Products (HFD-130)
PHARM/TOX REVIEWER: Elzbieta Chalecka-Franaszek, Ph.D.
PHARM/TOX SUPERVISOR: Barry Rosloff, Ph.D.
DIVISION DIRECTOR: Thomas Laughren, M.D.
PROJECT MANAGER: Keith Kiedrow, Pharm. D.

Date of review submission to Division File System (DFS): September 29, 2006

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability:

The preclinical studies submitted in support of the NDA for paliperidone are sufficient to recommend approval of the application from a pharmacology/toxicology perspective.

B. Recommendation for nonclinical studies:

The Oral (Gavage) Pre and Post-Natal Developmental Toxicity Study in the Rat (reproductive toxicology study segment III) is inadequate, based on the lack of an MTD in female rats. Apparently, instead of maternal toxicity parameters, reduced pup survival at 2.5 mg/kg/day in the dose range-finding study (No. TOX6710) was used to justify selection of 1.25 mg/kg/day as the top dose for this study. This reviewer notes that there was no reason to decrease the top dose of 2.5 mg/kg/day because it clearly did not exceed the MTD based on maternal parameters, for example maternal body weights. It is recommended that the study be repeated using higher doses during Phase IV.

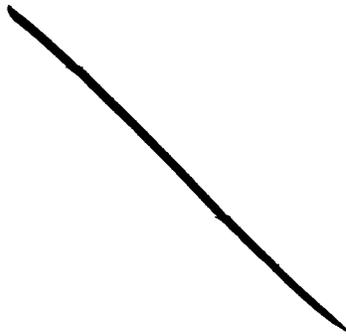
C. Recommendations on labeling:

Pharmacodynamics:

Sponsor's proposal:

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Reviewer's proposal:

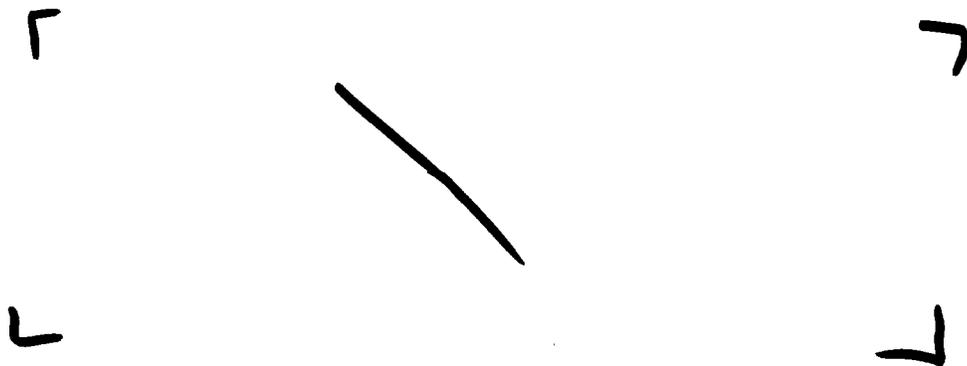
The mechanism of action of paliperidone, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine Type 2 (D₂) and serotonin Type 2 (5HT_{2A}) receptor antagonism.

Paliperidone is also active as an antagonist at α_1 and α_2 adrenergic receptors and H₁ histaminergic receptors. Antagonism at receptors other than D₂ 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. Paliperidone is the major active metabolite of risperidone.

Carcinogenesis:

Sponsor's proposal:



Reviewer's proposal:

Carcinogenicity studies of paliperidone were not performed.

Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone on a mg/m² basis (see Risperdal labeling). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D₂

antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see PRECAUTIONS, General – Hyperprolactinemia)

Mutagenicity:

Sponsor's proposal:

[_____]

Reviewer's proposal:

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:

Sponsor's proposal:

[_____]

Reviewer's proposal:

In a study of fertility, the percentage of treated female rats which became pregnant was not affected at oral doses of paliperidone up to 2.5 mg/kg/day, a dose causing a slight maternal toxicity. However, pre- and post-implantation loss was increased and the number of live embryos was slightly decreased at 2.5 mg/kg. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose on a mg/m² basis. The fertility of male rats was not affected at doses up to 2.5 mg/kg/day, although sperm count as well as 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 – 5 mg/kg) resulted in decreased serum testosterone and sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after treatment was discontinued.

Pregnancy*Sponsor's proposal:*

Reviewer's proposal:

Pregnancy Category C

In studies in 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 dose tested (10 mg/kg in rats and 5 mg/kg rabbits, which is 8 times the maximum recommended human dose on a mg/m² basis).

In reproductive studies of risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths have been seen at oral doses less than the maximal recommended human dose of risperidone on a mg/m² basis (see Risperdal labeling).

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

II. Summary of nonclinical findings**A. Brief overview of nonclinical findings**

Pharmacology: Paliperidone (R076477 or 9-hydroxy-risperidone) is the major active metabolite of risperidone in humans, as well as in all laboratory animal species tested. Paliperidone, similar to risperidone, exhibits the characteristics of an atypical antipsychotic. In nonclinical studies paliperidone generally closely resembled the pharmacological profile of risperidone. Both compounds have high affinity for the serotonin type 2A (5-HT_{2A})- and the dopamine type 2 (D₂)-receptors, and lower affinity for the histamine type 1 (H₁)-, and α_1 - and α_2 -adrenergic receptors. Paliperidone is a racemic mixture of the enantiomers R078543(+) and R078544(-). The binding profiles for paliperidone, risperidone

and the two paliperidone enantiomers R078543(+) and R078544(-) were comparable. Paliperidone and 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 D₂ 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 IC₅₀ 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.

Pharmacokinetics: The majority of pharmacokinetic data were generated as toxicokinetic measurements in toxicology studies. Exposure to paliperidone in general increased with increasing dose without accumulation after prolonged p.o. treatment. For both paliperidone enantiomers, similar elimination half-lives ($t_{1/2}$) were estimated after p.o. dosing with both compounds that ranged in rats from 1.2 to 2.3 hours. Bioavailability of paliperidone after p.o. solution administration in dogs was high (94%). The p.o. availability in rats was not assessed. The sponsor estimated the F_{abs} value at 46% in male rats and 78% in female rats by comparison of data from separate studies. However, the relative bioavailability of paliperidone following 2 mg ER tablet administration p.o. was only 15% in dogs. ER tablets administered to dogs were recovered in the feces as whole units without tears, perforations or indentations. Estimated gastrointestinal transit times were between 7.7 to 45.1 hours and the average residual paliperidone was 0.46 mg (range 0.01 to 0.92 mg). The distribution of radiolabelled paliperidone was investigated in general distribution and in brain distribution studies in rats. Highest values of paliperidone derived activity were observed in the liver, small intestinal tissue and salivary gland. In all non melanin containing tissues, the radioactivity declined in parallel to plasma concentrations. In melanin-containing tissues (eyeballs and pigmented skin and fur) there was an extensive retention of paliperidone-related radioactivity. Paliperidone was also well absorbed after subcutaneous administration. Maximum plasma concentrations were observed at 0.5 h after administration. Plasma levels of paliperidone rapidly declined with a half life of 2.3 h. Brain concentrations of unchanged drug (UD) and non-volatile radioactivity rapidly increased after subcutaneous administration. Peak levels of UD were observed at 0.5 h in cerebellum, at 1 h in rest of brain and frontal cortex, and at 4 h in striatum. In frontal cortex and striatum, brain regions with high concentrations of 5-HT₂ or D₂ receptor, C_{max}, T_{max} and AUCs and half-lives of paliperidone were higher than in cerebellum, a region with few of these receptor binding sites. In vivo mass balance studies with radiolabelled paliperidone in rats,

dogs, and humans indicated that the major biotransformation pathways in vivo and in vitro and across the species are the same. Paliperidone metabolism was extensive in vivo in rats and less extensive in dogs and humans. The amount recovered as unchanged drug was 3.19% and 6.42% in rats, 32.4% in dogs and 59.4% in humans. Individual metabolites each accounted for 3-5% of the administered dose. The metabolites observed following administration of paliperidone have also been observed following risperidone administration. All metabolites observed in humans were also observed in at least one of the toxicological species. In dogs and humans, paliperidone-related radioactivity was excreted mainly in urine; in rats with the feces. In humans, the cumulative excretion in the urine was ~80% of the dose.

Toxicology: The nonclinical toxicity profile of paliperidone has been characterized in single-dose toxicity studies and repeat-dose toxicity studies. A 12-month repeat-dose toxicity study in dogs was not performed with paliperidone; this study was bridged to a study previously conducted with risperidone. Some of the repeat-dose toxicity studies also included risperidone to allow a direct comparison between the two test articles. Most toxicity studies were conducted with immediate release formulations for p.o. administration (aqueous solution) while some employed other formulations (diet, powder in gelatin capsules, i.v. solutions). According to the sponsor, these modes of administration were selected in order to maximize systemic exposure, which is not achievable upon p.o. administration of paliperidone ER tablets in dogs nor dietary administration of paliperidone in rodents. A 3-month repeat-dose toxicity study with paliperidone ER tablets was conducted only in dogs. The administration of paliperidone ER tablets is not feasible in rats and mice because the dimensions of the tablet are too large compared with the diameter of the GI tract in rodents.

Repeat-dose toxicity: Various treatment-related findings, which were consistently observed in the repeat-dose paliperidone toxicity studies, are thought to be mediated by dopamine D₂-antagonistic activity of paliperidone. Clinical signs of sedation, reduced general activity and palpebral ptosis observed in several studies in mice, rats, rabbits and dogs are considered to be related to D₂ receptor antagonistic action. The same properties are responsible for hyperprolactinemia observed in paliperidone- and risperidone-treated rats and dogs. In repeat-dose toxicity studies, body weight and body weight gain was generally dose-dependently decreased in paliperidone treated male rats and mice. However, in females body weight and body weight gain was generally increased at the low and medium dose levels and slightly decreased or unchanged at the highest dose. Changes in body weight occurred in parallel with changes in food consumption. Increased body weight and body weight gain in female rats and mice are most likely related to the increased prolactin levels. Increased prolactin release is also likely responsible for the following observations in the repeat dose toxicity studies with paliperidone in mice, rats and dogs, as well as in the carcinogenicity studies in rats and mice conducted with risperidone:

Pituitary gland: Increased incidence of prolactin-immuno-positive cells in the anterior pituitary gland of rats was observed in the comparative 3-month repeat-dose toxicity study with paliperidone and risperidone. This observation suggests increased activity of prolactin producing cells. Immunohistochemical staining of the pituitary was not conducted in other studies. Hyperplasia of the pituitary gland (adenohypophysis) was observed in the 3-month repeat-dose toxicity study with paliperidone and risperidone in mice and in carcinogenicity studies with risperidone in mice. A dose-related increase in the incidence of pituitary gland adenomas occurred in female mice dosed with risperidone in the carcinogenicity study. The pituitary gland was not affected in dogs treated with paliperidone or risperidone. No pituitary tumor response was seen in risperidone treated male mice or rats. **Mammary gland:** Increased mammary gland stimulation i.e. enhanced glandular development in female mice and rats and increased secretory activity in female rats, as well as female aspect of the mammary glands in male rats (i.e. tabulo acinar development) was observed in studies with paliperidone and risperidone. For example, in the 6-month study in rats, female rats showed minimal (multi) focal hyperplasia of the mammary gland at the highest dose level tested (10 mg/kg/day) of paliperidone and risperidone. In addition, increased incidence of mammary gland adenocarcinomas in rats and female mice were observed in the carcinogenicity studies with risperidone. These effects are considered to be mediated by prolonged stimulation of the mammary gland due to hyperprolactinemia. In contrast to the mammary gland stimulation seen in rats and mice, the mammary gland in dogs treated with paliperidone and risperidone showed a resting aspect. Prolactin-mediated mammary carcinogenesis in rodents seen in the risperidone carcinogenicity studies is well known. **Female reproductive organs:** Reduced cyclic activity and resting aspect of the female reproductive organs (ovaries, uterus, vagina) was observed in rats and mice, and a delay in sexual maturity was observed in female dogs after treatment with paliperidone and risperidone. Similar findings were observed in rodents in carcinogenicity studies with risperidone. Pseudopregnancy (resting aspect of female genital tract and a stimulation of the mammary gland) is a frequently observed response to treatment with dopamine D₂-receptor antagonists in rodents. **Male reproductive/accessory sex organs:** Low glandular epithelium of the coagulating glands and seminal vesicles of male rats, increased inflammation in the dorsolateral prostate in male rats and atrophy with decreased glandular development of the prostate in male dogs were observed after treatment with paliperidone. There were no effects on prostate in mice. There were no inflammatory changes in prostate in dogs. Treatment-related changes in the male accessory sex organs were also noted in the rat carcinogenicity study with risperidone. According to the sponsor, there is no evidence that prolactin induces inflammation in the human prostate. **Endocrine pancreas:** Increased incidence of pancreas endocrine adenomas in male rats observed in carcinogenicity studies with risperidone was attributed to hyperprolactinemia. There were no findings in the pancreas in studies conducted with paliperidone submitted to this NDA. **Adrenal glands:** Swollen cortical cells of the zona fasciculata of the adrenals were observed in paliperidone- and risperidone-treated male rats in the 3- and 6-

month rat gavage toxicity studies. There were no findings in the adrenals in other toxicity studies in rats and in studies in dogs. In carcinogenicity studies with risperidone in rats, an increased incidence of adrenocortical ectasia and congestion was noted. Findings in the adrenals are likely related to increased prolactin levels.

Other treatment-related findings in studies with paliperidone included changes in the red pulp of the spleen and QT-prolongation. **Spleen:** The increase in erythrocyte accumulation in the splenic red pulp of rats and dogs accompanied by an increase in relative spleen weight was observed. This effect is considered by the sponsor to be due to the inhibition of the contraction of the splenic smooth musculature in response to the α_1 -adrenergic receptor blocking activity of paliperidone and is related to the method of euthanasia, and of no relevance to humans. Other effects related to α_1 -adrenergic receptor blocking activity of the paliperidone in animal studies include hypotension, sedation and palpebral ptosis seen in many studies. Increase in heart rate in studies with paliperidone is likely α_2 -adrenergic receptor-mediated. Slight **QTc interval prolongation** was observed in dogs in the 3-month repeat-dose toxicity study with paliperidone ER tablets and paliperidone bulk powder. In another 3-month repeated dose oral toxicity study in dogs, daily administration of paliperidone and risperidone solution by the oral route (gavage) resulted also in slight QTc interval increases in all test article-dosed groups after one month and after three months of treatment. Heart rate increased after one and three months. According to the sponsor, administration of paliperidone and risperidone had no influence on blood pressure. However, this reviewer notes slight decreases in the mean group diastolic and systolic blood pressures in all groups, when compared to the predose values and control group after three months of paliperidone or risperidone administration. These data in combination with the safety pharmacology data indicated that paliperidone affected the cardiovascular system in dogs.

The oral toxicity profile of paliperidone in comparative repeat dose toxicity studies was comparable with that of risperidone. The NOAELs for repeat-dose toxicity studies are shown on page 76 of this review.

Carcinogenicity: No standard carcinogenicity studies with p.o. paliperidone were performed because the sponsor requested a waiver from these studies based on considerations that the carcinogenic potential of paliperidone in rodents was adequately addressed in the 18-month dietary carcinogenicity study with risperidone in albino Swiss (CD1) mice (dose levels: 0, 0.63, 2.5 and 10 mg/kg/day) and the 24-month dietary carcinogenicity study with risperidone in Wistar Wiga rats (dose levels: 0, 0.63, 2.5 and 10 mg/kg/day). Both carcinogenicity studies were previously conducted in support of Risperdal.

There have been numerous discussions with the sponsor on this point. The Agency agreed that the carcinogenicity could be waived if it were shown that (1) the toxicologic profiles of paliperidone and risperidone were similar, (2) human

systemic exposure to paliperidone at therapeutic doses of paliperidone does not exceed that at therapeutic doses of risperidone, (3) the enantiomeric ratio of paliperidone in humans receiving therapeutic doses of paliperidone is similar to that in humans receiving therapeutic doses of risperidone, and (4) no metabolites are formed in humans after therapeutic doses of paliperidone that are not seen after therapeutic doses of risperidone.

This reviewer evaluated the toxicological profiles of paliperidone and risperidone in animal studies. Based on submitted data, it can be concluded that these profiles are similar. In addition, this reviewer compared the metabolites formed in humans after administration of paliperidone and risperidone. New metabolites were identified in the paliperidone study in humans which were not seen in a previous risperidone study. According to the sponsor, these metabolites may have been present in samples of the previous risperidone study but might not have been adequately identified. In a recent study conducted with risperidone using more advanced techniques, the metabolites which were detected in humans after paliperidone administration, were also found after oral dosing with risperidone. Other issues were reviewed by Dr. Ronald Kavanagh. Based on his review, all other requirements have been met. Therefore, carcinogenicity studies for paliperidone can be waived from the pharmacology/toxicology perspective.

Genetic toxicology: Paliperidone was tested in a full battery of genotoxicity studies, including bacterial reverse mutation assays, in vitro mouse lymphoma assays and in vivo rat micronucleus assay, and showed no genotoxic properties.

Reproductive toxicology: Paliperidone was tested in a series of reproduction toxicity studies including male and female rat fertility and early embryonic developmental toxicity studies, rat and rabbit embryo-fetal developmental toxicity studies (including a rabbit dose-ranging study), a combined pre- and postnatal dose-ranging developmental toxicity and juvenile toxicity study in rats, and pre- and postnatal developmental toxicity study in rats.

There were no treatment related effects on fertility in the male fertility study in rats. In the female rat fertility and early embryonic developmental toxicity study, pseudopregnancies considered as a consequence of prolactin mediated effects were observed. The pre-coital interval was increased. Adverse effects on fertility and reproductive capacities at the highest dose level were evidenced by increases in pre- and post-implantation loss resulting in decreases in the number of implantations and live fetuses 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 in this study.

Embryo-fetal development was investigated in the oral developmental toxicity study in the rat. Even at maternally toxic dose levels, there were no relevant changes at external, visceral and skeletal examination in the fetuses. There were no other pregnancy, litter and fetal changes. The maternal NOAEL was

considered to be 0.63 mg/kg/day. The fetal NOAEL was considered to be 10 mg/kg/day. In the embryotoxicity and teratogenicity study with paliperidone administered by oral gavage to albino rabbits, the effects on pregnant rabbits and on embryo-fetal development were assessed. Administration during Days 6 to 18 of pregnancy revealed maternal toxicity. Slight post-implantation loss increase was observed at 5 mg/kg/day associated with a slight increase in the number of embryonic/fetal resorptions and fetal death. According to the sponsor, these findings are similar to those obtained in a previously conducted rabbit embryo-fetal developmental study with risperidone. No test article-related teratogenicity was seen. There were no other toxic fetal effects. The NOAEL for maternal toxicity was established as 0.31 mg/kg/day (based on lethargy seen in dams at 1.25 mg/kg). The NOAEL for embryo-fetal toxicity was 1.25 mg/kg/day based on the increase in post-implantation loss and the slight decrease in the number of live fetuses at 5 mg/kg/day.

Prenatal and postnatal development was also assessed in the oral (pre and post-natal developmental toxicity study in the rat. 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. The 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 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 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 is questionable for this study. This reviewer notes that there was no reason (based on the dose-range finding study) to decrease the top dose of 2.5 mg/kg/day because this dose 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). Therefore, the dose selection for the pre and post-natal developmental toxicity study in the rat is inadequate. The sponsor should be asked to repeat this study as a phase IV commitment.

Pharmacologic activity

Paliperidone (9-hydroxy-risperidone) is the major active metabolite of risperidone in all laboratory animal species as well as in humans. Paliperidone and risperidone have very similar pharmacologic profile and exhibit the characteristic of an atypical antipsychotic. Both compounds have high affinity for the serotonin 5-HT_{2A}- and the dopamine D₂-receptors, and lower affinity for the histamine H₁, adrenergic- α_1 and adrenergic- α_2 receptors. The binding profiles for the two paliperidone enantiomers R078543(+) and R078544(-) are comparable. The affinity of paliperidone towards serotonin 5-HT_{2A}- and the dopamine D₂-receptors is most likely related to its beneficial effects on the negative and positive

symptoms of schizophrenia. Interactions with other receptors may result in side effects, such as orthostatic hypotension (α_1 adrenergic receptor), heart rate increase (α_2 adrenergic receptor) or sedation (histamine H₁ receptor).

B. Nonclinical safety issues relevant to clinical use

Target organs of paliperidone toxicity in animals include central nervous system, cardiovascular system, male and female reproductive organs and mammary glands, pituitary gland, pancreas and adrenals. Effects of prolonged treatment of humans with paliperidone on these tissues, organs or systems cannot be excluded.

Appears This Way
On Original

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-999

Review number: 1

Sequence number/date/type of submission: N-0000/November 30, 2005/NDA original application

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Janssen, L.P. (sponsor), Johnson and Johnson Pharmaceutical Research and Development L.L.C. (authorized U.S. agent), 1125 Trenton-Harbourton Road, P.O. Box 200, Titusville, NJ 08560

Manufacturer for drug substance: (1) Janssen Pharmaceutica N.V., Janssen Pharmaceuticaaan 3, B-2440 Geel, Belgium, and (2) Janssen Pharmaceutical Ltd., Little Island, County Cork, Ireland

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

Division name: Division of Psychiatry Products

HFD #: 130

Review completion date: August 8, 2006

Drug:

Trade name: _____

Generic name: paliperidone

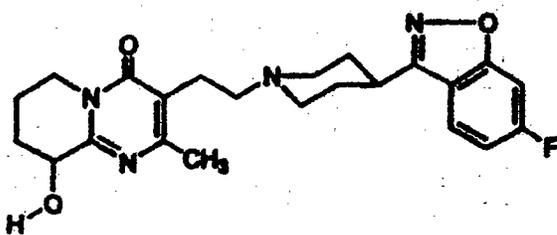
Code name: JNJ16232411; R076477

Chemical name: (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4H-pyrido[1,2a]pyrimidin-4-one

CAS registry number: 144598-75-4

Molecular formula/molecular weight: C₂₃H₂₇FN₄O₃/426.49

Structure:



paliperidone (9-hydroxy-risperidone)

Relevant INDs/NDAs/DMFs: IND 65,850 for Paliperidone; NDA 20272 for Risperdal (risperidone) Caplets; _____

Drug class: An antagonist on serotonin 5-HT_{2A} and dopamine D₂ receptors; an atypical antipsychotic

Intended clinical population: adult patients with schizophrenia

Clinical formulation: 3 mg, 6 mg, 9 mg, 12 mg tablets

Route of administration: oral

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

Studies reviewed within this submission: all submitted studies on paliperidone and all comparative paliperidone/risperidone studies

Studies not reviewed within this submission: studies on risperidone performed and previously submitted to support the marketing application of risperidone (Risperdal) (reviewed by Dr. Lois Freed) that have been resubmitted with this application

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Paliperidone (R076477, R76477, or 9-hydroxy-risperidone) is the major active metabolite of risperidone in humans, as well as in all laboratory animal species tested. Risperidone is an atypical antipsychotic approved for the treatment of schizophrenia (Risperdal®). Paliperidone is pharmacologically very similar to the parent compound, and mediates its *in vivo* biological activity. Paliperidone is a racemic mixture of the enantiomer R078543 (+) and R078544 (-). The pharmacological profile of the racemate and the enantiomers is very similar, both *in vitro* and *in vivo*. Interconversion between both enantiomers occurs in solution and in the body. Paliperidone, similar to risperidone, exhibits the characteristic of an atypical antipsychotic. Both compounds have high affinity for the serotonin type 2A (5-HT_{2A})- and the dopamine type 2 (D₂)-receptors, and lower affinity for the histamine type 1 (H₁)-, and α_1 - and α_2 -adrenergic receptors.

Since risperidone is primarily converted to paliperidone and both compounds exhibit a similar pharmacological profile at comparable dose levels, the pharmacological action of risperidone is determined by the systemic exposure to the active fraction, i.e. the sum of unchanged risperidone and paliperidone. Based on AUC_{0-24h} values, paliperidone is the major contributor to the active fraction after repeated oral dosing of risperidone across species, i.e., approximately: 70% in humans, 90-94% in dogs, 80% in mice, and 78-54% in rats. Most of the nonclinical pharmacology studies on paliperidone were performed at the time when studies were conducted to support the marketing application of Risperdal™.

Safety pharmacology: There were no separate CNS safety pharmacology studies submitted to this NDA. Cardiovascular effects of paliperidone were evaluated in several safety pharmacology studies *in vitro* and *in vivo*. An *in vitro* I_{Kr} assay indicated slight effect of paliperidone on the K⁺ current. At higher concentrations of 3 x 10⁻⁷ M or above,

paliperidone dose-dependently attenuated the K^+ current with the IC_{50} of 1.2 μ M in HERG-transfected HEK293 cells. Paliperidone also significantly inhibited the rapid-activating component of the delayed rectifier potassium channel I_{Kr} in ventricular myocytes from guinea pig hearts. In isolated right atrium of the guinea pig paliperidone reduced the rate of contraction. In other models paliperidone increased the duration of action potential in bradycardic and normal conditions. In isolated rabbit hearts, early after depolarizations and TdPs were observed in one out of five preparations. In vivo, paliperidone induced an increase in heart rate, heart contractility and a decrease in mean, systolic and diastolic arterial blood pressure in many studies. The duration of the QTc interval was slightly prolonged in some (but not all) studies. Please see individual study reviews for further details. There were no toxicologically significant findings in the respiratory function safety pharmacology study.

2.6.2.2 Primary pharmacodynamics

Mechanism of action and drug activity related to proposed indication:

1. Study title: In vivo receptor binding by (+-) -9-OH-risperidone (R076477) and its racemates (A)-(+)-9-OH-risperidone (R078543) and (B)-(-)-9-OH-risperidone (R078544); a comparison with risperidone.

The in vitro neurotransmitter receptor binding profile of paliperidone racemate, its enantiomers and risperidone was investigated in animal brain after single subcutaneous administration. Male Wistar rats were treated with vehicle or test compounds at seven dosages ranging from 0.01 to 40 mg/kg. Guinea pigs were treated at the same dosages for H_1 receptor binding studies. Cloned human receptors have been also used. No difference in affinity of these test articles was observed for the $5-HT_{2A}$ and D_2 receptors, as well as many other receptors. All four compounds demonstrated clearly a higher affinity for $5-HT_{2A}$ than for D_2 receptors. These results are shown in the following sponsor's table:

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Table 3: *In vitro* receptor binding of R076477, R078543 and R078544, K_i-values (nM), n = 2-6

Receptor	Species	Brain area / cells	REF	(+)-	(+)-(A)-	(-)(B)-
			R076477	9-OH-R R076477	9-OH-R R078543	9-OH-R R078544
5-HT _{1A}	rat	Hip	250	380	315	939
5-HT _{1A}	cl. human	Ha-6 cells	420	590	412	N/A
5-HT _{1B}	rat	CPu	2720	3250	>5000	>5000
5-HT _{1D}	cl. human	C6-glioma	9.8	12	15	25
5-HT _{1D}	cl. human	L929	140	170	N/A	N/A
5-HT _{2A}	rat	Fr	0.16	0.25	0.14	0.19
5-HT _{2A}	cl. human	L929	0.52	1.0	0.60	1.1
5-HT _{2C}	pig	ChP	63	71	44	81
5-HT ₂	mouse	NXG 108OC15 cells	>5000	>5000	>5000	>5000
D ₁	rat	CPu	620	670	557	504
D ₂	rat	CPu	3.3	4.0	3.4	2.6
D ₂	cl. human	CHO cells	5.9	4.8	10	14
D ₃	cl. rat	COS7 cells	13	8.3	N/A	N/A
D ₃	cl. human	CHO cells	14	6.4	8.1	7.9
D _{4L}	cl. human	CHO cells	16	30	21	12
α ₁	rat	Cx	2.3	4.0	1.2	1.5
α ₂	rat	Cx	7.5	17	36	10
α _{2A}	cl. human	CHO-1E5 cells	23	30	45	25
α _{2B}	cl. human	CHO-3B3 cells	8.5	9.5	12	11
α _{2C}	cl. human	CHO-11A9 cells	9.1	11	19	15
β ₁	cl. human	E. Coli	>5000	>5000	>5000	>5000
β ₂	cl. human	E. Coli	>5000	>5000	>5000	>5000
AChM	rat	CPu	>5000	3570	>5000	>5000
H ₁	guinea-pig	Cbn	2.6	10	18	13
H ₁	cl. human	CHO cells	27	32	N/A	N/A
sigma ₁	guinea-pig	MO	950	1460	1695	1068
Ca ⁺⁺ ch	rat	Cx	>5000	>5000	>5000	>5000
Na ⁺ ch	rat	Cx	3860	>5000	>5000	>5000

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Fr: frontal cortex
 ChP: choroid plexus
 CPu: caudate-putamen (striatum)
 cl. cloned
 Cx: total cortex
 Cbn: Cerebellum
 MO: Medulla Oblongata
 N/A: Not available

Very similar results were obtained by ex-vivo radioligand receptor binding study following subcutaneous injection of single doses of four test articles in rodents. Occupancy of all selected receptors was measured in the selected areas of each individual brain by autoradiography. Brain areas known to show high receptor density were examined. These results are shown in the sponsor's table below:

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Table 4: *In vivo* receptor occupancy profile of R076477, R078543 and R078544 in rodent brain after subcutaneous administration, measured *ex vivo* by quantitative autoradiography, ED₅₀-values (95% confidence limits), mg/kg s.c., 2 h

Receptor	Brain area	Risperidone	(+)-R-OB-	(+)-S-OB-	(+)-R-OB-
			R076766	R076477	R078543
5-HT _{2A}	FrLA	0.062 (0.045-0.079)	0.35 (0.18-0.51)	0.25 (0.13-0.37)	0.29 (0.13-0.46)
5-HT _{2C}	ChP	> 10	13 (8-31)	36 (6-66)	31 (8-54)
D ₁	CPu	> 10	> 10	N/A	N/A
D ₂	CPu	1.2 (0.83-1.5)	3.7 (2.7-4.7)	2.3 (1.4-3.1)	2.4 (1.9-3.0)
D ₃	KCj	> 10	> 10	N/A	N/A
α ₁	Tha	1.6 (1.2-2.1)	7.6 (4.7-10)	2.2 (1.1-3.4)	9.1 (2.5-16)
α ₂	Ent	3.7 (2.0-5.4)	> 10	24 (7-43)	7.1 (4.4-10)
H ₁	Chm (gp)	0.44 (0.20-0.68)	2.4 (0-6.1)	N/A	N/A
n animals per dose		3-12	6	3	3

Hip: hippocampus
 FrLA: fourth layer of the frontal cortex
 ChP: choroid plexus
 CPu: caudate-putamen (striatum)
 Ent: entorhinal cortex
 Chm (gp): guinea-pig cerebellum
 N/A: not available

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2. Study title: In vitro receptor binding and neurotransmitter uptake inhibition profile of R 64 766, R 76 477, R 78 543 and R 78 544.

Risperidone and the isomers of paliperidone were investigated for inhibition of radioligand binding to neurotransmitter receptor sites, drug receptor binding sites, ion channel binding sites, peptide receptor binding sites, tetrabenazine sensitive release sites, thromboxane-A₂, PAF and leukotriene-D₄ receptor binding sites and for inhibition of neurotransmitter uptake in rat brain synaptosome preparations using standard binding techniques. The profile of the paliperidone was similar to that of risperidone. There were no toxicologically significant differences in potency of paliperidone enantiomers. The test-articles revealed subnanomolar binding affinity for serotonin 5-HT₂ receptors and were significantly less active or not active at all other 5-HT receptor subtypes. The test articles showed nanomolar binding affinity at dopamine D₂ receptors and were significantly less active at dopamine D₁ receptors. The test articles showed also nanomolar binding affinity for α₁-adrenergic (9-times less than for α₂-adrenergic) and histamine H₁ receptors. These compounds were very weakly active or not active up to the highest tested concentrations of 10 μM in the other sites. The K_i values are shown in the following sponsor's table:

Table 2b : Profile of R 64766, R 76477, R 78543 and R 78544 for in vitro binding to receptor sites and for inhibition of monoamine uptake

			R 64766 risperidone	R 76477 (±)ROR-risperidone	R 78543 (+)-ROR-risperidone	R 78544 (-)-ROR-risperidone
Neurotransmitter receptor sites			Ki SD n	Ki SD n	Ki SD n	Ki SD n
Serotonin-5HT2	3H-5HT2A	rat frontal cortex	0.12 0.02 4	0.22 0.04 4	0.10 0.02 3	0.24 0.04 3
Serotonin-5HT1A	3H-5HT1A	rat hippocampus	271 87 3	267 37 4	216 24 3	950 82 3
Serotonin-5HT1B	3H-5HT1B	rat striatum	3728 1673 3	2520 320 2	3690 250 2	
Serotonin-5HT1C	3H-5HT1C	rat substantia nigra	62 16 4	123 20 2	123 14 3	163 88 3
Serotonin-5HT1D	3H-5HT1D	rat thalamus	47 6 3	11 48 4	34 2 3	42 6 3
Serotonin-5HT3	3H-5HT3	MG 109CC16 cells	na	na	na	na
alpha1-Adrenergic						
alpha2-Adrenergic	3H-WB4101	rat forebrain	0.61 0.14 4	1.3 0.2 4	1.2 0.1 3	1.4 0.2 3
beta1-Adrenergic	3H-clonidine	rat cortex	7.9 1.2 4	15 8 3	21 10 3	12 1 3
beta2-Adrenergic	125I-cyanopindolol	E coli He-basal	na	na	na	na
	125I-cyanopindolol	E coli He-basal	na	na	na	na
Dopamine D2						
Dopamine D1	3H-haloperidol	rat striatum	2.0 0.6 4	4.1 0.7 3	2.8 0.5 3	2.8 0.5 3
	3H-SCH23399	rat striatum	620 106 3	660 104 4	530 67 3	460 106 3
Histamine H1						
Histamine H2	3H-pyramine	guinea pig cerebellum	2.1 0.9 3	7.0 0.5 3	15 3 4	10 1 3
	3H-thioperazine	guinea pig striatum	890 290 3	4620 300 3	1040 0 2	
Cholinergic muscarinic						
	3H-diazepam	rat striatum	na	na	na	na
Drug receptor binding sites						
ms-opiate	3H-oxycodone	rat forebrain	na	na	na	na
Haloperidol sensitive sigma	3H-haloperidol	guinea pig medulla oblongata	605 216 3	1327 6 3	1600 170 3	945 106 3
Sumatriptan	3H-sumatriptan	rat forebrain	na	na	na	na
7CP-AMDA sites	3H-TCP	rat hippocampus	na	na	na	na
Ion channel ligand binding sites						
Ca++-channel	3H-flunarizine	rat cortex	na	na	na	na
Na+-channel	3H-tetrodotoxin-B	rat cortex	2850 450 3	8040 1840 3	6470 2580 3	11700 2100 3
Peptide receptor binding sites						
Substance-P	3H-substance P	rat striatum	na	na	na	na
Neurotensin	3H-neurotensin	rat forebrain	na	na	na	na
CGK-A	3H-CCK	rat pancreas	na	na	na	na
CGK-B	3H-CCK	guinea pig cortex	na	na	na	na
Tetrazolazine sensitive release sites						
	3H-tetrazolazine	rat striatum	132 28 3	384 116 4	568 97 3	664 156 3
Various						
Trastuzumab A2	3H-SQ29546	human platelets	na	na	na	na
PAF	3H-PAF	rabbit platelets	na	na	na	na
Leukotriene D4	3H-leukotriene D4	guinea pig lung	na	na	na	na

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Continued:

			R 64766 risperidone	R 76477 (±)ROR-risperidone	R 78543 (+)-ROR-risperidone	R 78544 (-)-ROR-risperidone
Neurotransmitter uptake			IC50 SD n	IC50 SD n	IC50 SD n	IC50 SD n
Serotonin	3H-serotonin	rat cortex	544 76 4	2020 480 4	1070 336 3	2170 208 3
Norepinephrine	3H-norepinephrine	rat cortex	2544 478 4	1680 340 3	4148 280 3	834 150 3
Dopamine	3H-dopamine	rat striatum	4740 386 3	2010 400 3	10800 3150 3	9810 3690 3
GABA	3H-GABA	rat cortex	na	na	na	na

3. Study title: Comparative pharmacology of risperidone, its major metabolite R 76 477(+,-) and the corresponding enantiomers R 78 543(+) and R 78 544(-) in rats and dogs.

Risperidone, paliperidone and its enantiomers were compared in several pharmacology studies conducted in Wistar rats and Beagle dogs. Apomorphine, tryptamine and norepinephrine antagonism was tested in rats. Apomorphine antagonism was also tested in dogs. Moreover, a general observation test was conducted in rats, including palpebral opening, pupil diameter, body temperature, behavioral changes, tail withdrawal test, antidiarrheal activity and anticonvulsant activity. The compounds were potent antagonists of apomorphine-, tryptamine-, and norepinephrine-induced effects in rats. All compounds tested showed comparable pharmacological profile, although paliperidone and its enantiomers were generally slightly less potent than risperidone. The compounds were equipotent in blocking apomorphine-induced emesis in dogs. The observed behavioral effects (catalepsy, postration, decrease in palpebral opening, decrease of body

temperature, muscular hypotonia) were consistent with blockade of α -adrenoreceptors and central dopamine receptors. Tremors were observed only after treatment with risperidone, probably due to slightly greater potency of risperidone. It can be concluded that all tested articles are very similar in their potency, pharmacological profile and onset and duration of action. The summary of the general pharmacological profile of tested articles after the i.p. dose of 40 mg/kg/day in the general observational test in rats is shown in the following sponsor's table:

Tests	n active/n tested	
	R 78 477	Risperidone
CNS stimulant activity		
sniffing	0/3	0/3
licking	0/3	0/3
rearing	0/3	0/3
preening	0/3	0/3
chewing	0/3	0/3
excitation	0/3	0/3
Cholinergic activity		
lacrimation	0/3	0/3
salivation	0/3	0/3
diarrhea	0/3	0/3
ptosis	0/3	0/3
miosis	1/3	1/3
Central dopamine antagonistic or other sedative activity		
passivity	0/3	0/3
sedation	0/3	1/3
prostration	3/3	1/3
cataplexy	3/3	2/3
muscular hypotonia	3/3	3/3
palpebral ptosis	3/3	3/3
Central nicotinic activity		
blockade of pinna reflex	0/3	0/3
blockade of cornea reflex	0/3	0/3
muscular hypertonia	0/3	0/3
inhibition tail withdrawal reflex	0/3	0/3
Anticonvulsant or hypnotic activity		
ataxia	0/3	1/3
hypnosis	0/3	0/3
activity against pentylentetrazole	0/3	0/3
Peripheral anticholinergic activity		
mydriasis	0/3	0/3
α-Adrenoreceptor agonist activity		
exophthalmos	0/3	0/3
ptosis	0/3	0/3
α-Adrenoreceptor antagonist activity		
palpebral ptosis	3/3	3/3
Antidarrheal activity		
activity against castor oil	1/3	2/3
Aspecific effects		
pallor	0/3	0/3
decrease of body temperature	3/3	3/3
increase of body temperature	0/3	0/3
Toxic effects		
cyanosis	0/3	0/3
tremors	0/3	2/3
convulsions	0/3	0/3
dyspnea	0/3	0/3
dead	0/3	0/3

4. Study title: Comparison of the in vivo pharmacological profile of (+)-R 78 543 and (-)-R 78 544, the enantiomers of 9-hydroxyrisperidone.

The enantiomers of risperidone (+)-R078543 and (-)-R078544, were tested to compare their pharmacological profile to that of the racemate and risperidone. Pharmacological tests included assessment of serotonin 5-HT₂-, dopamine D₂-, histamine H₁-, α ₁-adrenergic and α ₂-adrenergic receptor-related antagonism as well as behavioral effects. 5-HT₂-antagonism was tested in the tryptamine antagonism test in rats (reversal of tryptamine cyanosis, inhibition and blockade of tryptamine seizures, and inhibition of

tryptamine tremors); D₂-antagonism was tested in the blockade of apomorphine emesis in dogs, inhibition and blockade of apomorphine behavior in rats, behavioral disinhibition, inhibition and depression in amphetaminised rats tests; H₁- antagonism was tested in the protection from compound 48/80 lethality test in rats; α₁-adrenergic receptor-related antagonism was tested in the protection from norepinephrine-induced lethality test in rats; α₂-adrenergic receptor-related antagonism was tested in the reversal of clonidine's antidiarrheal effects in rats and reversal of xylazine loss of righting in rats. Behavioral test conducted included evaluation of induction of catalepsy, palpebral ptosis, muscular hypotonia and hypothermia in rats, decrease of palpebral opening in apomorphine-challenged rats and tryptamine-challenged rats. There were no toxicologically important differences in ED₅₀'s obtained for the test compounds in the various tests. Therefore, the results of these studies indicated comparable pharmacological profile of paliperidone enantiomers, racemate and risperidone.

5. Study title: In vivo pharmacological profile of 9-hydroxyrisperidone, the major metabolite of the novel antipsychotic risperidone: comparison with risperidone and haloperidol.

Paliperidone was compared with risperidone, ritanserin and haloperidol in several pharmacological tests in rats. These tests were related to 5-HT₂ antagonism, D₂ antagonism, body posture, palpebral opening, muscular tone, body temperature and motor activity, neurotransmitters or mediators (norepinephrine, histamine, acetylcholine and others). Pharmacological profiles of paliperidone and risperidone were similar in these studies. Both compounds reach the same receptors (5HT₂, D₂, H₁, α₁, α₂). Quantitatively, there are slight differences which may be related to the ratio of brain penetration. The tests are listed and their results (ED₅₀'s) are shown in the following sponsor's figure:

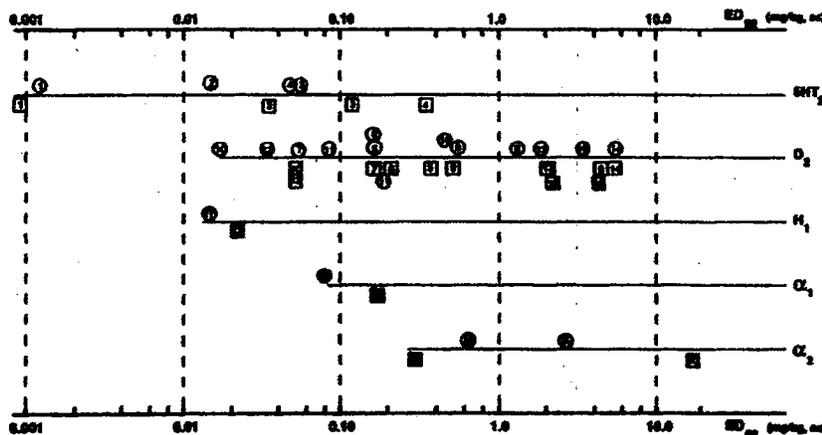


Fig. 2: ED₅₀'s (mg/kg, sc) obtained with risperidone (circles) and 9-OH-risperidone (squares) for the following peripheral effects (arched symbols) and central effects (open symbols): 1: reversal of tryptamine cyanosis; 2: inhibition of tryptamine bilateral seizures; 3: blockade of tryptamine bilateral seizures; 4: inhibition of tryptamine tremors; 5: inhibition of apomorphine agitation/stereotypy; 6: blockade of apomorphine agitation/stereotypy; 7: inhibition of amphetamine agitation; 8: pronounced inhibition of amphetamine agitation; 9: blockade of amphetamine agitation; 10: inhibition of amphetamine oxygen consumption; 11: blockade of amphetamine oxygen consumption; 12: behavioral disinhibition in amphetamine rats (lower threshold); 13: behavioral disinhibition in amphetamine rats (upper threshold); 14: behavioral depression in amphetamine rats; 15: slight catalepsy; 16: pronounced catalepsy; 17: protection from compound 48/80 induced lethality; 18: protection from norepinephrine-induced lethality; 19: reversal of the antidiarrheal effect of clonidine; 20: reversal of xylazine-induced loss of righting reflex

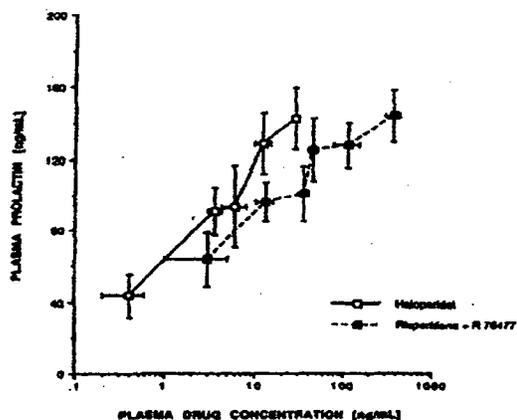
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2.6.2.3 Secondary pharmacodynamics

1. Study title: Effects of Risperidone on Prolactin Release in Rats In Vivo and in Cultured Rat Anterior Pituitary Cells In Vitro.

This study was designed to investigate mechanisms which might explain risperidone's *in vivo* prolactin stimulating effects. The intrinsic activity of risperidone and other D₂ antagonists (e.g. haloperidol) to directly stimulate dopamine-suppressed prolactin release was measured *in vitro* using cultured rat anterior pituitary cells. Each compound dose-dependently reversed the suppression of prolactin release due to dopamine. The compounds' potency to stimulate prolactin release in this model was consistent with their potencies to antagonize striatal D₂ receptor binding *in vitro*. The same compounds were tested *in vivo* to examine their effects on prolactin levels in rats after oral or intravenous administration. Both risperidone and haloperidol increased prolactin levels in rats in this model as shown in the following sponsor's figure:

FIGURE 8: RELATIONSHIP BETWEEN PLASMA PROLACTIN LEVELS AND PLASMA CONCENTRATIONS OF EITHER HALOPERIDOL OR TOTAL RISPERIDONE + R 76477 IN MALE RATS AT ONE HOUR AFTER ORAL ADMINISTRATION OF EITHER HALOPERIDOL OR RISPERIDONE. EACH POINT CORRESPONDS TO A SINGLE DOSE OF A COMPOUND. VALUES ARE MEAN ± SEM.



Since risperidone is extensively metabolized to paliperidone by *in vitro* incubation with liver supernatant or *in vivo*, paliperidone is involved in the mechanism of increase of prolactin levels *in vivo*.

2. Study title: Effects of a single oral administration of haloperidol, risperidone and of its 9-hydroxy-metabolite R 76 477 on serum prolactin levels in female rats.

The effects of haloperidol, risperidone and paliperidone on serum prolactin levels were examined after a single oral administration of vehicle, 0.01, 0.05, 0.25, 1 and 5 mg/kg of each test article to groups of 5 female rats sacrificed 0.5, 1, 2, 4 and 8 hours after drug administration. Risperidone and paliperidone increased serum prolactin levels in rats at a low doses (0.01, 0.05 mg/kg) but haloperidol did not. Administration of higher doses of all compounds tested increased serum prolactin levels. Prolactin levels were determined using radioimmunoassay. Maximum peak serum levels of prolactin (300 ng/ml) were

reached 1 and 2 hours after 1 and 5 mg/kg of haloperidol, respectively, 0.5 hours after 1 mg/kg of risperidone (700 ng/ml) and 0.5 hours after 5 mg/kg of paliperidone (425 ng/ml).

2.6.2.4 Safety pharmacology

Neurological effects:

According to the sponsor, safety pharmacology concerning the CNS was assessed within the toxicology testing program. There were no separate safety pharmacology studies submitted to this NDA.

Cardiovascular effects:

1. Study title: Effect of 9-OH risperidone (R076477) on the membrane K⁺ current I_{Kr} in HERG-transfected HEK293 cells. The effects of paliperidone on the membrane currents in a human cell line expressing HERG (gene encoding potassium channel) were investigated. A range of concentrations of paliperidone (from 3 X 10⁻⁸ to 10⁻⁵ M) was tested using whole-cell voltage clamp technique. At lower concentrations paliperidone had a small effect on the K⁺ current. At higher concentrations of 3 x 10⁻⁷ M or above, paliperidone dose-dependently attenuated the K⁺ current with the IC₅₀ of 1.2 ± 0.06 μM. This effect was reversible upon washout.

2. Study title: Comparative effects of risperidone, 9-OH risperidone and other antipsychotic compounds on human D_{2L} and human 5-HT_{2A} receptors versus the I_{Kr}-like membrane K⁺ current in HERG-transfected HEK293 cells. The potency (IC₅₀ in nM) of several antipsychotic drugs for attenuating the I_{Kr}-like current in HERG-transfected HEK293 cells (using voltage clamp measurements) was assessed and compared to that for inhibiting the binding of a specific label to human D_{2L} and 5-HT_{2A} receptors in isolated membranes (K_i in nM). All compounds studied attenuated the I_{Kr} current in HERG-transfected cells in a concentration-dependent fashion. However, the concentrations needed for such an effect differed substantially. All compounds tested attenuated the binding of a specific label to human D_{2L} and human 5-HT_{2A} receptors. According to the sponsor, these data corroborate the large safety index for risperidone and paliperidone for effects on I_{Kr} in HERG-transfected cells versus effects on target receptors. IC₅₀ values for the inhibition of the HERG-mediated membrane K⁺ current by antipsychotic compounds, the potency for reducing the binding of a specific label to these human receptors (K_i in nM) and ratios of potency for HERG versus human D_{2L} and HERG versus human 5-HT_{2A} receptors are shown in the sponsor's table below:

Compound	HERG*	human D _{2L} *	human 5-HT _{2A} *	Ratios**	
	IC ₅₀ (nM)	K _i (nM)	K _i (nM)	HERG/hD _{2L}	HERG/h5-HT _{2A}
Sertindole	20	11.5	0.11	x 1.74	x 187
Haloperidol	66	2.0	302	x 32	x 0.22
Ziprasidone	260	6.8	2.1	x 38	x 124
Risperidone	650	1.4	0.16	x 464	x 4062
9-OH risperidone	1200	4.3	0.79	x 281	x 1518
Clozapine	5600	178	6.3	x 31	x 888
Olanzapine	17000	63	2.3	x 269	x 7252

*: data from Table 6-1 and Table 6-2, recalculated to the same unit (nM)

** : ratios for relative potencies

3. Study title: Effects of R064766 and R076477 on ion currents (potassium, sodium, calcium) in isolated guinea-pig myocytes. This study was designed to investigate effects of risperidone and paliperidone on the two components (I_{Kr} and I_{Ks}) of the delayed rectifier potassium current (I_K), on the inward rectifier potassium current (I_{K1}), on the TTX-sensitive fast sodium current (I_{Na}) and on the L-type calcium current (I_{Ca, L}) in isolated ventricular cardiomyocytes of the guinea pig using the whole-cell patch clamp technique. Results indicated that risperidone and paliperidone inhibit the rapid component of the delayed rectifier potassium tail current I_{Kr} by 75% and 85%, respectively (solvent only by 9%). Test compounds did not inhibit I_{Ks} and I_{K1}. However, I_{Na} and I_{Ca, L} were moderately inhibited by both test articles (by 15-16% and 14%, respectively). Although this study demonstrated inhibitory effects of test compounds on potassium current I_{Kr}, it has to be taken into consideration that a very high concentration (10 μM) of both of them was applied. This concentration exceeds the maximum risperidone and paliperidone levels found in the plasma after therapeutic doses of risperidone. These results are shown in the following sponsor's table:

Species	Tests/assays, observations/effects, route of administration/time interval, Conclusion	Active dose or concentration
Guinea-pig	<u>In vitro concentration-dependent effects of risperidone and 9-OH risperidone on the delayed rectifier potassium current in cardiac myocytes: measurement of membrane currents by means of the whole-cell voltage-clamp technique</u>	
	<u>Measurements of rapid component of the delayed rectifier potassium current</u> (tail current at -20 mV)	<u>Effects compared to solvent group</u> (values are calculated as a relative change versus their own baseline; mean ± SEM)
	risperidone; concentration tested: 10 μM	decrease of 75 ± 5%, n=6 (solvent: -9 ± 6%, n=5)
	9-OH risperidone; concentration tested: 10 μM	decrease of 85 ± 3%, n=6 (solvent: -9 ± 6%, n=5)
	<u>Reference compounds:</u> <u>doxetilide</u> concentration tested: 0.03 μM	decrease of 78 ± 10%, n=6 (solvent: -12 ± 25%, n=7)
	<u>terfenadine:</u> concentrations tested: 0.4 μM	decrease of 79 ± 5%, n=14 (solvent: -18 ± 7%, n=6)
	<u>Measurements of slow component of the delayed rectifier potassium current</u> (tail current at +40 mV)	<u>Effects compared to solvent group</u> (values are calculated as a relative change versus their own baseline; mean ± SEM)
	risperidone; concentration tested: 10 μM	decrease of 26 ± 6%, n=6 (solvent: -16 ± 3%, n=5)
	9-OH risperidone; concentration tested: 10 μM	decrease of 25 ± 4%, n=6 (solvent: -16 ± 3%, n=5)

Continued:

Guinea-pig <i>In vitro</i> concentration-dependent effects of risperidone and 9-OH risperidone on fast sodium current and L-type calcium current in cardiac myocytes: measurement of membrane currents by means of the whole-cell voltage-clamp technique	
<u>Measurements of fast sodium current</u> (maximum peak current at -25 mV)	<u>Effects compared to solvent group</u> (values are calculated as a relative change versus their own baseline; mean \pm SEM)
risperidone; concentration tested: 10 μ M	decrease of 16 \pm 3%, n=5 (solvent: +1 \pm 1%, n=5)
9-OH risperidone; concentration tested: 10 μ M	decrease of 15 \pm 3%, n=5 (solvent: +1 \pm 1%, n=5)
<u>Reference compound lidocaine:</u> concentration tested: 30 μ M (maximum peak current at -30 mV)	decrease of 51 \pm 6%, n=6, at 30 μ M (solvent: -5 \pm 1%, n=6)
<u>Measurements of L-type calcium current</u> (maximum peak current at +10 mV)	<u>Effects compared to solvent group</u> (values are calculated as a relative change versus their own baseline; mean \pm SEM)
risperidone; concentration tested: 10 μ M	decrease of 14 \pm 1%, n=6 (solvent: -6 \pm 1%, n=9)
9-OH risperidone; concentration tested: 10 μ M	decrease of 14 \pm 1%, n=5 (solvent: -6 \pm 1%, n=9)
<u>Reference compound nifedipine;</u> concentrations tested: 0.001, 0.01, 0.03, 0.1, 0.3, 1, and 10 μ M	IC ₅₀ : 109 nM; Hill slope: 0.9 (estimated by fitting the concentration-response curve)
Conclusion: At a concentration of 10 μ M, risperidone and 9-OH risperidone decrease the rapid component of the delayed rectifier potassium current by 75% and 85%, respectively. The compounds do not have an effect on the slow component of the delayed rectifier potassium current and the inward rectifier potassium current. At 10 μ M, the compounds moderately reduce the fast sodium current by 16 and 15%, respectively. At the same concentration, both compounds attenuate the L-type calcium current by the equal amount of 14%.	
Study conducted by the applicant: yes <x> no <>	
Study in compliance with GLP: yes <> no <x> not required <>	

4. Study title: Effects of paliperidone (JNJ-16232411-AAA) on the isolated, spontaneously beating right atrium of the guinea-pig [Antipsychotic]. This test was designed to detect compounds that affect Na⁺, K⁺ or Ca⁺ currents in cardiac cells and agents that influence sinus node activity or compounds that stimulate cardiac receptors (e.g. adrenergic and serotonergic receptors). A broad range of paliperidone concentrations was tested. Results indicated that the rate of contraction at high concentrations of paliperidone (10⁻⁶ M to 10⁻⁵ M) was slightly reduced when compared to a solvent control. However, these concentrations are several times in excess of expected clinical exposure. The force of contraction as well as the frequency of electrical stimulation not followed by contraction was not significantly affected by paliperidone.

5. Study title: Electrophysiological effects of risperidone and 9-OH risperidone in canine Purkinje fibers and guinea pig papillary muscles in vitro. Microelectrode techniques were used to examine effects of a broad range of concentrations of risperidone and paliperidone (from 1 x 10⁻⁸ to 1 x 10⁻⁵ M) on the electrophysiological characteristics of canine Purkinje fibers and guinea pig papillary muscles. Tests were performed in conditions of normokalaemia and normal rhythm as well as in conditions of hypokalaemia and bradycardia to identify even minor electrophysiological defects. Results indicated that both test articles have no effects on the resting membrane potential,

amplitude of the action potential, maximum rate of depolarization during the upstroke and contractile force of papillary muscles. At low concentrations matching the plasma levels reached after therapeutic doses in man neither test articles have relevant effects on the duration of the action potential, effective refractory period and recovery time. At higher concentrations potential trends for prolongation of the action potential duration were observed. However, these effects were modest in comparison with those of other neuroleptic drugs. None of the preparations used in this study developed early depolarizations or triggered activity after exposure to test articles. There were no other significant findings.

6. Study title: Electrophysiological evaluation of R076477 in isolated rabbit Purkinje cells. Electrophysiological effects of paliperidone in isolated rabbit Purkinje fibers were investigated at a range of concentrations (from 1×10^{-7} to 3×10^{-6} M) using microelectrode techniques. Tests were performed in conditions of normal rhythm as well as in conditions of bradycardia to identify even minor electrophysiological defects. In both conditions, paliperidone at low concentrations did not significantly changed any electrophysiological parameters including the amplitude of the action potential, duration of action potential duration at 90% repolarization, resting membrane potential, effective refractory period, recovery time, and maximum upstroke velocity. Paliperidone at low concentrations did not induce also any after depolarizations. According to the sponsor, these low concentrations (1×10^{-7} to 3×10^{-7} M) cover plasma levels of paliperidone reached after its oral administration to man at 1 mg of the compound. However, high concentrations of paliperidone (1×10^{-6} to 3×10^{-6} M) prolonged the duration of the action potential at 90% repolarization. The effective refractory period and recovery time were significantly increased during a normal rhythm at 20 min after the infusion and during extreme bradycardia at 25 min after the infusion in isolated rabbit Purkinje cells in this study. These concentrations are in excess of the plasma levels of paliperidone reached after its oral administration in man.

7. Study title: Electrophysiological effects of paliperidone (JNJ-16232411-AAA-10117548; R076477) in isolated Langendorff-perfused, female rabbit hearts. Electrophysiological effects of paliperidone in the isolated Langendorff-perfused female rabbit hearts were investigated at a range of concentrations (from 1×10^{-7} M to 1×10^{-5} M) using microelectrode techniques. The results and conclusions are shown in the following modified sponsor's table:

Measurements	Effect compared to solvent
APD ₆₀ :	No significant effect with the compound at 1×10^{-7} M and 3×10^{-7} M. Significantly prolonged by the compound at 1×10^{-6} M and 3×10^{-6} M and 1×10^{-5} M (+18%, +45% and +51% from baseline versus +1%, -1% and 0% from baseline with solvent, respectively; $p < 0.05$).
Triangulation of the action potential:	No significant effect with the compound at 1×10^{-7} M and 3×10^{-7} M. Significantly increased by the compound at 1×10^{-6} M and 3×10^{-6} M and 1×10^{-5} M (+22%, +72% and +88% from baseline versus -21%, -26% and -20% from baseline with solvent, respectively; $p < 0.05$).
Instability of the action potential:	No significant or physiologically relevant effect with the compound 1×10^{-7} M, 3×10^{-7} M and 1×10^{-6} M. Significant increase by the compound at 3×10^{-6} M and

	<p>1×10^{-5} M (+24 ms and +6 ms from baseline versus +2 ms and +2 ms from baseline with solvent; $p < 0.05$).</p>
Reverse-use dependency of the action potential:	No significant effect with the compound at increasing concentrations of 1×10^{-7} M, 3×10^{-7} M, 1×10^{-6} M, 3×10^{-6} M and 1×10^{-5} M.
Index of proarrhythmia:	No significant effect with the compound at increasing concentrations of 1×10^{-7} M, 3×10^{-7} M, 1×10^{-6} M, 3×10^{-6} M and 1×10^{-5} M.
Coronary flow	No significant effect with the compound at increasing concentrations of 1×10^{-7} M, 3×10^{-7} M, 1×10^{-6} M, 3×10^{-6} M and 1×10^{-5} M.
IVC:	No significant effect with the compound at increasing concentrations of 1×10^{-7} M, 3×10^{-7} M, 1×10^{-6} M, 3×10^{-6} M and 1×10^{-5} M. Tended to increase with the compound at 3×10^{-6} M and 1×10^{-5} M (+11% and +25% from baseline versus -1% and 0% from baseline with solvent; $p > 0.05$).
Early afterdepolarizations (EADs):	One incidence out of the 5 hearts with the compound at 3×10^{-6} M and one at 1×10^{-5} M (versus 0 out of the 6 hearts with solvent).
Ventricular tachycardia (VT):	No incidence with the compound at the concentrations tested (1×10^{-7} M to 1×10^{-5} M).
Ventricular fibrillation (VF):	No incidence with the compound at the concentrations tested (1×10^{-7} M to 1×10^{-5} M).
Torsades de pointes (TdPs):	One incidence out of the 5 hearts with the compound at 3×10^{-6} M (versus 0 out of the 6 hearts with solvent).
Conclusion:	<p>The present study in isolated Langendorff-perfused, female rabbit hearts shows that paliperidone at increasing concentrations of 1×10^{-7} M to 1×10^{-5} M had no significant effects on the reverse-use dependency of the action potential, the index of proarrhythmia, and coronary flow and did not elicit VT or VF. Furthermore, paliperidone at 1×10^{-7} M and 3×10^{-7} M did not significantly change the duration and triangulation of the action potential. Paliperidone had no notable or significant effects on instability of AP and IVC at concentrations up to 1×10^{-6} M. However, paliperidone increased APD₆₀ and triangulation at concentrations from 1×10^{-6} M to 1×10^{-5} M, instability and IVC at concentrations of 3×10^{-6} M and 1×10^{-5} M, and elicited EADS in 1 out of the 5 hearts at 3×10^{-6} M and 1×10^{-5} M, and TdPs in 1 out of the 5 hearts at 3×10^{-6} M.</p> <p>The concentration at which paliperidone was without effects (3×10^{-7} M), represents a margin of 38 relative to the estimated free plasma exposure at an expected therapeutic dose of 9 mg.</p> <p>In conclusion, paliperidone at concentrations exceeding the estimated therapeutic level, did not have significant effects on coronary flow and electrophysiological parameters, and did not elicit severe arrhythmia including EADs, VT, VF or TdPs in isolated Langendorff-perfused, female rabbit hearts.</p>

8. Study title: Effects of paliperidone on cardio-hemodynamic and electrophysiological parameters in anesthetized guinea-pigs: intravenous infusion of 0.16 mg/kg/min during 30 min (total dose = 4.8 mg/kg). Electrophysiological and cardio-hemodynamic effects of paliperidone as well as compound concentration in plasma were investigated in the guinea pig at the dose indicated in the study title. Paliperidone had no effect on the

duration of the QRS interval but decreased mean arterial blood pressure and the duration of the PQ, QT and QTcB interval. An increase in heart rate was observed in 3/7 pigs. No changes in ECG morphology were noted (apart from changes in ST segment in one animal). The results are shown in the following modified sponsor's table:

Measurements:	Effects of increasing intravenous doses of paliperidone compared to solvent									
<u>Cardio-hemodynamic parameters:</u> Heart rate:	Although no statistically significant effect was noted on heart rate, an increase in heart rate was observed in three out of seven guinea-pigs.									
Mean arterial blood pressure:	Decrease starting at 5 min after the onset of the infusion (median peak effect: -31% versus baseline at 5 min after the onset of the infusion; solvent: +3%).									
<u>ECG parameters</u> PQ interval:	Decrease starting at 5 min after the onset of the infusion (median peak effect: -14% versus baseline at 10 and 15 min after the onset of the infusion; solvent: 0% and +3%, respectively).									
QRS interval:	No statistically significant effect.									
QT interval:	Decrease starting at 10 min after the onset of the infusion (median peak effect: -16% versus baseline at 10 min after the onset of the infusion; solvent: +5%).									
QTcB interval:	Decrease starting at 10 min after the onset of the infusion (median peak effect: -16% versus baseline at 20 min after the onset of the infusion; solvent: +1%).									
<u>ECG morphology:</u>	<table border="1"> <thead> <tr> <th></th> <th>Paliperidone</th> <th>Solvent</th> </tr> </thead> <tbody> <tr> <td>No changes</td> <td>6/7</td> <td>7/7</td> </tr> <tr> <td>ST-elevation</td> <td>1/7</td> <td>0/7</td> </tr> </tbody> </table>		Paliperidone	Solvent	No changes	6/7	7/7	ST-elevation	1/7	0/7
	Paliperidone	Solvent								
No changes	6/7	7/7								
ST-elevation	1/7	0/7								
<u>Plasma levels:</u>	Plasma levels of paliperidone at 30 min after the end of the infusion at 4.8 mg/kg i.v. over 30 min (60 min after the onset of the infusion) amounted to a median value of 928 ng/ml.									

9. Study title: Effects of paliperidone (JNJ-16232411-AAA, R076477) on cardio-haemodynamic and electrophysiological parameters in anaesthetized guinea-pigs: doses 0.08, 0.16, 0.32, 0.64, 1.25 and 5 mg/kg intravenously. Electrophysiological and cardio-hemodynamic effects of paliperidone as well as compound concentration in plasma were investigated in the guinea pig at the doses indicated in the study title. Paliperidone did not change the duration of QRS except decreasing this parameter at doses of 0.32 and 0.64 mg/kg. PQ and heart rate remained unchanged at all doses except at 0.16 and 0.32 mg/kg at which paliperidone increased heart rate and decreased the duration of the PQ interval. Paliperidone decreased mean arterial blood pressure starting at 0.08 mg/kg and the duration of QT starting at a dose of 0.16 mg/kg. QTcB was slightly shortened starting at a dose of 0.16 mg/kg. No changes in ECG morphology were seen in 5/7 animals administered paliperidone. In one animal ventricular premature beats and in another an

enlargement of the T wave was noted. These results are shown in the following modified sponsor's table:

Measurements:	Effects of increasing intravenous doses of paliperidone compared to solvent												
<u>Cardio-haemodynamic parameters:</u>													
Heart rate:	No statistically significant effect at doses of 0.08, 0.64, 1.25 and 5 mg/kg i.v. Increase after administration of 0.16 and 0.32 mg/kg i.v. (compound +14% and +7% versus baseline at 0.16 and 0.32 mg/kg i.v., respectively; solvent -9% and -5%, p < 0.05).												
Mean arterial blood pressure:	Decrease starting at 0.08 mg/kg i.v. (compound -31%, -23%, -29%, -26%, -25% and -32% versus baseline at 0.08, 0.16, 0.32, 0.64, 1.25 and 5 mg/kg i.v., respectively; solvent -2%, -9%, 0%, +2%, -5% and -5%; p < 0.05 at 0.08, 1.25 and 5 mg/kg i.v.).												
<u>ECG parameters:</u>													
PQ interval:	No statistically significant effect at doses of 0.08, 0.64, 1.25 and 5 mg/kg i.v. Decrease after administration of 0.16 and 0.32 mg/kg i.v. (compound -7% versus baseline at 0.16 and 0.32 mg/kg i.v., respectively; solvent +3% and 0%, p < 0.05)												
QRS interval:	No relevant effect at doses of 0.08, 0.16, 1.25 and 5 mg/kg i.v. At doses of 0.32 and 0.64 mg/kg i.v., the duration of the QRS complex tends to decrease (compound: -6% versus baseline at both doses; solvent: 0% at both doses; p < 0.05 at 0.64 mg/kg i.v.).												
QT interval:	No statistically significant effect at a dose of 0.08 mg/kg i.v. Decrease at doses of 0.16 mg/kg to 5 mg/kg i.v. (compound -16%, -9%, -13%, -13% and -4% versus baseline at 0.16, 0.32, 0.64, 1.25 and 5 mg/kg i.v., respectively; solvent +6%, +7%, +8%, +7% and +7%; p < 0.05 at 0.16 to 5 mg/kg).												
QTcB interval:	Decrease starting at dose of 0.16 mg/kg i.v. (compound -11%, -7%, -13%, -13% and -7% versus baseline at 0.16, 0.32, 0.64, 1.25 and 5 mg/kg i.v., respectively; solvent +2%, +3%, +4%, +2% and +1%; p < 0.05 at 0.64 to 5 mg/kg i.v.).												
<u>ECG morphology:</u>	<table border="1"> <thead> <tr> <th></th> <th>Paliperidone</th> <th>solvent</th> </tr> </thead> <tbody> <tr> <td>No changes</td> <td>5/7</td> <td>7/7</td> </tr> <tr> <td>VPBs</td> <td>1/7*</td> <td>0/7</td> </tr> <tr> <td>ST-elevation</td> <td>1/7**</td> <td>0/7</td> </tr> </tbody> </table> <p>*starting at dose of 0.64 mg/kg i.v. **after administration of 5 mg/kg i.v.; an enlargement of the T wave was also observed in this animal starting at 0.32 mg/kg i.v.</p>		Paliperidone	solvent	No changes	5/7	7/7	VPBs	1/7*	0/7	ST-elevation	1/7**	0/7
	Paliperidone	solvent											
No changes	5/7	7/7											
VPBs	1/7*	0/7											
ST-elevation	1/7**	0/7											
<u>Heart, lung and plasma levels:</u>													
Plasma level:	Median plasma level of paliperidone amounted to 1502 ng/ml at 5 min after the intravenous injection of the highest dose.												
Heart and lung tissue level:	The median concentration of paliperidone in lung tissue was 129500 ng/g and in heart tissue 29650 ng/g.												

10. Study title: Effects of paliperidone on cardio-hemodynamic and electrophysiological parameters in anesthetized guinea-pigs: intravenous infusion of 0.31 mg/kg/min during 60 min (total dose = 18.6 mg/kg). Electrophysiological and cardio-hemodynamic effects

of paliperidone as well as compound concentration in plasma were investigated in the guinea pig at the dose indicated in the study title. Paliperidone had no relevant effects on the duration of the QRS complex, induced no changes in ECG morphology, increased transiently heart rate, decreased mean arterial blood pressure and the duration of the PQ interval, and after transient increase, decreased the duration of the QT and QTcB interval. These results are shown in the following modified sponsor's table:

Measurements	Effects of paliperidone compared to solvent			
<u>Cardio-hemodynamic parameters:</u>				
Heart rate:	An increase from 10 to 30 min after the onset of the infusion (median peak effect: +22% versus baseline at 10 min after the onset of the infusion; solvent: -3%).			
Mean arterial blood pressure:	A decrease starting at 2 min after the onset of the infusion (median peak effect: -24% versus baseline at the end of the infusion; solvent: 0%).			
<u>ECG parameters:</u>				
PQ interval:	A decrease starting at 5 min after the onset of the infusion (median peak effect: -12% versus baseline at 20 min after the onset of the infusion; solvent: -2%).			
QRS interval:	No relevant and consistent effect.			
QT interval:	After an increase during the first 5 min of the infusion, a decrease (median peak effect: -23% versus baseline at 20 min after the onset of the infusion; solvent: +5%).			
QTcB interval:	After an increase during the first 5 min of the infusion, a decrease (median peak effect: -16% versus baseline at 20 min after the onset of the infusion; solvent: +3%).			
<u>ECG morphology:</u>				
Plasma levels:	<table border="0"> <tr> <td>No changes</td> <td style="text-align: center;"><u>Paliperidone</u> 7/7</td> <td style="text-align: center;"><u>Solvent</u> 7/7</td> </tr> </table> <p>Plasma levels of paliperidone at the end of the infusion (total dose infused: 18.6 mg/kg i.v.) amounted to a median value of 3246 ng/ml.</p>	No changes	<u>Paliperidone</u> 7/7	<u>Solvent</u> 7/7
No changes	<u>Paliperidone</u> 7/7	<u>Solvent</u> 7/7		

11. Study title: Effects of 9-OH risperidone on cardiac electrophysiology in anaesthetized rabbits, challenged with methoxamine (α_1 -adrenoceptor agonist).

The effects of paliperidone on the cardiac electrophysiology and on arrhythmography in anesthetized rabbits after infusion with methoxamine were investigated. Paliperidone was tested at three different intravenous doses (0.04, 0.08, and 0.16 mg/kg/min i.v. for 60 min; total doses of 2.4, 4.8 and 9.6 mg/kg i.v.). Findings at all dose levels were similar. Paliperidone had no significant effect on heart rate, PQ interval, QRS duration and QT dispersion. However, paliperidone increased QT-, QTcB-, JT- and JTc-intervals from 4 minutes onwards. There were no paliperidone-induced ventricular premature beats, atrioventricular blocks, ventricular tachycardia, ventricular fibrillation or cardiac arrest.

These results are shown in the following modified sponsor's table:

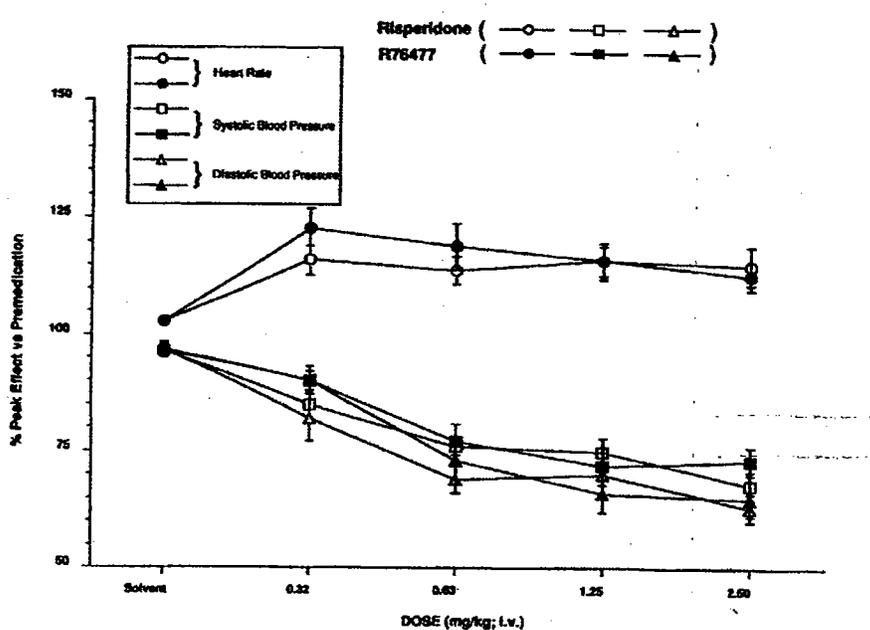
Measurements	Effects of paliperidone compared to solvent
Heart Rate (HR):	No significant effects during 60 min infusion of 9-OH risperidone at 0.04, 0.08 or 0.16 mg/kg/min i.v. (total dose of 2.4, 4.8 or 9.6 mg/kg i.v.) when compared to solvent.
Mean arterial blood pressure (BPm):	Significantly lower after 4 min infusion of the compound at 0.04 mg/kg/min i.v. (22%, -27%, -24%, -23%, -22% and -24% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion versus -3%, +3%, +5%, +17%, +24% and +26% of the baseline value with solvent). Significantly lower after 4 min infusion of the compound at 0.08 mg/kg min i.v. (-35%, -37%, -36%, -35%, -34% and -34% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion versus -3%, +3%, +5%, +17%, +24% and +26% of the baseline value with solvent). Significantly lower after the compound infusion at 0.16 mg/kg/min i.v. (-38%, -41%, -40%, -36%, -36% and -38% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion versus -3%, +3%, +5%, +17%, +24% and +25% of the baseline value with solvent).
PQ-interval:	No significant effects during 60 min infusion of 9-OH risperidone at 0.04, 0.08 or 0.16 mg/kg/min i.v. (total dose of 2.4, 4.8 or 9.6 mg/kg i.v.) when compared to solvent.
QRS-duration:	No significant effects during 60 min infusion of 9-OH risperidone at 0.04, 0.08 or 0.16 mg/kg/min i.v. (total dose of 2.4, 4.8 or 9.6 mg/kg i.v.) when compared to solvent.
QT-interval:	Significantly higher from 4 min onwards during infusion of the compound at 0.04 mg/kg/min (or from 0.16 mg/kg i.v. onwards): +6%, +15%, +21%, +35%, +47% and +58% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +2%, +2%, +3%, +5%, +10% and +17% of baseline with solvent). Significantly higher at 4 min during infusion of the compound from 0.16 mg/kg/min onwards (or from 0.64 mg/kg i.v. onwards): +14%, +32%, +41%, +54%, +63% and +70% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +2%, +2%, +3%, +5%, +10% and +17% of baseline with solvent).
QTcB-interval:	Significantly higher from 4 min during infusion of the compound at 0.04 mg/kg/min onwards (or from 16 mg/kg i.v. onwards): +5%, +13%, +19%, +28%, +36% and +42% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus 0%, +1%, +1%, +1%, +3% and +2% of the baseline with solvent). Significantly higher from 4 min during infusion of the compound at 0.08 mg/kg/min onwards (or from 0.32 mg/kg i.v. onwards): +9%, +21%, +23%, +34%, +43% and +52% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus 0%, +1%, +1%, +1%, +3% and +2% of the baseline with solvent).
QTcB-interval:	Significantly higher from 4 min during infusion of the compound at 0.16 mg/kg/min onwards (or from 0.64 mg/kg i.v. onwards): +14%, +28%, +34%, +42%, +46% and +50% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus 0%, +1%, +1%, +1%, +3% and +2% of the baseline with solvent).
QT dispersion:	No significant effects during 60 min infusion of 9-OH risperidone at 0.04, 0.08 or 0.16 mg/kg/min i.v. (total dose of 2.4, 4.8 or 9.6 mg/kg i.v.) when compared to solvent.

JT-interval:	Significantly higher from 4 min during infusion of the compound at 0.04 mg/kg/min onwards (or from 0.16 mg/kg i.v. onwards): +8%, +18%, +27%, +44%, +57% and +70% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +2%, +3%, +4%, +7%, +11% and +19% of the baseline with solvent).
JT-interval:	Significantly higher from 4 min during infusion of the compound at 0.08 mg/kg/min onwards (or from 0.32 mg/kg i.v. onwards): +8%, +25%, +31%, +46%, +66% and +82% of the baseline values at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +2%, +3%, +4%, +7%, +11% and +19% of the baseline with solvent). Significantly higher from 4 min during infusion of the compound at 0.16 mg/kg/min onwards (or from 0.64 mg/kg i.v. onwards): +16%, +38%, +49%, +65%, +75% and +84% of the baseline values at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +2%, +3%, +4%, +7%, +11% and +19% of the baseline with solvent).
JTcB-interval:	Significantly higher from 4 min during infusion of the compound at 0.04 mg/kg/min onwards (or from 0.16 mg/kg i.v. onwards): +7%, +17%, +23%, +35%, +46% and +53% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +1%, +1%, +1%, +2%, +2% and +3% of the baseline with solvent).
JTcB-interval:	Significantly higher from 4 min during infusion of the compound at 0.08 mg/kg/min onwards (or from 0.32 mg/kg i.v. onwards): +11%, +26%, +29%, +41%, +54% and +63% of the baseline values at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +1%, +1%, +1%, +2%, +2% and +3% of the baseline with solvent). Significantly higher from 4 min during infusion of the compound at 0.16 mg/kg/min onwards (or from 0.64 mg/kg i.v. onwards): +17%, +35%, +43%, +52%, +57% and +62% of the baseline value at 4 min, 8 min, 15 min, 30 min, 45 min and 60 min during infusion (versus +1%, +1%, +1%, +2%, +2% and +3% of the baseline with solvent).
Cardiac arrhythmias: Intraventricular conduction effects:	No incidence after 9-OH risperidone at an infusion rate of 0.04 mg/kg/min i.v. for 60 min (a total dose of 2.4 mg/kg i.v.). No incidence after the compound at an infusion rate of 0.08 mg/kg/min (at a dose of 4.8 mg/kg i.v.). One out of 8 incidences after the compound at an infusion rate of 0.16 mg/kg/min i.v. (at 4.64 mg/kg i.v.) (versus 0% with solvent; p>0.05).
Second degree or complete AVB:	No incidence
Ventricular premature beats	No incidence
Ventricular tachycardia:	No incidence
Ventricular fibrillation:	No incidence
Cardiac arrest:	No incidence

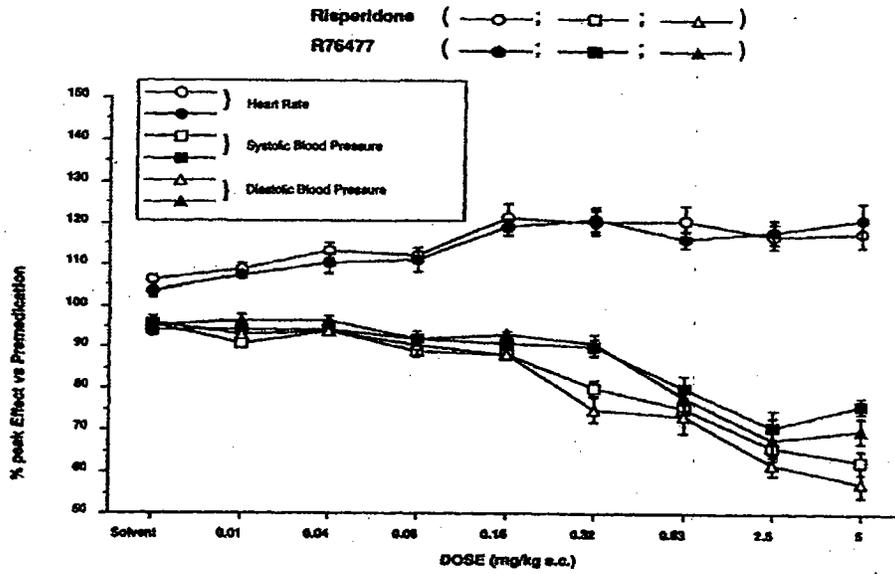
12. Study title: Cardiovascular effects of high intravenous doses of 9-OH risperidone and of risperidone in awake rats and anaesthetized dogs. In awake rats, high intravenous doses (0.32 to 2.5 mg/kg i.v.) of risperidone and paliperidone have similar results when compared to other studies, including transient increase in heart rate and reductions in systolic and diastolic blood pressures. In anaesthetized dogs, the injection of paliperidone

and risperidone (0.005 to 1.25 mg/kg i.v.) resulted also in increase in heart rate and slight reduction of diastolic and diastolic blood pressure. These results in both species are consistent with documented antagonism of both compounds at vascular alpha-adrenoreceptors causing vasodilatation and a reduction in systemic vascular resistance.

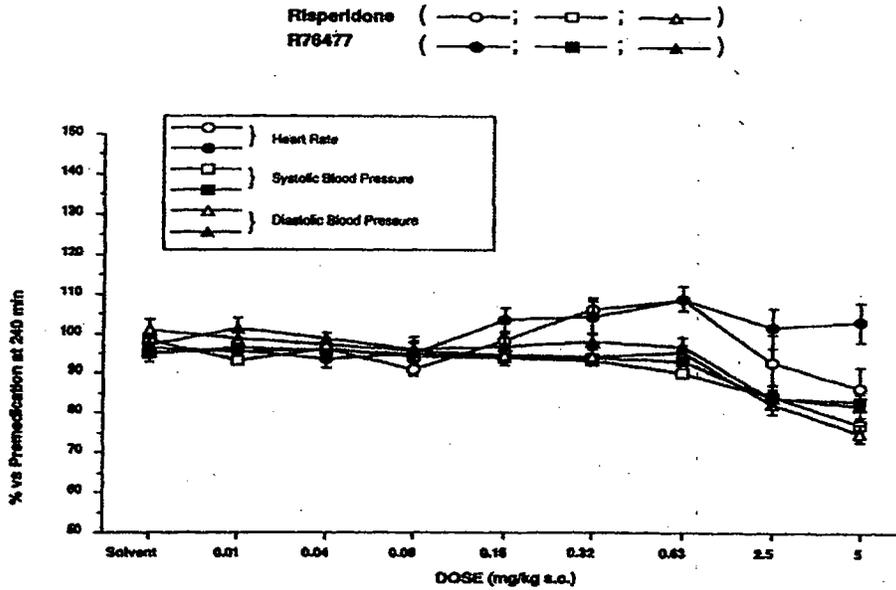
Peak effects of intravenously administered risperidone and paliperidone on heart rate, systolic and diastolic blood pressure in awake rats is shown in the following sponsor's figure:



13. Study title: Cardiovascular effects of 9-OH risperidone and risperidone in awake rats. Paliperidone and risperidone were administered subcutaneously (0.01 to 5 mg/kg s.c.) and the effects on cardiovascular parameters (heart rate, systolic and diastolic blood pressure) were evaluated in awake rats. Peak changes in heart rate after administration of risperidone and paliperidone varied between 12% to 21% and 16% to 21% increase, respectively, relative to premedication values after 0.016 to 5 mg/kg s.c. compared to a 4.9% maximal increase after solvent. Peak changes in systolic blood pressure after administration of risperidone and paliperidone varied between 11% to 37% and 9% to 29% decrease, respectively, relative to premedication values after 0.08 to 5 mg/kg s.c. compared to a 5.2% maximal decrease after solvent. Peak changes in diastolic blood pressure after administration of risperidone and paliperidone varied between 10% to 42% and 22% to 32% decrease, respectively, relative to premedication values after 0.08 to 5 mg/kg s.c. compared to a 5.4% maximal decrease after solvent. These results are shown in the following sponsor's figure:



Risperidone and paliperidone had no protracted effect in heart rate and slight effects on blood pressure 240 min after medication. These results are shown in the following sponsor's figure:



14. Study title: Effects of 9-OH risperidone, on cardiovascular and behavioral parameters in instrumented, awake dogs: dose 0.08 and 0.31 mg/kg orally. Male beagle dogs were surgically instrumented for subsequent recording of cardiovascular parameters in order to correlate changes in heart rate and QTc intervals to

the plasma levels of paliperidone reached after a single dose. Heart rate increased after 0.08 and 0.31 mg/kg (by up to 32% and 54%, respectively). At a dose of 0.08 mg/kg, there were no changes in the duration of the QTc interval. At a dose of 0.31 mg/kg, there were no changes in the duration of the QTc- Fridericia and QTc-Van de Water intervals. A slight increase in the duration of the QTc-Bazett-interval (peak effect +13%) was observed. These results are shown in the following sponsor's table:

Table 3: Comparative effects of 9-OH risperidone, 0.08 and 0.31 mg/kg given orally, on heart rate, QTc Bazett, QTc Fridericia and QTc Van de Water in awake, trained dogs.

Solvent (n=3)	Change (median % versus premedication ^a)				ng/ml ^a
	Heart rate	QTcB	QTcF	QTcV	
30 min	-2	-5	-5	-4	/
60 min	-2	+2	+2	+2	/
240 min	+14	+7	+5	+5	/
9-OH Risperidone					
0.08 mg/kg (n=4)					
30 min	+32	-5	-6	-6	64.2
60 min	+22	+3	-1	0	90.4
240 min	+27	-3	-6	-5	55.3
9-OH Risperidone					
0.31 mg/kg (n=4)					
30 min	+54	+7	0	0	311
60 min	+44	+13	+5	+5	281
240 min	+53	+9	0	+1	192.5

Premedication values are:

Heart rate: solvent = 95 beats/min; 9-OH risperidone 0.08 mg/kg = 65 beats/min; 9-OH risperidone 0.31 mg/kg = 86.5 beats/min.

QTc Bazett (B): solvent = 187 ms; 9-OH risperidone 0.08 mg/kg = 213 ms; 9-OH risperidone 0.31 mg/kg = 221.5 ms.

QTc Fridericia (F): solvent = 185 ms; 9-OH risperidone 0.08 mg/kg = 201.5 ms; 9-OH risperidone 0.31 mg/kg = 215 ms.

QTc Van de Water (V): solvent = 187 ms; 9-OH risperidone 0.08 mg/kg = 205 ms; 9-OH risperidone 0.31 mg/kg = 216.5 ms.

- Plasma levels of 9-OH risperidone in ng/ml, median values.

15. Study title: Effects of paliperidone on cardiac electrophysiological, cardio-hemodynamic and behavioral parameters in instrumented, awake dogs: doses: intravenous infusion of 0.08 mg/kg over a period of 10 min, 0.08 mg/kg over a period of 60 min, 0.31 mg/kg over a period of 10 min and 0.31 mg/kg over a period of 60 min.

Chronically instrumented and trained dogs were divided into 5 groups (N=3 for each group) in these pilot investigations. Dogs were dosed as indicated in the title of this study. Paliperidone increased heart rate at a dose of 0.08 mg/kg over 60 min and at 0.31 mg/kg over both 10 and 60 min and decreased systolic and diastolic blood pressure after both doses and both dose regimens (except for diastolic blood pressure at 0.08 mg/kg

over 60 min). Paliperidone tended to decrease the duration of the PQ interval at 0.31 mg/kg infused over 60 min and at a dose of 0.08 mg/kg decreased the duration of the PQ interval over 10 and 60 min. There were no effects on the QRS duration, QT dispersion and ECG morphology. A decrease in the duration of the QT was observed at a dose of 0.31 mg/kg given over 10 and 60 min. Paliperidone had no effect on the duration of the QTcB, QTcF and QTcVDW interval at a dose of 0.08 mg/kg over 60 min and minimally increased the QTc intervals when administered over 10 min (up to 17% above baseline level; solvent: 1%). At the dose of 0.31 mg/kg i.v. over both 10 and 60 min an increase in the QTcB and QTcF was noted (up to 27% above baseline level; solvent: 5%), while there was no clear effect on the QTcVDW.

16. Study title: Preclinical Cardiac Electrophysiology of Risperidone and its Active Metabolite 8-OH Risperidone. Status on June 21st, 2002.

In this report, the sponsor provided an evaluation of preclinical data available as of June 21, 2002 for the assessment of cardiovascular effects of paliperidone and risperidone. Since then, several additional studies have been completed and submitted to this NDA.

Pulmonary effects:

Study title: Effects of R076477 on Respiration Rate and Tidal Volume in Rats (Study No. TOX6952). This study was conducted to assess the effects of paliperidone on respiration rate and tidal volume in conscious male Sprague-Dawley rats (8/group) dosed p.o. by gavage at 2.5, 10 and 20 mg/kg. There were no effects on tidal volume at any dose. Respiration rate was increased in the 2.5 and 10 mg/kg groups when compared with the vehicle group. However, there was no increase in respiration rate at the high dose. These effects were not considered to be toxicologically important because they were not dose-related and a decreased respiration rate was present in comparison with pre-treatment values. These results are summarized in the following sponsor's table:

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Group	Treatment	Tidal Volume (mL) at Time Post-Dose			
		Pre-dose	60 min	180 min#	480 min
C	Vehicle (10 mL/kg p.o.)	1.59 ± 0.07	1.53 ± 0.08	1.61 ± 0.08	1.58 ± 0.04 (7)
A	R076477 (2.5 mg/kg p.o.)	1.52 ± 0.09	1.55 ± 0.06	1.74 ± 0.08	1.64 ± 0.05 (7)
B	R076477 (10 mg/kg p.o.)	1.48 ± 0.06	1.47 ± 0.07	1.60 ± 0.10	1.66 ± 0.12
D	R076477 (20 mg/kg p.o.)	1.58 ± 0.06	1.38 ± 0.05	1.59 ± 0.13	1.82 ± 0.11

Group	Treatment	Respiration Rate (breaths/min)			
		Pre-dose	60 min	180 min#	480 min
C	Vehicle (10 mL/kg p.o.)	140.66 ± 7.78	125.90 ± 7.35	100.93 ± 7.19	85.81 ± 4.10 (7)
A	R076477 (2.5 mg/kg p.o.)	169.60 ± 12.93	155.70 ± 11.95	149.75 ± 7.83**	122.56 ± 9.57** (7)
B	R076477 (10 mg/kg p.o.)	155.00 ± 13.90	126.62 ± 2.70	124.58 ± 5.98	116.15 ± 6.68**
D	R076477 (20 mg/kg p.o.)	153.50 ± 7.00	109.65 ± 8.81	97.96 ± 6.31	97.44 ± 4.80

Data acquired at approximately 210 min due to technical failure.

Vehicle for R076477 was a solution of tartaric acid (1.4 mg/mL) in demineralised water with diluted NaOH at final pH 5.0 ± 0.1.

n = 8 animals per group, unless otherwise stated in parenthesis.

Data are expressed as mean ± s.e. mean.

** P < 0.01 when compared to vehicle group data (ANOVA and Dunnett's t-test).

All R076477 data were compared to vehicle group data.

Renal effects:

No safety pharmacology animal studies were conducted to evaluate specifically the potential of paliperidone to induce renal effects.

Gastrointestinal effects:

A 3-month repeat-dose toxicity study was conducted in dogs to evaluate the local tolerability of the paliperidone ER tablets in the gastrointestinal tract. The review of this study can be found within repeated-dose toxicity studies section on page 97 of this review. There were no other safety pharmacology studies conducted to assess gastrointestinal tolerability of paliperidone.

Abuse liability:

According to the sponsor, based on the pharmacological profile of paliperidone, the risk of abuse and dependence potential is thought to be minimal. Moreover, clinical experience with risperidone (resulting in high exposure to paliperidone), with paliperidone itself, and other typical and atypical neuroleptics does not reveal any risk of abuse or dependence. Therefore, no further animal studies were conducted to evaluate the abuse and dependence potential of paliperidone.

Other:Study title: Effects of risperidone and 9-OH risperidone on human platelet function, plasma coagulation and fibrinolysis in vitro (Study No. N108177/1)

The objective of this study was to examine effects of risperidone and paliperidone on human platelet function, plasma coagulation and fibrinolysis in vitro. Test systems capable of detecting inhibition but also activation and amplification of human platelet shape change, adhesion/aggregation, release of thromboxane B₂, arachidonic acid metabolism by human platelets and rat aortic rings, human plasma coagulation (activated partial thromboplastin time, thrombin time, prothrombin time) and fibrinolysis (diluted human whole blood clots lysed in the presence and absence of rt-PA) were used. The rationale for these studies was based on the fact that platelets carry functional serotonergic receptors and are involved in hemostatic and thrombotic processes while risperidone and paliperidone are potent antagonists of 5-HT₂ receptors.

Results of this study indicated that neither risperidone nor paliperidone induced a platelet shape change and/or aggregation upon addition of the compounds to stirred platelet-rich plasma and did not amplify the ADP-induced platelet response. Moreover, both compounds exert no functionally relevant antagonism or agonism at platelet receptors for collagen, ADP, thromboxane A₂, prostaglandin endoperoxides and display no inhibition or stimulation of cyclo-oxygenase, thromboxane A₂ synthase-, phosphodiesterase type III enzymatic activity in human platelets and of prostacyclin synthase activity in vessel wall cells. This indicates that risperidone and paliperidone do not have agonistic effects on a variety of platelet functions.

Neither risperidone nor paliperidone affect plasma coagulation or fibrinolysis in whole blood with or without the addition of rt-PA. These results are shown in the following sponsor's tables:

Table 8: Pharmacological effects on plasma coagulation.

Compound	Plasma coagulation test ⁽¹⁾		
	APTT	TT	PTT
Solvent	28 ± 0.3	26.3 ± 0.3	15.6 ± 0.2
Risperidone (1 × 10 ⁻⁵ M)	27.9 ± 0.2	26.2 ± 0.4	15.4 ± 0.2
9-OH risperidone (1 × 10 ⁻⁵ M)	27.9 ± 0.2	26.3 ± 0.4	15.3 ± 0.2
Heparin (0.1 U/ml)	66.5 ± 1.1 ⁽²⁾	> 500 ± 0 ⁽²⁾	16.1 ± 0.3

(1) Activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PTT) in human plasma, expressed in sec. Mean ± S.E.M., n = 12.

(2) p < 0.05 versus solvent.

Table 9: Pharmacological effects on diluted human whole blood clot lysis.

Compound	Residual blood clot (μ l) after rt-PA (ng/ml) ⁽¹⁾				
	0	0.1	0.3	0.5	1
Solvent	157.7 \pm 5.5	155.8 \pm 4.9	144.5 \pm 7	119.7 \pm 13.9	13.8 \pm 12.1
Risperidone (1×10^{-5} M)	162.5 \pm 2	158 \pm 3.3	152.8 \pm 3.3	130.2 \pm 7.7	2 \pm 0.2
9-OH risperidone (1×10^{-5} M)	165.3 \pm 3.2	159 \pm 2.8	153.9 \pm 2.5	135.4 \pm 6.1	1.7 \pm 0.2
Aprotinin (1000 U/ml)	157.5 \pm 5	160.3 \pm 3.1	162.6 \pm 4.4	161.5 \pm 4 ⁽²⁾	160.4 \pm 4.8 ⁽²⁾

(1) Residual blood clot (in μ l whole blood) relative to a non-lysed sample after 1 h at 37° C in the presence of compounds and increasing concentrations of rt-PA. Mean \pm S.E.M., n = 6.

(2) p < 0.05 versus solvent.

Risperidone and paliperidone potently inhibited 5-HT-induced human platelet aggregation in a concentration dependent manner (IC₅₀ for the speed of the aggregation: risperidone: 0.0016 μ M; paliperidone: 0.0005 μ M). At high concentrations both compounds also partially attenuated the reaction elicited by epinephrine. These effects are likely mediated by 5-HT₂ receptors and alpha₂-adrenergic receptors, respectively. Therefore, anti-thrombotic effects of risperidone and paliperidone may be expected based on the results of this study.

2.6.2.5 Pharmacodynamic drug interactions

See studies No. 3, 4 and 6 in the Metabolism section (2.6.4.5) of this review (page 62, 63 and 64, respectively)

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Tables provided by the sponsor are long and therefore not suitable for this review. The most important tabulated data can be found within review of the individual study reports.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

The majority of pharmacokinetic data were generated as toxicokinetic measurements in toxicology studies. Exposure to paliperidone in general increased with increasing dose without accumulation after prolonged treatment. For both paliperidone enantiomers, similar elimination half-lives (t_{1/2}) were estimated after dosing with both compounds that ranged from 1.2 to 2.3 hours. Please see the review of repeat-dose toxicity studies for further details. Bioavailability of paliperidone after p.o. solution administration in dogs was high (94%). The p.o. availability in rats was not assessed. The sponsor estimated the F_{abs} value at 46% in male rats and 78% in female rats by comparison of data from separate studies. However, the relative bioavailability of paliperidone following ER tablet administration was only 15% in dogs. ER tablets administered to dogs were recovered in the feces as whole units without tears, perforations or indentations. Estimated gastrointestinal transit times were between 7.7 to 45.1 hours and the average residual paliperidone was 0.46 mg (range 0.01 to 0.92 mg). The distribution of radiolabelled paliperidone was investigated in general distribution and in brain distribution studies. Highest values of paliperidone derived activity were observed in liver, small intestinal tissue and salivary gland. In all non melanin containing tissues, the radioactivity declined

in parallel to plasma concentrations. In melanin-containing tissues (eyeballs and pigmented skin and fur) there was an extensive retention of paliperidone-related radioactivity up to the last time point measured (336 h). Paliperidone was also well absorbed after subcutaneous administration. Maximum plasma concentrations were observed at 0.5 h after administration. Plasma levels of paliperidone rapidly decline with a half life of 2.3 h. Brain concentrations of unchanged drug (UD) and non-volatile radioactivity rapidly increased after subcutaneous administration. Peak levels of UD were observed at 0.5 h in cerebellum, at 1 h in rest of brain and frontal cortex, and at 4 h in striatum. In frontal cortex and striatum, brain regions with high concentrations of 5-HT₂ or D₂ receptor, C_{max}, T_{max} and AUCs and half-lives of paliperidone were higher than in cerebellum, a region with few of these receptor binding sites. In vivo mass balance studies with radiolabelled paliperidone in rats, dogs, and humans indicated that the major biotransformation pathways in vivo and in vitro and across the species are the same. Paliperidone metabolism was extensive in vivo in rats and less extensive in dogs and humans. The amount recovered as unchanged drug was 3.19% and 6.42% in rats, 32.4% in dogs and 59.4% in humans. Individual metabolites each accounted for 3-5% of the administered dose. The metabolites observed following risperidone administration of paliperidone have also been observed following risperidone administration. All metabolites observed in humans were also observed in at least one of the toxicological species. In dogs and humans, paliperidone-related radioactivity was excreted mainly in urine; in rats with the feces. In humans, the cumulative excretion in the urine was ~80% of the dose.

2.6.4.2 Methods of Analysis

see under individual study reviews

2.6.4.3 Absorption

1. Study title: In vitro study on the transepithelial transport mechanism of paliperidone across Caco-2 monolayers (Study No. FK4856).

The transepithelial transport mechanisms of paliperidone, possible effects of typical substrates and inhibitors for various transporters on the in vitro transepithelial transport of paliperidone and possible inhibition of human P-glycoprotein by paliperidone were investigated in this study using Caco-2 cell model. Since orally dosed paliperidone in human volunteers undergoes only limited metabolism and ~ 60 % of administered radioactivity excreted in urine, renal excretion plays an important role in paliperidone elimination. Caco-2 monolayer is widely accepted human in vitro model for the bi-directional transepithelial drug transport mechanisms. Apparent permeability coefficients (P_{app}) for paliperidone in the absorptive direction across Caco-2 monolayers increased from 21 to 30 for concentrations between 3 and 100 μM. Comparison of paliperidone permeation rates with those of reference compounds indicated that paliperidone is a high permeability drug (exhibits high transcellular permeation across Caco-2 cell monolayers). Corresponding P_{app} values in the secretory directions were 51 (at 3 μM) to 43 (at 100 μM), demonstrating slight transport polarity and some preference for the secretory direction. Efflux ratio (ER=secretory/absorptive P_{app}) decreased from 2.4 at 3 μM to 1.4

at 100 μ M suggesting some saturable paliperidone efflux. The slight polarity in paliperidone transport and a decreasing ER with concentrations indicate possible involvement of an efflux transporter (like P-glycoprotein) in transepithelial paliperidone transport. Additional data indicated that paliperidone transport is modulated with apical pH (gradual increase of absorptive permeation of paliperidone when apical pH is increased from 6.0 to 8.0). Co-incubation of paliperidone with human P-glycoprotein (P-gp) inhibitors (verapamil, imipramine and quinidine) significantly reduced the paliperidone ER from 1.8 to 0.8, indicating that P-gp may play some role in the transepithelial movement of paliperidone. The potential of paliperidone to inhibit human P-glycoprotein activity was evaluated by determining the effect of paliperidone concentrations on polarized transport of the P-gp probe taxol across Caco-2 monolayers. Paliperidone appears to have a weak P-gp inhibitory effect. The sponsor concluded that clinical relevance of this effect is expected to be limited.

2. Study title: Absorption and tissue distribution of R076477 after single oral administration of 0.63 mg 14 C-R076477/kg in the male SPF Wistar rat (Study No. FK3018).

The absorption and tissue distribution of total paliperidone-related radioactivity were investigated in rats following oral administration of radiolabelled paliperidone. Paliperidone was rapidly absorbed. Maximum plasma concentrations were reached within 20 min after gavage and then declined to <1% of the peak value within 24 hours. Total radioactivity was rapidly distributed to tissues and then rapidly declined. No retention was observed in any of the investigated tissues. After 48 hours after administration, total radioactivity levels were below quantification limit in most tissues. Highest values were observed in liver, small intestinal tissue and salivary gland. AUC_{0-8h} values of mean tissue and plasma levels of total radioactivity are shown in the following sponsor's table and figure:

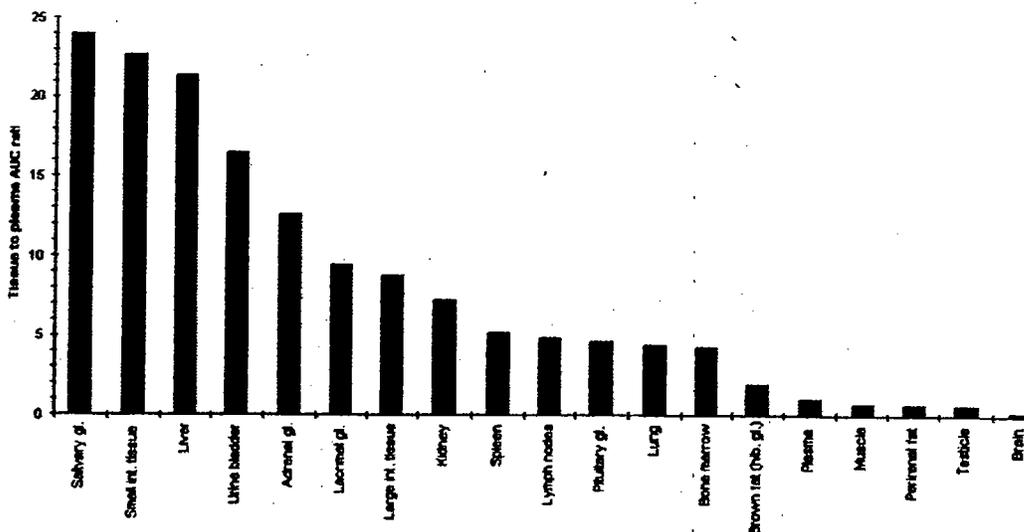
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Table 5-4: AUC_{0-24h}-values of total radioactivity (TR), calculated for plasma and tissues (for both calculated on mean data), in the male SPF Wistar rat after single oral administration of ¹⁴C-R076477 at 0.63 mg/kg.

Tissue	AUC _{0-24h} ($\mu\text{g}\cdot\text{eq}\cdot\text{h}/\text{ml}$ or g)	AUC _{0-24h} -ratio tissue/plasma
Plasma	0.508 (0.357 ¹⁾)	(1.00)
Brain	0.0465 ¹⁾	0.130 ¹⁾
Testicle	0.325	0.639
Perirenal fat	0.355	0.697
Muscle	0.365	0.717
Brown fat (hib. gl.)	0.997	1.96
Bone marrow	2.16	4.24
Lung	2.26	4.44
Pituitary gland	2.38	4.69
Lymph nodes	2.46	4.85
Spleen	2.65	5.21
Kidney	3.67	7.22
Large int. (tissue)	4.46	8.78
Lacrimal gland	4.82	9.48
Adrenal gland	6.41	12.6
Urine bladder (tissue)	8.38	16.5
Liver	10.9	21.4
Small int. (tissue)	11.5	22.7
Salivary gland	12.2	24.0

¹⁾ AUC_{0-24h}-value or tissue to plasma ratio.

Figure 5-4: Tissue to plasma AUC_{0-24h} ratios (AUC_{0-24h} ratio for brain) of total radioactivity (TR), calculated for plasma and tissues (on mean data), in the male SPF Wistar rat after single oral administration of ¹⁴C-R076477 at 0.63 mg/kg.

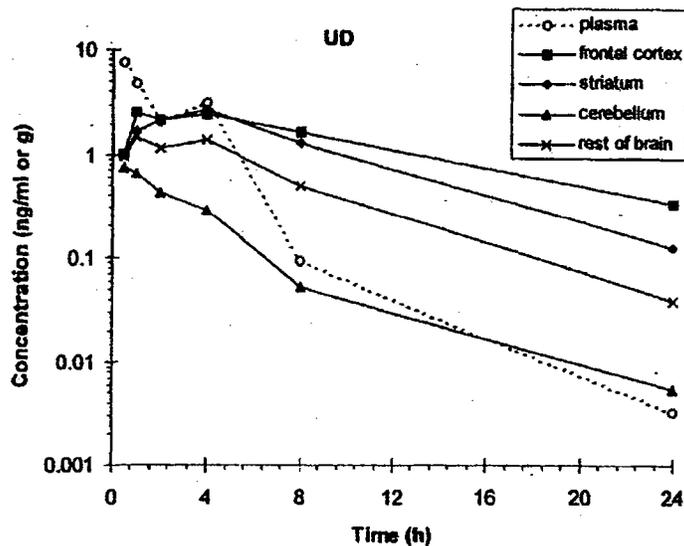


3. Study title: Regional brain distribution of paliperidone in the male Wistar rat after single subcutaneous administration at 0.02 mg/kg.

The absorption, plasma levels and regional brain distribution of paliperidone (UD) and non-volatile radioactivity (NVR) were studied in rat after administration of ³H

paliperidone. Paliperidone was well absorbed after subcutaneous administration. Maximum plasma concentrations of UD and NVR were observed at 0.5 h after administration and reached 7.49 ± 1.44 ng/ml and 7.65 ± 1.24 ng-eq/ml, respectively. Plasma levels of paliperidone rapidly decline with a half life of 2.3 h. Levels of NVR declined more gradually. Brain concentrations of UD and NVR rapidly increased after subcutaneous administration. Peak levels of UD were observed at 0.5 h in cerebellum, at 1 h in rest of brain and frontal cortex, and at 4 h in striatum. Highest levels of UD were observed in frontal cortex (2.5 ng/g) and striatum (2.69 ng/g). These data are shown in the following sponsor's figure:

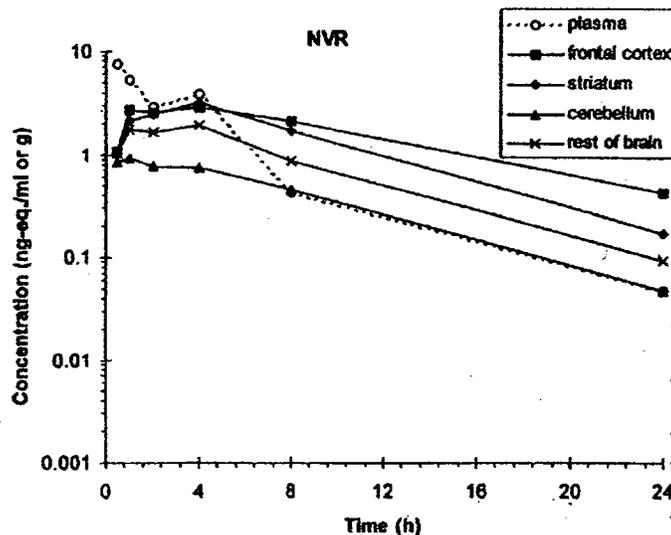
Figure 5-3: Mean plasma and brain region concentrations of unchanged drug (UD) in the male Wistar rat after single subcutaneous administration of ^3H -paliperidone at 0.02 mg/kg.



Peak levels of NVR were observed at 1 h in cerebellum and at 4 h in rest of brain, frontal cortex and striatum. Highest levels of NVR were observed in frontal cortex (2.91 ng/g) and striatum (3.19 ng/g). These data are shown in the following sponsor's figure:

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Figure 5-2: Mean plasma and brain region concentrations of non-volatile radioactivity (NVR) in the male Wistar rat after single subcutaneous administration of ^3H -paliperidone at 0.02 mg/kg.



In conclusion, in frontal cortex and striatum, brain regions with high concentrations of 5-HT₂ or D₂ receptor, C_{max}, T_{max} and AUCs and half-lives of paliperidone were higher than in cerebellum, a region with few of these receptor binding sites.

4. Study title: Toxicokinetics of paliperidone enantiomers in SPF Sprague Dawley rats and SPF Swiss mice in repeated dose toxicity studies with paliperidone (R076477) and risperidone (R064766) after 3 months of oral dosing at 10 mg/kg/day (Study No. FK4855)

Plasma samples obtained from rats and mice dosed with paliperidone or risperidone at 10 mg/kg/day for 3 months in studies TOX5708 and TOX5721 were analyzed individually for the paliperidone enantiomers (+) PAL (R078543) and (-) PAL (R078544). In the mouse, the plasma levels of (-) paliperidone were substantially higher than (+) paliperidone in the two sexes after dosing with either paliperidone or risperidone. The enantiomer C_{max} and AUC_{0-24h} ratios after dosing with paliperidone to that after risperidone administration were similar. For both paliperidone enantiomers, similar elimination half-lives (t_{1/2}) were estimated after dosing with both compounds that ranged from 1.5 to 2.7 hours. In the rat, the plasma levels of (-) paliperidone were also higher than (+) paliperidone in the two sexes after dosing with either paliperidone or risperidone. In male rats, the enantiomers C_{max} and AUC_{0-24h} ratios after dosing with paliperidone and risperidone were largely comparable. In females, (-)/(+) ratios of C_{max} and AUC_{0-24h} after dosing with paliperidone were twice those after dosing with risperidone. For both paliperidone enantiomers, similar elimination half-lives (t_{1/2}) were estimated (in males only) after dosing with both compounds that ranged from 1.2 to 2.3 hours. In both species, plasma levels of the enantiomers were markedly higher after paliperidone than after risperidone administration.

5. Study title: Pharmacokinetics and absolute bioavailability of 9-hydroxy-risperidone (R76477) in the beagle dog after intravenous and oral administration of 9-hydroxy-risperidone at 0.31 mg/kg (Study No. FK1212)

The pharmacokinetics of paliperidone was investigated in dogs after i.v. and p.o. administration. After intravenous administration, the plasma levels of paliperidone declined with an elimination half-life of 14.4 h. The fraction of risperidone converted to paliperidone was estimated at 77.6%. Other PK data are shown in the following sponsor's table:

Table 2: Individual and mean (± S.D., n=4) pharmacokinetic parameters of 9-hydroxy-risperidone (R 76477) after intravenous administration at 0.31 mg/kg to beagle dogs.

Dog No.	8983	9688	9640	9691	Mean ± S.D.
Parameter (units)					
B (h ⁻¹)					0.051 ± 0.013
t _{1/2β} (h)					14.4 ± 3.6
V _{dss} (ml/kg)					837 ± 159
Cl (ml/h/kg)					51.4 ± 20.4
AUC _{0-∞} (ng.h/ml)					6794 ± 2631
AUC ratio ¹⁾					77.6 ± 34.1

¹⁾ The ratio of the AUC-value of 9-hydroxy-risperidone metabolically formed after intravenous administration of risperidone (from ref. 6), to that after intravenous dosing of 9-hydroxy-risperidone.

After oral administration, the plasma levels of paliperidone declined with an elimination half-life of 17.5 h. The absolute bioavailability of paliperidone was 94.4 %. Other PK data obtained after oral administration are shown in the following sponsor's table:

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Table 4: Individual and mean (\pm S.D., n=4) pharmacokinetic parameters of 9-hydroxy-risperidone (R 76477) after oral administration of 9-hydroxy-risperidone at 0.31 mg/kg to beagle dogs.

Dog No.	8983	9688	9640	9691	Mean \pm S.D.
Parameter (units)					
C_{max} (ng/ml)					352 \pm 114
T_{max} (h)					1.4 \pm 1.1
$t_{1/2\beta}$ (h)					17.5 \pm 4.5
$AUC_{0-\infty}$ (ng.h/ml)					6431 \pm 3029
F (%)					94.4 \pm 15.0
AUC ratio ¹⁾					88.1 \pm 26.6

¹⁾ The ratio of the AUC-value of 9-hydroxy-risperidone metabolically formed after oral administration of risperidone (from ref. 6), to that after oral dosing of 9-hydroxy-risperidone.

6. Study title: The absorption, metabolism and excretion of R076477 in the male Beagle dog after a single oral dose of ¹⁴C-R076477 at 0.63 mg/kg (Study No. FK4463)

Three male beagle dogs received a single oral dose of 0.63 mg/kg ¹⁴C-R076477 (10 μ Ci). Urine, feces and plasma were collected up to one week after dosing. Radioactivity levels were measured by liquid scintillation counting. Metabolite profiles were investigated by radio-HPLC and LC-MSMS. The major part of the radioactivity was excreted in urine. At 168 h after dose administration, 59.77% of the dose was excreted in urine and 32.37% of the dose was excreted in feces. At 168 h after dosing, 93.11% of the dose had been excreted. Unchanged paliperidone accounted also for a major part of the radioactivity in urine and to a lesser extent in feces.

The unchanged paliperidone accounted for 82% of the total radioactivity in plasma. Plasma levels of total radioactivity and plasma levels of unchanged paliperidone as well as the pharmacokinetic parameters of total radioactivity and unchanged paliperidone are listed in the following sponsor's table:

Table 5-2: Plasma concentrations and pharmacokinetics of total radioactivity and unchanged R076477 after single oral administration of ¹⁴C-R076477 to three male beagle dogs at a dose of 0.63 mg/kg.

Time (h)	Total radioactivity (ng-eq./ml)					Unchanged R076477 (ng/ml)				
	19298	19320	19323	Mean ± SD	SD	19298	19320	19323	Mean ± SD	SD
0				<3.4					<0.5	a
0.25				373 ± 118					333 ± 122	
0.5				506 ± 71.5					462 ± 87.1	
1				475 ± 74.0					436 ± 75.3	
2				409 ± 72.8					371 ± 69.9	
4				324 ± 65.1					281 ± 68.6	
6				248 ± 46.4					216 ± 47.0	
8				215 ± 59.0					186 ± 56.7	
24				69.2 ± 33.0					55.0 ± 31.6	
32				41.9 ± 25.3					30.8 ± 21.1	
48				17.6 ± 10.4					11.4 ± 8.7	
72				8.10 ± 5.31					5.81 ^{b)}	
96				5.60 ^{b)}					2.15 ± 1.89	
168				<3.4						
C _{max} (ng/ml)	449	586	482	506 ± 72		386	557	443	462 ± 87	
T _{max} (h)	0.5	0.5	0.5	0.5 ± 0.0		0.5	0.5	0.5	0.5 ± 0.0	
t _{1/2} (h)	14.3	20.7	26.9	20.6 ± 6.3		16.3	23.5	17.0	18.9 ± 4.0	
β (1/h)	0.0483	0.0335	0.0257	0.0358 ± 0.0115		0.0426	0.0295	0.0407	0.0376 ± 0.0071	
AUC ₀₋₂₄ (ng.h/ml)	3700	5982	4264	4649 ± 1189		3162	5377	3527	4022 ± 1188	
AUC _{0-t} (ng.h/ml)	4540	8197	5100	5946 ± 1970		3712	7162	3992	4955 ± 1916	
AUC _{0-inf} (ng.h/ml)	4633	8430	5232	6098 ± 2041		3742	7183	4013	4979 ± 1913	
AUC Ratio UD/TR						0.81	0.85	0.77	0.81 ± 0.04	

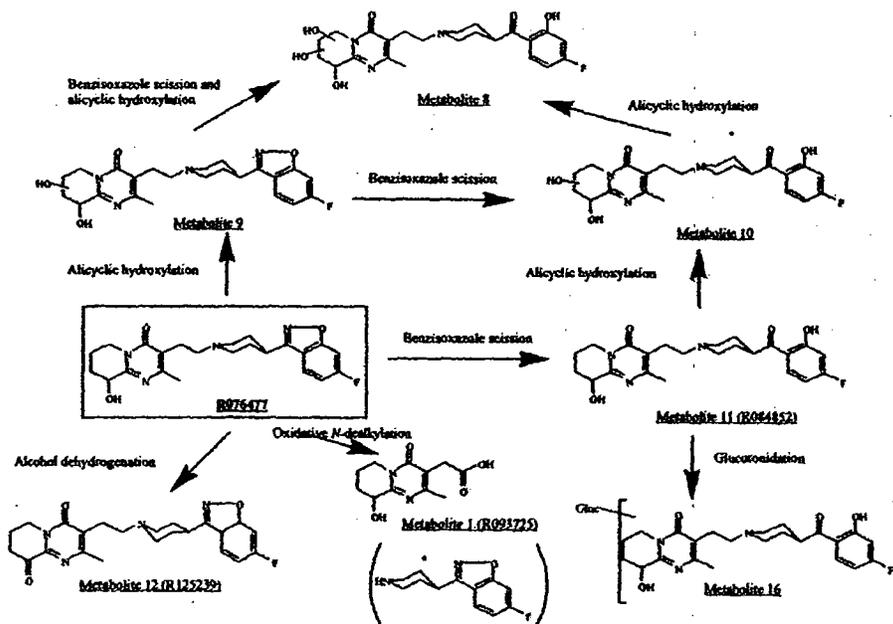
a) Standard deviation not calculated.
 b) Mean for the dogs Nos. 19320 and 19323

Five metabolites could be detected in urine. In dog feces, besides unchanged drug, 3 metabolites could be identified. The metabolites identified in dog are listed in the following sponsor's table and figure:

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Metabolite code	Identification method	Identity
<u>Urine</u> 1	LC-MS/MS Co-elution	Oxidative N-dealkylation (R093725) - acid metabolite
16	LC-MS/MS Enzymatic hydrolysis	Benzisoxazole scission & glucuronidation (glucuronide of metabolite 11)
9	LC-MS/MS	Mono-hydroxylation of alicyclic ring of paliperidone
UD	LC-MS/MS Co-elution	Paliperidone (R076477)
11	LC-MS/MS Co-elution	Benzisoxazole scission (R084852)
12	LC-MS/MS Co-elution	Alcohol dehydrogenation - ketone metabolite originating from the 9-hydroxy function of paliperidone (R125239)
<u>Faeces</u> 8	LC-MS/MS	Benzisoxazole scission & di-hydroxylation of alicyclic ring
10	LC-MS/MS	Benzisoxazole scission & mono-hydroxylation of alicyclic ring
UD	LC-MS/MS Co-elution	Paliperidone (R076477)
11	LC-MS/MS Co-elution	Benzisoxazole scission - R084852

Figure 5-11: Biotransformation pathways for R076477 in the male beagle dog after single oral administration of ¹⁴C-R076477 at 0.63 mg/kg.



7. Study title: A pilot study on the plasma concentrations of the enantiomers of 9-hydroxy-risperidone (R078543 and R078544) in the beagle dog after single oral and subcutaneous administration of R078543 or R078544 at 0.01 and 0.04 mg/kg (Study No. FK2078)

This study was conducted to compare the primary pharmacology and plasma kinetics of R078543 and R078544. After administration of the enantiomers, plasma samples were taken from the dogs of the 0.01 mg/kg groups at 0, 1, 2, 4, 8, 24, 48, 56 and 72 h after dose administration and from the dogs of the 0.04 mg/kg groups after 16 hours of dosing. No marked differences in pharmacokinetic parameters of paliperidone after single oral or subcutaneous administration of two enantiomers were observed between the enantiomers or two administration routes. The data are provided in the following sponsor' tables:

Table 1-3: Individual and mean (± SD, n = 4) plasma concentrations (ng/ml) and some basic pharmacokinetic parameters of 9-hydroxy-risperidone in beagle dogs after oral and subcutaneous administration of R078543 at 0.01 mg/kg.

R078543 (+)PO		9-hydroxy-risperidone			
Animal number	10561	10693	10422	10423	Mean ± S.D.
Time (h) after dosing					
0					< 0.20
1					4.97 ± 1.86
2	█	█	█	█	5.14 ± 1.99
4	█	█	█	█	4.30 ± 1.90
8	█	█	█	█	3.68 ± 1.70
24	█	█	█	█	2.05 ± 0.98
48	█	█	█	█	0.48 ± 0.27
56	█	█	█	█	< 0.20 ^d
72	█	█	█	█	< 0.20
C _{max} (ng/ml)	7.24	4.07	2.94	6.31	5.14 ± 1.98
T _{max} (h)	2	2	1	2	1.8 ± 0.5
t _{1/2} (h)	7.03 ^{a)}	9.80 ^{a)}	16.7 ^{b)}	8.63 ^{b)}	10.5 ± 4.3
AUC ₀₋₄ (ng.h/ml)	171	80.9	57.0	133	110 ± 51
AUC ₀₋₇₂ (ng.h/ml)	175	84.8	65.5	138	116 ± 50
R078543 (+)SC		9-hydroxy-risperidone			
Animal number	10135	10547	9269	9270	Mean ± S.D.
Time (h) after dosing					
0					< 0.20
1					3.47 ± 0.72
2					3.89 ± 0.70
4	█	█	█	█	3.82 ± 0.67
8	█	█	█	█	2.79 ± 0.59
24	█	█	█	█	1.69 ± 0.54
48	█	█	█	█	0.43 ± 0.19
56	█	█	█	█	0.26 ^{b)}
72	█	█	█	█	< 0.20
C _{max} (ng/ml)	4.65	3.45	4.33	3.45	3.97 ± 0.61
T _{max} (h)	2	4	4	2	3.0 ± 1.2
t _{1/2} (h)	11.1 ^{a)}	10.2 ^{a)}	11.9 ^{b)}	18.3 ^{b)}	12.9 ± 3.7
AUC ₀₋₄ (ng.h/ml)	98.3	64.0	117	79.1	89.6 ± 23.0
AUC ₀₋₇₂ (ng.h/ml)	105	67.1	124	87.3	95.9 ± 24.3

^{a)} t_{1/2} is calculated between 48 and 56 h.
^{b)} t_{1/2} is calculated between 24 and 48 h.
^{c)} Median value.

Table 1-4: Individual and mean (± SD, n = 4) plasma concentrations (ng/ml) and some basic pharmacokinetic parameters of 9-hydroxy-risperidone in beagle dogs after oral and subcutaneous administration of R078544 at 0.01 mg/kg.

R078544 (-)PO		9-hydroxy-risperidone				Mean ± S.D.
Animal number		7546	7547	10691	11329	
Time (h) after dosing						
0						< 0.20
1						3.79 ± 2.22
2						4.40 ± 1.49
4						4.63 ± 1.83
8						4.36 ± 1.86
24						2.46 ± 1.06
48						0.76 ± 0.32
56						0.44 ± 0.26
72						< 0.20 ^{d)}
C _{max}	(ng/ml)	6.13	7.12	4.24	2.71	5.05 ± 1.96
T _{max}	(h)	1	4	4	4	3.3 ± 1.5
t _{1/2}	(h)	8.17 ^{b)}	22.6 ^{c)}	10.9 ^{b)}	6.71 ^{b)}	12.1 ± 7.3
AUC ₀₋₄	(ng.h/ml)	130	217	107	80.4	134 ± 59
AUC ₀₋₇₂	(ng.h/ml)	135	236	112	83.2	142 ± 66
R078544 (-)SC		9-hydroxy-risperidone				Mean ± S.D.
Animal number		10402	10413	7586	7601	
Time (h) after dosing						
0						< 0.20
1						3.45 ± 0.98
2						4.05 ± 0.73
4						4.33 ± 1.20
8						3.45 ± 1.07
24						1.79 ± 0.79
48						0.29 ^{d)}
56						< 0.20 ^{d)}
72						< 0.20
C _{max}	(ng/ml)	5.46	3.36	3.22	3.63	4.42 ± 1.08
T _{max}	(h)	4	2	4	4	3.5 ± 1
t _{1/2}	(h)	8.9 ^{d)}	12.6 ^{e)}	11.6 ^{e)}	9.59 ^{e)}	10.7 ± 1.7
AUC ₀₋₄	(ng.h/ml)	115	45.1	135	83.3	94.6 ± 39.3
AUC ₀₋₇₂	(ng.h/ml)	119	61.2	142	87.1	102 ± 35

^{a)} Median value.
^{b)} t_{1/2} is calculated between 48 and 56 h.
^{c)} t_{1/2} is calculated between 48 and 72 h.
^{d)} t_{1/2} is calculated between 24 and 48 h.
^{e)} t_{1/2} is calculated between 8 and 24 h.
^{f)} t_{1/2} is calculated between 24 and 56 h.

8. Study title: System Transit, Drug Release and Pharmacokinetic Study of OROS® Paliperidone in Dogs (Study No. TR-02-5626-041)

This study evaluated the transit of the dosage form (including physical integrity and transit times), drug release and pharmacokinetic of an OROS® Push-Pull® paliperidone dosage form (2 mg) after oral administration to fasted male and female dogs. The system is designed to deliver 2 mg of paliperidone for a time period of approximately 20 hours. The system is a trilayer longitudinal compressed tablet. Two orifices are drilled through the drug layer side of the table. In the aqueous environment of the gastrointestinal (GI) tract, the water is imbibed through the membrane of the tablet at a controlled rate determined by the properties of the membrane and the osmolarity of the core constituents. This causes the push layer to swell and the drug layer to hydrate and become viscous. The push layer expands against the drug layer, which exits the system through the

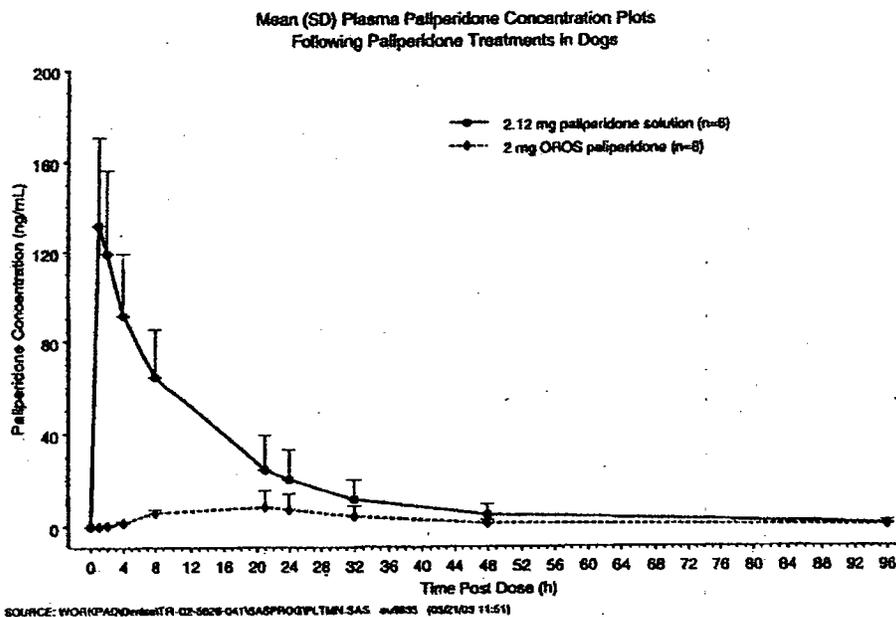
orifices in the membrane at the same rate that water is imbibed into the core. The insoluble membrane components, which form the tablet shell, are eliminated in the stool. Three male and three female dogs were administered 2.12 mg/dog of paliperidone oral dosing solution by orthogastric intubation. After 14 days, the same dogs received a single OROS® Push-Pull® paliperidone system (2 mg). All six administered OROS® systems were recovered in the feces as whole units without tears, perforations or indentations. Estimated gastrointestinal transit times were between 7.7 to 45.1 hours and the average residual paliperidone was 0.46 mg (range 0.01 to 0.92 mg). Both formulations were well tolerated. Transient sedation was observed approximately 2.5 – 3 hours after dosing of the solution formulation. Following administration of the oral dosing solution peak paliperidone plasma concentrations were observed ~1 hour post dose (mean value of 131.78 ng/ml). For the OROS® system, peak plasma concentrations were lower (mean value of 9.52 ng/ml) and occurred ~17 hours post dose. Peak plasma concentrations following OROS® paliperidone were approximately 7.2% of peak concentrations following the oral dosing solution. The AUC_{inf} was also considerably lower for OROS® paliperidone (253.9 ng.h/ml) compared to solution formulation (1760 ng.h/ml). In conclusion, bioavailability for OROS® paliperidone was only 15.1% in comparison to the dosing solution. A summary of paliperidone pharmacokinetic parameters is shown in the following sponsor's table:

TABLE A Paliperidone Pharmacokinetic Parameters

	Dosing Solution (2.12 mg)*	OROS® Paliperidone (2 mg)*
N	6	6
C _{max} (ng/mL)	131.78 ± 38.62	9.52 ± 6.07
T _{max} (h)	1.00 ± 0	16.67 ± 6.71
t _{1/2} (h)	13.16 ± 5.77	9.97 ± 3.57
AUC _t (ng.h/mL)	1711.0 ± 799.3	241.2 ± 206.9
AUC _{inf} (ng.h/mL)	1760.0 ± 834.4	253.9 ± 208.0
Relative F (%)	Reference	15.1 ± 10.9

*Mean±SD

Mean plasma paliperidone concentrations are shown in the sponsor's figure below:



9. Study title: Pharmacokinetics of 9-hydroxy-risperidone (R076477) and its enantiomers R078543 (+) and R078544 (-) in the male beagle dog after a single intravenous administration of 9-hydroxy-risperidone, R078543 and R078544 at 0.31 mg/kg and after a single intramuscular administration of 9-hydroxy-risperidone at 0.31 mg/kg (Study No. FK2501)

The pharmacokinetics of paliperidone and its enantiomers was studied as described in the title of the study. Plasma concentrations were measured by an enantioselective method after intramuscular and intravenous administration of paliperidone and by a non-enantioselective RIA method after intravenous administration of each enantiomer. After intravenous and intramuscular administration of paliperidone, plasma concentrations of R078543 declined at a faster rate than those of R078544. $T_{1/2}$ was on average calculated at 2.7 hours for R078543 and 8.8 hours for R078544. This resulted in an AUC value which was 5.1 times higher for R078544 than for R078543. Enantioselective analysis of the plasma samples after intravenous administration of R078543, this test article was converted largely into R078544. Plasma levels of R078543 after R078544 administration remained very low. It can be concluded that after intravenous and intramuscular administration of paliperidone, R078543 was converted largely into R078544. Plasma concentrations and pharmacokinetic parameters of the enantiomers R078543 and R078544 after single i.v. or i.m. administration of paliperidone are given in sponsor's table below:

Table 5-3: Mean (n = 4) plasma concentrations (ng/ml) (measured by enantioselective HPLC) and some pharmacokinetic parameters of the enantiomers R078543 and R078544 after single intravenous or intramuscular administration of 9-hydroxy-risperidone (R076477) at 0.31 mg/kg.

Time (h) after dosing	IV		IM	
	R078543	R078544	R078543	R078544
0	< 20	< 20	< 20	< 20
0.13	232 ± 46	192 ± 24	184 ± 46	140 ± 26
0.25	202 ± 48	189 ± 18	181 ± 49	150 ± 26
0.5	160 ± 42	181 ± 25	164 ± 46	165 ± 29
1	131 ± 48	187 ± 36	138 ± 35	185 ± 27
2	89 ± 40	192 ± 46	104 ± 38	201 ± 53
4	60 ¹⁾	182 ± 61	59 ¹⁾	178 ± 56
6	39 ¹⁾	154 ± 88	34 ¹⁾	148 ± 60
8	25 ¹⁾	121 ± 62	27 ¹⁾	133 ± 66
24	< 20	44 ¹⁾	< 20	48 ¹⁾
48	< 20	< 20	< 20	< 20
C_{max} (ng/ml)	- ²⁾	- ²⁾	187 ± 48	208 ± 42
T_{max} (h)	- ²⁾	- ²⁾	0.19 ± 0.07	2.25 ± 1.26
$t_{1/2\beta}$ (h)	2.65 ± 1.41	7.89 ± 3.77	2.79 ± 1.42	9.69 ± 6.42
AUC_{0-4} (ng.h/ml)	526 ± 278	2549 ± 1312	537 ± 269	2673 ± 1361
$AUC_{0-\infty}$ (ng.h/ml)	655 ± 352	3138 ± 1689	686 ± 334	3620 ± 2128

¹⁾ Median

²⁾ Parameter not calculated or determined

10. Study title: Pharmacokinetics of 9-hydroxy-risperidone in pigs after single intravenous administration of an aqueous hydroxypropyl- β -cyclodextrin solution of 9-hydroxy-risperidone (R076477) at 0.31 mg/kg (Study No. FK2929)

The plasma kinetics of paliperidone was studied in pigs after single intravenous administration of the aqueous hydroxypropyl- β -cyclodextrin solution of paliperidone. Plasma samples were analyzed for paliperidone using RIA-method. Plasma levels of paliperidone declined biphasically with a mean elimination half-life on an average 7.0 hours. The total clearance was on average 247 ml/h/kg. The volume of distribution was on average 1.2 l/kg and $V_{d\beta}$ was on average 2.5 l/kg. In comparison with the dog, the clearance was about 5 times higher in the pig. The volume of distribution at steady-state was higher (about 46%) in pigs than in dogs. The results from this study are shown in the sponsor's table below:

Table 5-2: Individual and mean (\pm SD) ($n = 3$) plasma concentrations (ng/ml) and some basic pharmacokinetic parameters of 9-hydroxy-risperidone (R076477) in pigs after single intravenous administration of an aqueous HP- β -CD solution of 9-hydroxy-risperidone at 0.31 mg/kg.

Time (h) after dosing	Plasma concentration (ng/ml)			
	2230 ¹	2231	2232	Mean \pm S.D.
0				< 0.20 ²
0.1				331 \pm 75
0.3				297 \pm 50
0.5				260 \pm 55
1				261 \pm 25
2				216 \pm 5
4				95.7 \pm 15.6
8				31.3 \pm 1.6
12				17.3 \pm 1.7
24				3.11 \pm 0.49
32				1.00 \pm 0.19
48				< 0.20 ²
72				< 0.20 ²
80				< 0.20 ²
α (h ⁻¹)	0.353	0.203	0.442	0.332 \pm 0.121
$t_{1/2,\alpha}$ (h)	1.97	3.42	1.57	2.32 \pm 0.98
β (h ⁻¹)	0.127	0.067	0.137	0.110 \pm 0.038
$t_{1/2,\beta}$ (h)	5.45	10.39	5.05	6.96 \pm 2.97
Vd_{ss} (ml/kg)	1249	1403	1025	1225 \pm 190
Vd_p (ml/kg)	2093	3628	1704	2475 \pm 1017
Cl (ml/h/kg)	266	242	234	247 \pm 17
AUC ₀₋₁ (ng.h/ml)	1165	1280	1326	1257 \pm 83
AUC _{0-∞} (ng.h/ml)	1173	1285	1332	1263 \pm 82

¹ Pig numbers

² Median

2.6.4.4 Distribution

1. Study title: A pilot study on the plasma protein binding of paliperidone enantiomers, R078543 and R078544, in man, dog and rat (Study No. FK3009). The protein binding of the ¹⁴C-labeled paliperidone enantiomers was studied by a chiral radio-HPLC method. The analysis of plasma samples indicated that there was no inversion of enantiomers and both enantiomers were stable in all the plasma matrices (in vitro). The average plasma protein binding for ¹⁴C-R078543 in male human subjects, male beagle dogs, male and female rats was 82.8%, 85.9%, 68.0% and 71.5%, respectively. Corresponding values for ¹⁴C-R078544 were 65.9%, 77.4%, 87.0% and 90.2%, respectively. Higher protein binding was observed for ¹⁴C-R078543 than for ¹⁴C-R078544 in human and dog plasma, whereas the reverse was true in case of rat plasma. Therefore, it can be concluded that plasma protein binding of enantiomers was found to be stereoselective and stereoselectivity was species dependent. These data are summarized in the following sponsor's table:

Species (gender)	% Plasma protein binding	
	¹⁴ C-R078543	¹⁴ C-R078544
Human (male)	82.84 ± 3.05	65.87 ± 3.60
Beagle dogs (male)	85.93 ± 2.62	77.40 ± 3.61
Wistar rats (male)	68.00 ± 4.52*	87.00 ± 3.66**
Wistar rats (female)	71.52 ± 4.30*	90.24 ± 2.29**

(each value represents the mean ± S.D. of n=5 points; * & ** Paired t- test comparisons for each enantiomer, p> 0.05).

2. Study title: The protein binding of ¹⁴C-paliperidone (R076477) and its individual enantiomers (¹⁴C-R078543 and ¹⁴C-R078544) in plasma from healthy subjects and Sprague-Dawley rats (Study No. FK5209). The protein binding of the ¹⁴C-labeled paliperidone and its enantiomers was investigated. Within the tested concentration range (50 to 250 ng/ml), the protein binding was independent on the concentrations both for paliperidone and its enantiomers in human plasma. The average plasma protein binding in human plasma across the concentration range was 73.2% (26.8% unbound), 81.6% (18.4% unbound) and 63.2% (36.8% unbound) for paliperidone, R078543 and R078544, respectively. Therefore, there is a two-fold difference in the free fraction of the two enantiomers in human plasma. The average plasma protein binding of paliperidone was 71.5% in male rats and 72.3% in female rats. In the rat, the binding of R078544 was higher than that of R078543. An overview on the plasma protein binding of test articles in human plasma and protein solutions and in plasma from rats is shown in the sponsor's table below:

Table 5-5: Pharmacokinetics: Plasma Protein Binding

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Study System:		Equilibrium dialysis was carried out on plasma samples fortified with ¹⁴ C-R076477 or with the enantiomers ¹⁴ C-R078543 or ¹⁴ C-R078544. Plasma or solutions of isolated human plasma proteins was dialyzed against 0.067 M phosphate buffer, pH 7.17 or pH 7.40, respectively, at 37 °C for 4 hours. Concentration of the radiolabelled test compounds in dialysis compartments was evaluated by radioactivity levels determined by liquid scintillation counting.				
Target Entity, Test System, and Method:		Test Article: R076477/R078543/R078544				
Parameter Measured	R076477	Human Plasma, Male	Human Serum albumin (4.3 % w/v)	Human α ₁ -acid glycoprotein (0.1 % w/v)	Plasma Male Sprague-Dawley rat	Plasma Female Sprague-Dawley rat
Concentration Tested (ng/mL)		50 - 250	50	50	100	100
% Bound		73.2	43.8	81.0	71.5	72.3
% Free		26.8	56.2	19.0	28.5	27.7
Parameter Measured	R078543	Human Plasma, Male	Human Serum albumin (4.3 % w/v)	Human α ₁ -acid glycoprotein (0.1 % w/v)	Plasma Male Sprague-Dawley rat	Plasma Female Sprague-Dawley rat
Concentration Tested (ng/mL)		50 - 250	50	50	100	100
% Bound		81.6	38.5	85.1	64.7	61.8
% Free		18.4	61.5	14.9	35.3	38.2
Parameter Measured	R078544	Human Plasma, Male	Human Serum albumin (4.3 % w/v)	Human α ₁ -acid glycoprotein (0.1 % w/v)	Plasma Male Sprague-Dawley rat	Plasma Female Sprague-Dawley rat
Concentration Tested (ng/mL)		50 - 250	50	50	100	100
% Bound		63.2	46.5	75.4	79.8	81.3
% Free		36.8	53.5	24.6	20.2	18.7
Study No.				FK5209		

Additional Information
 Plasma obtained from five male subjects was pooled, three pools of plasma were prepared from 2 male and 3 female rats each. Within the tested concentration range of 50 to 250 ng/ml, the protein binding was independent on the concentration both for paliperidone and its enantiomers in human plasma. There is a two-fold difference in the free fraction of the R078544 versus the R078543 enantiomer in human plasma (36.8 versus 18.4 %). In the rat the binding of R078544 was higher than that of R078543.

3. Study title: Absorption and tissue distribution of paliperidone (R076477) after single oral administration of ¹⁴C-R076477 at 0.63 mg/kg in the pigmented male rats (Study No. FK4462)

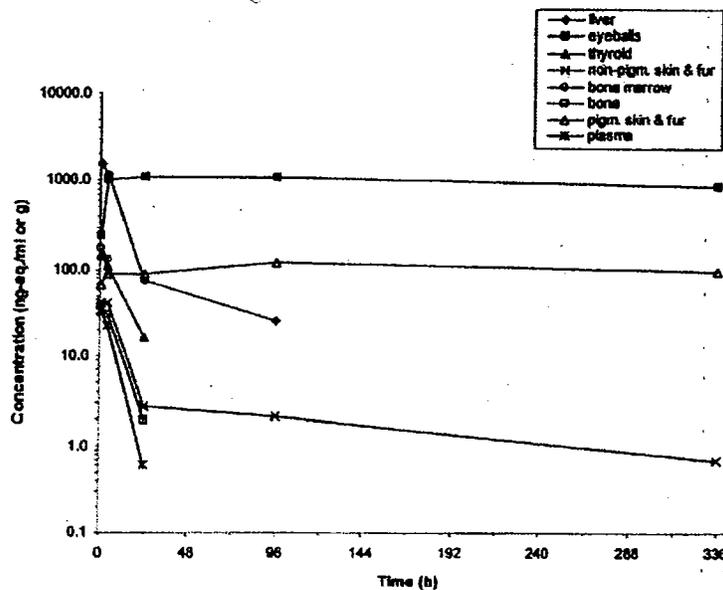
Plasma kinetics and tissue distribution of paliperidone was investigated in male pigmented Long Evans rats as indicated in the table below. The C_{max} in plasma was reached at 1 hour after dosing. The mean $AUC_{0-\infty}$ was 418 ng-eq·h/ml. In most tissues peak level of total radioactivity was noted at 1 hour after administration, except in eyeballs and pigmented skin and fur, where peak levels were observed at 24 hours and 96 hours, respectively. Highest C_{max} values were noted in liver and eyeballs. Radioactivity in the liver represented 10% of the dose. Highest exposure to total radioactivity based on AUC was observed in liver, eyeballs and pigmented skin and fur with total radioactivity tissue to plasma ratios of 31, 57 and 50, respectively. Radioactivity was measurable in liver and in non-pigmented skin up to 96 hours after dosing. Levels in pigmented tissues (eyeballs and pigmented skin and fur) were still measurable at 336 hours after dosing (last investigated time point). Peak levels in other tissues rapidly declined between 4 and 24 hours after administration. In conclusion, paliperidone seems to distribute extensively to melanin-containing tissues. These results are shown in the following sponsor's table and figure:

Table 6-3: Mean concentrations (± S.D., n=3) of total radioactivity (TR in ng-eq/g) as a function of time and some pharmacokinetic parameters calculated from the mean concentrations in various tissues of the male pigmented Long Evans rat after single oral dose administration of ^{14}C -R076477 at 0.63 mg/kg.

Study No.	FK4462							
Species	Rat							
Gender (M/F)/Number of Animals	M/3							
Vehicle/Formulation	Demineralized water							
Route	Gavage							
Dose (mg/kg)	0.63 mg/kg							
Radioisotope	^{14}C							
Specific Activity	1.97 MBq/mg							
Sampling Time Tissues/Organs	Mean TR tissue concentration (ng-eq./g of wet tissue)							
	1 h	4 h	24 h	96 h	336 h			
Plasma	60.8 ± 34.2	41.8 ± 22.1	1.20 ± 0.60	< 0.800	< 0.800			
Bone	37.6 ± 14.4	30.0 ± 9.1	1.91 ± 0.18	< 1.18 ¹⁾	< 1.18 ¹⁾			
Bone marrow	173 ± 59	132 ± 19	< 6.48 ¹⁾	< 6.48 ¹⁾	< 6.48 ¹⁾			
Eyeballs	243 ± 97	1030 ± 141	1105 ± 88	1093 ± 216	880 ± 30			
Liver	1558 ± 270	1159 ± 240	76.4 ± 9.4	25.7 ± 5.6	< 4.03			
Non-pigmented skin and fur	42.4 ± 14.0	41.8 ± 3.9	2.68 ± 0.18	2.12 ± 0.69	0.706 ²⁾			
Pigmented skin and fur	68.3 ± 28.1	89.4 ± 37.1	88.2 ± 76.6	121 ± 18	100 ± 62			
Thyroid	144 ± 52	112 ± 40	16.1 ²⁾	< 13.5 ¹⁾	< 13.5 ¹⁾			
	Plasma	Bone	Bone Marrow	Eyeballs	Liver	Non-pigm. Skin & Fur	Pigm. Skin & Fur	Thyroid
C_{max}	60.8	37.6	173	1105	1558	42.4	121	144
T_{max}	1	1	1	24	1	1	96	1
AUC (ng × h/mL)	411	324	NC ³⁾	23380	12790	433	20470	1440
(Time for calculation -h)	(0-24h)	(0-24h)	(0-24h)	(0-24h)	(0-24h)	(0-24h)	(0-24h)	(0-24h)
AUC ratio tissue: plasma		0.79	1.3 ¹⁾	57	31	1.1	50	3.5
AUC (ng × h/mL)	418	324	542	338311	16138	993	36024	1440
(Time for calculation -h)	(0-∞)	(0-24h)	(0-4h)	(0-336h)	(0-96h)	(0-336h)	(0-336h)	(0-24h)

1) LLOQ are estimated based on mean organ weights; 2) median value; 3) NC: not calculated; more than 25% extrapolation was needed to obtain $AUC_{0-\infty}$; 4) Ratio calculated using $AUC_{0-\infty}$ in tissue

Figure 6-1: Mean (n=3) plasma and tissue levels of total radioactivity (TR) in male pigmented Long Evans rats after single oral dose administration of ¹⁴C-R076477 at 0.63 mg/kg.



4. Study title: The binding of risperidone and its major metabolite 9-hydroxy-risperidone to synthetic melanin in vitro (Study No. FK1202)

The in vitro melanin binding of ³H-risperidone was studied by incubation for various periods of time and at different initial ³H-risperidone concentrations. After removal of ³H-risperidone bound to melanin , the amount of free drug in the supernatant was determined by liquid scintillation counting. The melanin binding of ³H-risperidone was rapid and ranged from 80.9% to 92.2%. Maximum binding was already obtained after 10 min. The melanin binding of ³H-risperidone was lower than that of haloperidol and chlorpromazine. Binding of paliperidone to melanin was smaller than that of risperidone. As the binding of risperidone to melanin depends on reversible electrostatic interaction with the pigment, according to the sponsor, this binding most probably will be without toxicological implications. These data are shown in the sponsor's table below:

Comparison of the melanin binding of risperidone with that of 9-hydroxy-risperidone, haloperidol, chlorpromazine and glucose. The various test compounds were incubated with melanin suspensions (1.36 mg/ml) at a final concentration of 400 μ M for 60 min as described in 2.4.1. _____, the amount of free drug in the supernatant was determined by liquid scintillation counting or _____. Results represent the mean \pm S.D. for four determinations.

Compound	% bound
Risperidone	76.0 \pm 0.2
9-Hydroxy-risperidone(1)	73.9 \pm 0.1
Haloperidol	81.9 \pm 0.3
Chlorpromazine	97.1 \pm 0.1
Glucose	8.5 \pm 2.0

(1) Duplicate samples, not corrected for background binding

2.6.4.5 Metabolism

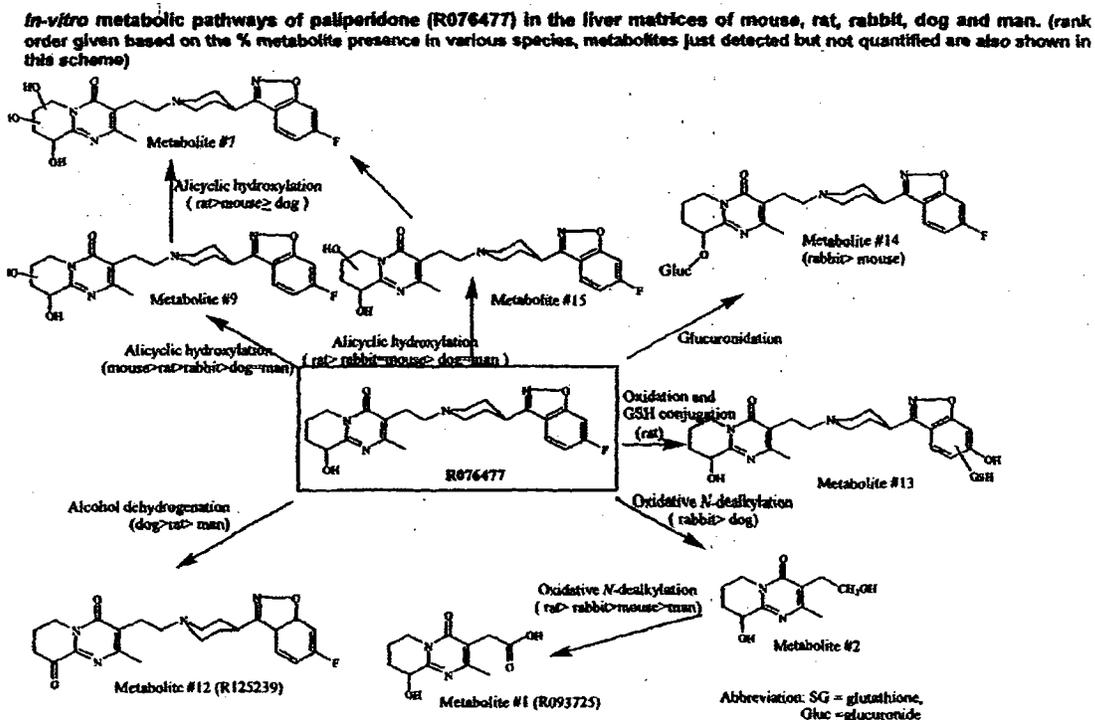
1. Study title: The in-vitro metabolism of paliperidone and its individual enantiomers (R078543 and R078544) in hepatocytes and liver subcellular fractions of male and female Swiss albino mice, male and female Wistar rat, female rabbit, male beagle dog and man (Study No. FK2995)

The in vitro metabolism of paliperidone and its enantiomers was studied in hepatocytes (suspension and primary cultures) and liver subcellular fractions (microsomes) in several animal species and man. Test compounds were incubated with the above matrices for various time periods and were analyzed by a radio-HPLC. Co-chromatography, enzyme hydrolysis and LC-MS/MS techniques were used for the identification of metabolites. A total of 8 metabolites were identified and the metabolic pathways of their formation were elucidated. A summary of various metabolites with the metabolite identification code, the techniques used in the identification and metabolite identity is shown in the sponsor's table below:

Metabolite code #	HPLC ~ Rt time	Technique	Identity
1	13.7 min	co-chromatography and LC-MS/MS	Oxidative N-dealkylation (R093725)- Acid metabolite
2	15.6 min	LC-MS/MS	Oxidative N-dealkylation - Alcohol metabolite
13	20.3 min	LC-MS/MS	Combination of oxidation to arene-oxide followed by glutathione conjugation
14	25.0 min	Enzymatic Hydrolysis and LC-MS/MS	Glucuronide of paliperidone
7	27.1 min	LC-MS/MS	Di-hydroxylation of alicyclic ring of paliperidone
9	29.0 min	LC-MS/MS	Mono-hydroxylation of alicyclic ring of paliperidone
15	30.1 min	LC-MS/MS	Mono-hydroxylation of alicyclic ring of paliperidone
UD	31.2 min	Co-chromatography and LC-MS/MS	Paliperidone
12	32.1 min	Co-chromatography	Ketone metabolite at the 9-hydroxy function of paliperidone (R125239)

This study demonstrated that paliperidone was metabolized to a very limited extent in human liver matrices and extensively metabolized in rat liver matrices. Metabolism rate of paliperidone in mouse, dog, and rabbit liver matrices was found to be low and more closer to human than to rat. The rank order of metabolism rate among the species was rat>rabbit>mouse>dog>man in hepatocytes and liver subcellular fractions. All metabolites that were observed with paliperidone, were also observed with individual enantiomers. All metabolites detected in human matrices were also detected in at least one animal species as shown in the following sponsor's figure:

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Based on the identification of metabolites and radio-HPLC chromatograms, % of the sample radioactivity associated with the individual metabolites and unchanged drug was compiled to obtain a mass balance in all the test species and matrices. In the matrices of mouse, >95% of the sample radioactivity was accounted for and the majority (>83%) of this was due to unchanged drug and remaining percentage was contributed by metabolites #1, #13, #7, #9 and #15. A very limited metabolism was observed in the matrices of rabbit (except primary hepatocyte cultures), dog and man. Therefore, unchanged paliperidone was the major contributor (>80%) of the sample radioactivity. The remaining % was contributed by various metabolites: in rabbit liver matrices: #1, #2, #14, #9 and #15; in dog liver microsomes: #2, #9 and #12. In human liver matrices majority of the drug remained unchanged and some traces of metabolites #1, #9, #15 and #12 were detected. In rat matrices, unlike in other test species, metabolites contribution to the mass balance was comparable to the unchanged drug and metabolites #7 and #13 are the major metabolites.

2. Study title: The in-vitro metabolism of ^{14}C -paliperidone and its individual enantiomers (^{14}C -R078543 and ^{14}C -R078544) in hepatocytes and liver subcellular fractions of male and female Sprague-Dawley rats (Study No. FK5206)

The in vitro metabolism of ^{14}C -paliperidone and its enantiomers was studied in hepatocytes (suspension and primary cultures) and liver subcellular fractions (microsomes) of male and female Sprague-Dawley rats. Test compounds were incubated with the above matrices for various time periods and were analyzed by a radio-HPLC. Co-chromatography and LC-MS/MS techniques were used for identification of

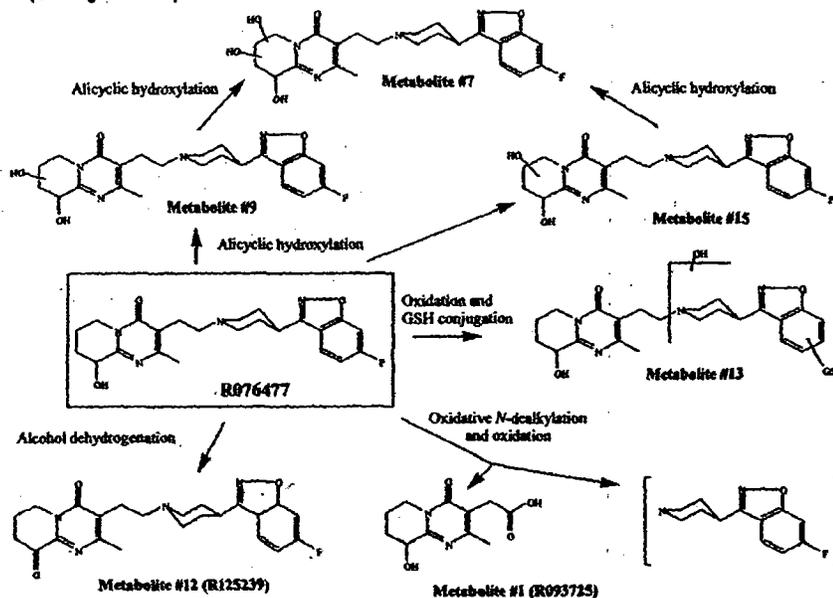
metabolites. Paliperidone was found to be extensively metabolized in hepatocyte suspensions obtained from both sexes. Metabolism was slower in primary cultured hepatocytes. Total of 6 metabolites were identified and metabolic pathways for their formation were proposed, as indicated in the following sponsor's table:

Metabolite code #	HPLC ~ Rt time	Technique	Identity
1	11.7 min	co-chromatography	Oxidative N-dealkylation (R093725)- Acid metabolite
13	19.1 min	LC-MS/MS	Combination of oxidation to arene-oxide followed by glutathione conjugation
7	28.3 min	LC-MS/MS	Di-hydroxylation of alicyclic ring of paliperidone
9	32.3 min	LC-MS/MS	Mono-hydroxylation of alicyclic ring of paliperidone
15	33.8 min	LC-MS/MS	Mono-hydroxylation of alicyclic ring of paliperidone
UD	35.3 min	Co-chromatography and LC-MS/MS	Paliperidone
12	36.7 min	Co-chromatography and LC-MS/MS	Ketone metabolite at the 9-hydroxy function of paliperidone (R125239)

There were no important differences in metabolic rates and profiles of the individual enantiomers compared to paliperidone racemate. There was a gender difference in the metabolism of paliperidone with higher rates in male than in female rats. The metabolism data for Sprague-Dawley rats were similar to those previously obtained in Wistar rats. The overall metabolic rate appeared to be somewhat faster in matrices from Sprague-Dawley compared to Wistar rats, although the results obtained in these two species were obtained in separate studies. Metabolic pathways of paliperidone in Sprague-Dawley rats are shown below:

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Figure S-14: *In-vitro* metabolic pathways of paliperidone (R076477) in the liver matrices of male and female Sprague-Dawley rat. (GSH = glutathione)



In the mass-balance analysis for all matrices used in this study, 70-99% of the sample radioactivity was accounted for by the parent compound and up to 6 metabolites.

3. Study title: An in-vitro study on the microtonal cytochrome P-450 form(s) involved in the metabolism of ^{14}C -labeled 9-hydroxy-risperidone and on the effect of 9-hydroxy-risperidone on the metabolism of specific human cytochrome P-450 probe substrates (Study No. FK3103).

The cytochrome P-450 forms involved in the metabolism of paliperidone were investigated in humans liver microsomes and in the heterologous expression systems expressing CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 in combination with human reductase. Paliperidone was not metabolized by human liver microsomes. Therefore, no cytochrome P-450 identification could be performed in human liver microsomes based on inhibition or correlation experiments. Metabolism experiments in heterologous expression systems (*E. Coli*) containing human CYP P-450 in combination with cytochrome P-450 reductase revealed possible involvement of CYP3A4 and CYP2D6 in the metabolism of paliperidone. Paliperidone was metabolized to R084852. The effect of paliperidone on the metabolism of typical P-450 probe substrates was investigated in the pooled batch h-INT-1 of human liver microsomes. Paliperidone did not affect the cytochrome P450 activity at in vitro concentrations which are clinically relevant. Therefore, no effect of paliperidone on the metabolism of co-administered drugs is expected.

4. Study title: An *in-vitro* study of the effect of paliperidone (R076477) on the metabolism of specific CYP2D6 and CYP3A4/3A5 probe substrates in pooled human liver microsomes (Study No. FK5304)

The effects of increasing concentrations of paliperidone (0-5000 ng/ml) on CYP2D6-mediated dextromethorphan O-demethylase, CYP3A4/3A5-mediated midazolam 1'-and 4-hydroxylase and CYP3A4-mediated testosterone 6- β hydroxylase activities was investigated in pooled human liver microsomes. At concentrations up to 250 ng/ml – paliperidone had no or only minor inhibitory effects on CYP2D6-, CYP3A4/3A5- and CYP3A4-mediated activities in human liver microsomes. This concentration, according to the sponsor, is close to steady-state peak plasma levels at the highest anticipated clinical dose of 15 mg ER OROS paliperidone.

5. Study title: The metabolism and excretion of ^{14}C -R076477 in the male and female SPF Wistar rat after single oral administration at 0.63 mg/kg (Study No. FK3022)

A single oral dose of 0.63 mg ^{14}C -paliperidone/kg was administered to male and female Wistar rats and the metabolism and excretion was examined. The radioactivity was excreted rapidly, predominantly in feces. The radioactivity excreted in urine and feces amounted to 15% and 86%, respectively in male and female rats. At 24 hours after dosing, 76% of the dose had been excreted by males and 77% of the dose had been excreted by females. From 24 to 48 hours, another 25% and 23% had been excreted by males and females, respectively. The radioactivity was completely excreted within 96 hours after dosing. Paliperidone was extensively metabolized by alicyclic hydroxylation, oxidative N-dealkylation and benzisoxazole scission. Urine and feces contained unchanged paliperidone, seven metabolites that each accounted for more than 1% of the dose and four metabolites that each accounted for less than 1% of the dose. These metabolites are shown in the following sponsor's table:

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Code	Identification method	Identity
1	Co-chromatography	Metabolite resulting from oxidative N-dealkylation (R093725)
2		Unknown (<1% of dose)
3		Unknown (<1% of dose)
4		Unknown (<1% of dose)
5		Unknown (<1% of dose)
6	LC/MS	Metabolite resulting from a dehydrogenation most probably on the piperidiny ring of the opened benzisoxazole equivalent of the parent
7	LC/MS	Metabolite resulting from two alicyclic hydroxylation reactions
8	LC/MS	Metabolite resulting from two alicyclic hydroxylation reactions and benzisoxazole scission
9	LC/MS	Metabolite resulting from one alicyclic hydroxylation reaction
10	LC/MS	Metabolite resulting from one alicyclic hydroxylation reaction and benzisoxazole scission
UD	LC-MS Co-chromatography	Unchanged drug (R076477)
11	LC-MS Co-chromatography	Metabolite resulting from benzisoxazole scission (R084852)
12	LC-MS Co-chromatography	Alcohol dehydrogenation-ketone metabolite at the 9-hydroxy function of paliperidone. (R125239)

6. Study title: Study on the induction and/or inhibition potential of risperidone towards drug-metabolizing enzymes in the liver of male Wistar rats (Study No. R64766/21)

Male Wistar rats were dosed orally by gavage for one week with risperidone at dose levels of 0.63, 2.5 and 10 mg/kg. Liver microsomes were prepared and the cytochrome P450, cytochrome b5, NADPH-cyt c-reductase and of microsomal enzyme activities, which are able to detect induction or inhibition of cytochromes P-450, were determined. Risperidone had no effect on the relative liver weights, microsomal protein content and on any of the components of the cytochrome P-450 dependent enzyme system that was investigated i.e. cytochrome P-450, cytochrome b5 or NADPH-cytochrome c-reductase.

2.6.4.6 Excretion

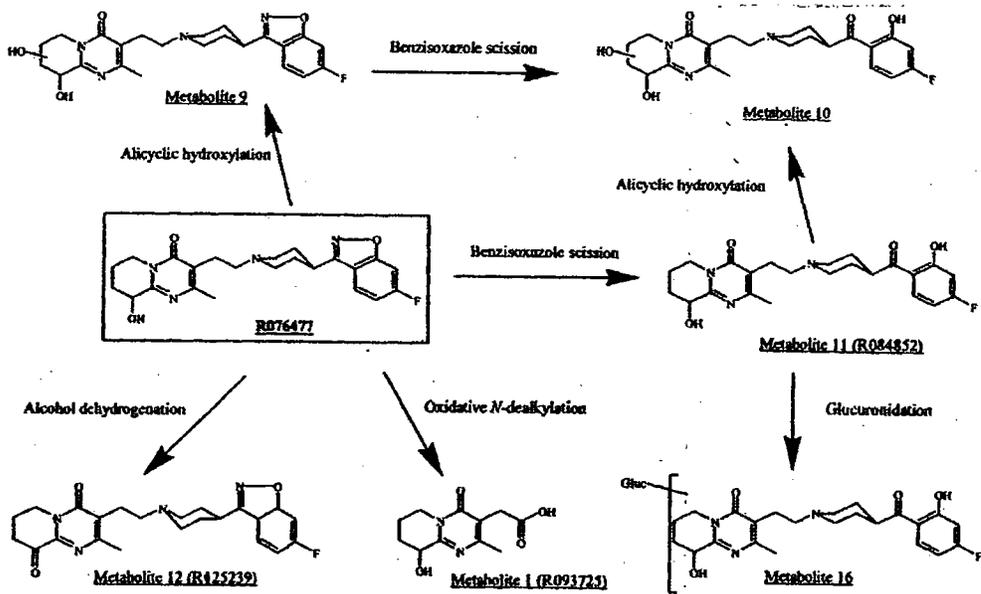
Study title: The absorption, metabolism, and excretion of paliperidone (R076477) after single oral dose of 1 mg in healthy male subjects (clinical trial R076477-P01-103) (Study No. FK4612)

(This clinical study report was the only one submitted by the sponsor under "Excretion" section of preclinical pharmacokinetics of this NDA)

Five healthy male subjects received a single oral dose of 1 mg ^{14}C -R076477 (16 μCi per subject). Urine, feces and plasma were collected up to one week after dosing. Radioactivity levels were measured by liquid scintillation counting and metabolite profile was investigated by radio-HPLC and LC-MSMS. Paliperidone was mainly excreted as unchanged drug (59.39% on average of dose) in the urine. Unchanged drug was not detected in feces. After one week, the radioactivity was mainly excreted in urine (79.63% of the dose) and to a lesser extent in feces (11.44%). Paliperidone was metabolized to only a limited extent. **In urine**, biotransformation of the drug occurred through oxidative N-dealkylation (formation of acid metabolite 1 - R093725; accounted for 4.55% of the dose in urine), mono-hydroxylation of the alicyclic ring (formation of metabolite 9 - accounted for 3.75% of the dose), alcohol dehydrogenation (formation of the ketone metabolite 12 - R125239; accounted for 2.74% of the dose in urine) and benzisoxazole scission (formation of metabolite 11 - R084852; accounted for 4.06% of the dose in urine) in combination (or not) with glucuronidation (metabolite 16) or alicyclic hydroxylation (metabolite 10). **In feces**, two metabolites (10 and 11) were present in extracts of each subject. The unidentified third metabolite was found in feces of the single subject. Each of the fecal metabolites accounted for about 0.4 -0.9% of the dose.

The structures of the identified paliperidone metabolites are shown below:

Figure 5-15: Metabolic pathways of ^{14}C -R076477 as detected after administration of a single oral dose of 1 mg to healthy male adult subjects.



One of the objectives of this study was to compare the metabolite profile of paliperidone in man with that of riperidone. Two new metabolites of paliperidone were identified in this study, likely due to more sophisticated analysis technology used at this time. Two new metabolites of paliperidone included the ketone metabolite 12 (R125239) and

metabolite 16, identified as the glucuronide of the benzisoxazole splitted metabolite R084852. According to the sponsor, these two metabolites were maybe present in samples of the previous risperidone study, but might not have been adequately identified.

In order to make a comparison of the metabolite profile of paliperidone with that of risperidone, urine samples obtained from a clinical study with risperidone in Japanese and Caucasian healthy subjects were analyzed (Study R064766 RISOP01-101). The presence of parent paliperidone and of its metabolites 1, 16, 9 and 12 in the urine samples was confirmed. In conclusion, the metabolites which were detected in humans after a single oral dose of 1 mg ^{14}C -paliperidone, were also found after oral dosing with risperidone.

2.6.4.7 Pharmacokinetic drug interactions

Paliperidone had no or only slight inhibitory effect on the major cytochrome P-450 activities. Paliperidone was also shown to be a P-gp substrate. Studies addressing pharmacokinetic drug interaction issues can be found under Metabolism section of this review (Studies No. 3, 4 and 6 on page 62, 63 and 64, respectively)

2.6.4.8 Other Pharmacokinetic Studies

Toxicokinetic studies: see under individual toxicity study reviews

2.6.4.9 Discussion and Conclusions

The majority of pharmacokinetic data were generated as toxicokinetic measurements in toxicology studies. Exposure to paliperidone in general increased with increasing dose without accumulation after prolonged treatment. For both paliperidone enantiomers, similar elimination half-lives ($t_{1/2}$) were estimated (in males only) after dosing with both compounds that ranged from 1.2 to 2.3 hours. Bioavailability of paliperidone after p.o. solution administration in dogs was high (94%). The p.o. availability in rats was not assessed. The sponsor estimated the F_{abs} value at 46% in male rats and 78% in female rats by comparison of data from separate studies. However, the relative bioavailability of paliperidone following ER tablet administration was only 15% in dogs. ER tablets administered to dogs were recovered in the feces as whole units without tears, perforations or indentations. Estimated gastrointestinal transit times were between 7.7 to 45.1 hours and the average residual paliperidone was 0.46 mg (range 0.01 to 0.92 mg). The distribution of radiolabelled paliperidone was investigated in general distribution and in brain distribution studies in rats. Highest values of paliperidone derived activity were observed in liver, small intestinal tissue and salivary gland. In all non melanin containing tissues, the radioactivity declined in parallel to plasma concentrations. In melanin-containing tissues (eyeballs and pigmented skin and fur) there was an extensive retention of paliperidone-related radioactivity up to the last time point measured (336 h). Paliperidone was also well absorbed after subcutaneous administration. Maximum plasma concentrations were observed at 0.5 h after administration. Plasma levels of paliperidone rapidly decline with a half life of 2.3 h. Brain concentrations of unchanged drug (UD) and non-volatile radioactivity rapidly increased after subcutaneous

administration. Peak levels of UD were observed at 0.5 h in cerebellum, at 1 h in rest of brain and frontal cortex, and at 4 h in striatum. In frontal cortex and striatum, brain regions with high concentrations of 5-HT₂ or D₂ receptor, C_{max}, T_{max} and AUCs and half-lives of paliperidone were higher than in cerebellum, a region with few of these receptor binding sites. In vivo mass balance studies with radiolabelled paliperidone in rats, dogs, and humans indicated that the major biotransformation pathways in vivo and in vitro and across the species are the same. Paliperidone metabolism was extensive in vivo in rats and less extensive in dogs and humans. The amount recovered as unchanged drug was 3.19% and 6.42% in rats, 32.4% in dogs and 59.4% in humans. Individual metabolites each accounted for 3-5% of the administered dose. The metabolites observed following risperidone administration of paliperidone have also been observed following risperidone administration. All metabolites observed in humans were also observed in at least one of the toxicological species. In dogs and humans, paliperidone-related radioactivity was excreted mainly in urine; in rats with the feces. In humans, the cumulative excretion in the urine was ~80% of the dose.

2.6.4.10 Tables and figures to include comparative TK summary

Tables provided by the sponsor are long and therefore not suitable for this review. The most important tabulated data can be found within review of the individual study reports.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Tables provided by the sponsor are long and therefore not suitable for this review. The most important tabulated data can be found within review of the individual study reports.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

The nonclinical toxicity profile of paliperidone has been characterized in single-dose toxicity studies and repeat-dose toxicity studies. A 12-month repeat-dose toxicity study in dogs was not performed with paliperidone; this study was bridged to a study previously conducted with risperidone. Some of the repeat-dose paliperidone toxicity studies also included risperidone to allow a direct comparison between the two test articles. Most toxicity studies were conducted with immediate release formulations for p.o. administration (aqueous solution) while some employed other formulation (diet, powder in gelatin capsules, i.v. solutions). According to the sponsor, these modes of administration were selected in order to maximize systemic exposure, which is not achievable upon p.o. administration of paliperidone ER tablets in dogs nor dietary administration of paliperidone in rodents. A 3-month repeat-dose toxicity study with paliperidone ER tablets was conducted only in dogs. The administration of paliperidone ER tablets is not feasible in rats and mice because of the dimensions of the tablet too large compared with the diameter of the GI tract in rodents.

The following toxicity studies were carried out with paliperidone during the development of paliperidone:

Single dose studies:

1. Single Dose Oral Toxicity Study in the SPF Albino Swiss Mouse (study No. 4892) with paliperidone at 0, 20, 40, or 80 mg/kg
2. Single Dose Intravenous Toxicity Study in the SPF Albino Swiss Mouse (study No. 4893) with paliperidone at 0, 10, 20, or 40 mg/kg
3. The Acute Oral Toxicity of R76477, the Major and Active Metabolite of the Antipsychotic Risperidone in Rats (study No. 2651) (Wistar Wiga rats) with paliperidone at 0, 20, 40, 80 or 160 mg/kg
4. Single Dose Intravenous Toxicity Study in the Wistar Rat (study No. 4894) with paliperidone at 0, 10, 20, or 40 mg/kg

Summary of results:

No mortality was observed in the single p.o. dose study in mice and in the single i.v. dose study in rats. Deaths occurred in mice dosed i.v. at 20 mg/kg or higher doses, as well as in rats dosed p.o. at 40 mg/kg or higher doses. In the single-dose p.o. and i.v. toxicity studies in rats and mice, CNS-related effects were seen, mainly sedation and ptosis. Catalepsy, clonic convulsions, hypotonia, hypothermia, prostration and tremors were observed in rats at very high p.o. doses of paliperidone. Gross pathology examination did not reveal any changes in tissues or organs in mice. In rats, orally dosed paliperidone showed petechia and vibices in the glandular stomach at very high dose levels.

Repeat dose studies:

DOGS:

1. 2-Week Repeated Dose Intravenous Toxicity Study in the Beagle Dog (Study No. TOX 6193)
2. One-Month Toxicity Study in Beagle Dogs (Study No. TOX 2850)
3. Toxicokinetics of paliperidone in One-Month Toxicity Study in Beagle Dogs (Study No. R76477/FK1402).
4. Three Month Repeated Dose Oral Toxicity Study in the Beagle Dog (Study No. 4604)
5. Toxicokinetic and Tissue Distribution of Paliperidone and of Risperidone in the Beagle Dog in a Three Month Repeated Dose Oral Toxicity Study (Study No. FK2931).

6. 3-Month Repeated Dose Oral Toxicity Study in the Beagle Dog
(Study No. TOX 6488) – study of GI tolerability of ER formulation

Summary of results:

In the pivotal study entitled, Three Month Repeated Dose Oral Toxicity Study in the Beagle Dog (Study No. 4604) the toxicity of paliperidone was assessed upon administration once daily by gavage at 0, 0.31, 1.25, or 5 mg/kg/day. A reference group, in which risperidone was administered at 5 mg/kg/day, was included. This comparative study was carried out with immediate release formulations for p.o. administration (i.e. aqueous solution). This mode of administration was selected to maximize systemic exposure, which was not achievable upon p.o. administration of paliperidone ER tablets in dogs. Administration of paliperidone to dogs resulted in a dose-dependent sedation at all dose levels. Salivation on the first day and tremors on the second day and an increased incidence of soft feces were also seen in the 5 mg/kg/day group. After administration of risperidone at 5 mg/kg/day, the presence of sedation was comparable to that after administration of paliperidone. However, the increased incidence of soft feces was seen only in dogs administered paliperidone (but not risperidone) at 5 mg/kg/day. Administration of paliperidone and risperidone resulted in transient, dose dependent decreases in body weight gain during the first three to four weeks of dosing in all dose groups. Body weight was comparable with the vehicle group in all paliperidone and risperidone groups afterwards. Body weight gain was slightly increased in animals administered paliperidone at 5 mg/kg/day in the last five weeks of dosing. However, body weight gain in the risperidone group was unchanged. Food consumption was transiently decreased during the first week of dosing in all treated groups, including the risperidone group. Dosing with paliperidone at 1.25 and 5 mg/kg/day and with risperidone at 5 mg/kg/day resulted in slight decreases in PQ and QT intervals and in an increase in heart rate. A slight increase in QTc interval was also noted in the 5 mg/kg paliperidone and risperidone groups. Treatment with paliperidone and risperidone at 5 mg/kg/day resulted in decreased hematocrit, hemoglobin and red blood cells count. Cholesterol was slightly increased in dogs administered paliperidone at 1.25 and 5 mg/kg and risperidone at 5 mg/kg/day. Paliperidone increased serum prolactin levels in male and female dogs at all dose levels tested. At higher doses, paliperidone elevated serum prolactin levels in males were higher (up to ~ 2-fold) than than prolactin levels increased by risperidone at 5 mg/kg/day. However, in females, prolactin levels were slightly lower at all doses of paliperidone than at 5 mg/kg/day of risperidone. Small prostate was seen macroscopically in all treatment groups. The most important findings in organ weights are the decreased prostate and increased spleen weight. Administration of paliperidone at all dose levels and risperidone resulted in histopathological changes in the ovaries, uterus, vagina, prostate and spleen. Changes in the reproductive organs are likely due to the interference of the test articles with prolactin and were described as a resting aspect. Prostate showed atrophy with decrease in glandular development. The increase in accumulation of red blood cells in the splenic red pulp is, according to the sponsor, due to their α -lytic effect of paliperidone and risperidone. At the dose of 5 mg/kg/day, the systemic exposure to pliperidone in paliperidone-treated dogs was slightly higher than the exposure to paliperidone in risperidone treated dogs. **The oral toxicity profile of**

paliperidone was qualitatively and quantitatively comparable with that of risperidone.

Findings in the i.v. paliperidone study (Study No. TOX 6193; doses of 0, 0.31, 1.25, or 5 mg/kg/day) in dogs were generally similar. In addition, at all dose levels white blood cells, reticulocytes, neutrophils and lymphocytes were decreased. Moreover, changes in testes and epididymides were found. Males showed a bilateral increase in the number (slight or moderate severity) of multinucleate spermatogenic cells in the somniferous tubules of the testes. These findings were noted in the epididymides which showed abnormal spermatogenic cells (slight or moderate) and a reduced number of spermatozoa in the ducts. In one of these dogs, a slight degree of degeneration/atrophy of the germinal epithelium in the testes was noted. According to the sponsor, the toxicological significance of these findings is unclear. However, they may represent the early stages of the test article related-changes in the germinal epithelium.

The second 3-month study in dogs was specifically designed to address the gastrointestinal tolerability of the 15-mg paliperidone ER tablet, the highest dose tested clinically. A much lower exposure was observed following administration of the OROS formulation at 90 mg/dog/day relative to the bulk powder at 60 mg/dog/day. However, the toxicity profile observed between animals dosed with tablets and with bulk powder was similar. At high dose levels, a 3-month repeated-dose study with paliperidone ER tablets demonstrated a relatively low exposure compared to p.o. solutions or capsules in other studies. The most important toxicological findings included sedation, tremors, a narrowed palpebral fissure, a slight increase in QTc intervals in females in all groups, swollen spleen, increase in spleen weight, decrease in the weight of the testes and prostate in males, a moderate decrease in the weight of ovaries in females, an increase in red blood cells, noted as "congestion", in the splenic red pulp in both sexes, a delay in sexual maturation and a decrease in mammary glandular development in females and a delay in prostate development or maturation in male dogs. There were no adverse histopathology observations in the gastrointestinal tract of dogs. Histopathological examinations and clinical signs did not indicate differences in gastrointestinal tolerability between dogs dosed with two formulations of paliperidone.

There were no other toxicologically significant findings in other toxicity studies in dogs.

RATS

1. 2-Week Repeated Dose Intravenous Toxicity Study in the Rat (Study No. TOX 6192)
2. 6-Month Repeated Dose Oral Toxicity Study in the Rat (Study No. TOX 5708)
3. One-Month Toxicity Study in SPF Wistar Rats (Study No. 2849)
4. Toxicokinetics of paliperidone and risperidone rats in the One-Month Toxicity Study in SPF Wistar Rats (Study No. R 76477/FK1399)

5. 3-Month Repeated Dose Oral Toxicity Study in the Rat (Study No. TOX 6343)
(gavage administration)

6. Three-Month Repeated Dose Oral Toxicity Study in the Wistar Rat (Study No. 4603)
(diet administration)

7. Toxicokinetics of paliperidone and risperidone in the Three-Month Repeated Dose Oral Toxicity Study in the Wistar Rats (Study No. FK2930)

Summary of results:

The 6-Month Repeated Dose Oral Toxicity Study in the Rat (Study No. TOX 5708) was designed as a comparative study of the longest duration. Paliperidone was administered once daily by the oral route (gavage) at 0, 0.63, 2.5 or 10 mg/kg/day to rats and its toxicity was compared with the toxicity of risperidone administered at 10 mg/kg/day. In this study, the toxicokinetics of paliperidone and risperidone was studied as well. The following clinical signs were observed in animals administered paliperidone or risperidone: ptosis, soft feces, sedation, hyperreactivity to touch, and vasodilatation. These signs were observed in the majority of all treated animals and their intensity increased in a dose-dependent manner. Daily oral dosing of paliperidone and risperidone at 10 mg/kg/day resulted in comparable observations of clinical signs. Body weights and body weight gains were moderately decreased in male rats administered paliperidone at 2.5 mg/kg and markedly decreased in males administered paliperidone and risperidone at 10 mg/kg/day. Therefore, the MTD was achieved for males. In females administered paliperidone at 0.63 or 2.5 mg/kg/day, body weight and body weight gain were slightly increased. There were no changes at 10 mg/kg/day when compared to the control values. Therefore, it is not clear whether the MTD was achieved in female rats. However, this reviewer considers this study minimally acceptable because the main purpose was to compare the toxicological profile of paliperidone and risperidone. Changes in body weights in rats administered paliperidone and risperidone were very similar. Food consumption was slightly decreased in males administered paliperidone and risperidone at 10 mg/kg/day and increased in females in all treatment groups (with the higher increases at the lowest dose levels). Changes in food consumption paralleled in general changes in body weights. Slight to moderate increases in hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were present in males and slight to moderate increases in the number of red blood cells, hemoglobin, hematocrit and in the number of white blood cells, neutrophils, lymphocytes, monocytes and eosinophils were noted in females treated with paliperidone or risperidone at all dose levels (except few parameters unchanged at 0.63 mg/kg/day). The most pronounced changes in clinical chemistry parameters noted in Week 27 of dosing at all dose levels included decreases in sodium and triglycerides and increases in albumin and creatinine in males, as well as increases in potassium, calcium, inorganic phosphorus and triglycerides, and decreases in glucose and creatinine in females. Gross pathology observations indicated yellow or dark stippled prostates in male rats and mammary gland stimulation and uterine changes indicating decreased cyclic activity in

female rats at all dose levels. An increased liver weight and weight of the gonads were seen in females. An increased weight of the adrenals was noted in males.

The following neoplastic lesions were observed in rats administered paliperidone: (1) a small Harderian gland adenoma in one male rat at 10 mg/kg/day, (2) a small hepatocytic adenoma in one female rat at 2.5 mg/kg/day, and (3) an incipient mammary fibroadenoma in one female rat at 10 mg/kg/day. These findings are considered to be incidental. The following toxicologically important non-neoplastic lesions were observed at all dose levels: a dose related increase in glandular development associated with the presence of secretion in the female mammary gland; a female appearance, characterized by tubular transformation of the acini in the male mammary gland; an increased incidence of pseudopregnancy-status in female reproductive tract (ovaries, oviduct, uterus, cervix, vagina), and prostate inflammation. An increase in amount of red blood cells in the splenic red pulp in most male and female rats and a minimal diffuse swelling of cells of the adrenocortical zona fasciculata in male rats dosed with paliperidone and risperidone at 10 mg/kg/day were observed. In addition, analysis of blood samples taken on Day 178 showed a clear increase in prolactin levels, reaching peak values at 0.5 h and declining gradually over 24 hours. Overall, it can be concluded that there was no difference in toxicity profile between paliperidone and risperidone in rats dosed orally for 6 months at 10 mg/kg/day.

Two additional comparative toxicity studies were conducted with paliperidone and risperidone: One-Month Toxicity Study in SPF Wistar Rats (Study No. 2849) and Three-Month Repeated Dose Oral Toxicity Study in the Wistar Rat (Study No. 4603):

The purpose of the one-month pilot (non-GLP) toxicity study in Wistar rats (Study No. 2849) was to assess the potential toxicity of paliperidone (aqueous solution) when administered orally by gavage to SPF Wistar rats (5/sex/group) at doses of 0, 0.63, 2.5 and 10 mg/kg/day for one month. An additional group received risperidone at 10 mg/kg/day by p.o. gavage for comparative purposes. A slight sedation evidenced by ptosis was noted at 0.63 mg/kg/day and more pronounced sedation was noted at 2.5 and 10 mg/kg/day. Clinical signs observed with paliperidone were similar to those observed with risperidone. Body weight and body weight gain were slightly increased in females at 0.63 mg/kg/day. There were no changes in males at this dose. At 2.5 and 10 mg paliperidone/kg/day, a slight to moderate decrease was noted in males, while in females, body weight was less affected. In males dosed with 10 mg/kg/day of risperidone, body weight gain was also moderately decreased. In females dosed with either 10 mg/kg/day of paliperidone and risperidone, body weight was slightly decreased. Body weight gain was also decreased in females treated with 10 mg/kg/day of paliperidone and risperidone. The effect of risperidone was more pronounced as compared to paliperidone treated groups. Food consumption was increased in females treated at 0.63 mg/kg/day. Food consumption was also slightly reduced in males treated with risperidone at 10 mg/kg/day and to a lesser degree in females. There were no changes in other groups. Hematology parameters were not affected at 0.63 and 2.5 mg/kg/day. At 10 mg/kg/day, the following effects were observed: an increase in white blood cell count in males treated with paliperidone and a decrease in thrombocytes in male and female rats treated with

paliperidone as well as in males treated with risperidone. Blood urea nitrogen was slightly increased in males at 10 mg/kg/day of paliperidone. A slight decrease in total protein at 2.5 and 10 mg/kg/day in males and in females was noted. The following urinalysis effects were noted: a slight decrease in creatinine and in specific gravity at 2.5 and 10 mg/kg/day in males and females, and an increased appearance in bacteria at 10 mg/kg/day in males and to a lesser extent in females. Gross pathology revealed an increased incidence of mammary gland stimulation in female rats at all dose levels of paliperidone and in risperidone-treated females. A decrease in the weight of ovaries was noted in all paliperidone and risperidone dosed groups. Histopathology was not conducted. In conclusion, findings in the paliperidone and risperidone-treated groups were similar. Moreover, observations in this study were generally similar to these in the 6-month study in rats, although they were less pronounced, likely due to shorter duration of the study.

In the Three-Month Repeated Dose Oral Toxicity Study in the Wistar Rat (Study No. 4603) paliperidone was administered by gavage at 0, 0.63, 2.5 and 10 mg/kg/day. In addition, risperidone was administered at 10 mg/kg/day. Ptosis and sedation (up to moderate level) was observed in all test-article treated groups. Hematocrit, hemoglobin and white blood cell parameters were slightly increased in males and females after 13 weeks of treatment. There were only slight changes in clinical chemistry parameters. A slight decrease in specific gravity of the urine was noted in both sexes. Gross pathology indicated stimulation of the female mammary glands at all dose levels. Changes in organ weights (absolute and relative to body) were slight and included slight increases in the adrenals weight in males and slight decreases in the liver, reproductive organs and thymus weights in females. Mean serum prolactin levels were markedly increased in both sexes at all dose levels. Test article-dependent histopathological changes were observed in the mammary gland (increased alveolar development and secretion in females and female aspect in males), prostate (focal interstitial fibrosis, granulocytes, round cells and focal tubuli with granulocytes in dorsolateral prostate), pituitary gland (increase in prolactin-immuno positive cells in males and females and erythrosinophils in the adenohypophysis in males) and female reproductive tract (reduced cyclic activity with a tendency to pseudopregnancy, including increased amount and clear aspect of the interstitial tissue and decreased corpora lutea in the ovaries; decrease in granulocytes in the endometrium and decreased vacuolated/karyorrhectic cells in the epithelium of the uterus; increased mucification, increased number of necrotic epithelial cells and decreased thickness of the epithelium of the vagina) at all dose levels of paliperidone (mainly 2.5 and 10 mg/kg/day) and risperidone. At 10 mg/kg/day of paliperidone or risperidone, male animals showed low epithelium of the coagulating glands (this effect was slight at 2.5 mg/kg/day) and seminal vesicles. In the splenic red pulp, increases in red blood cells and hemosiderin pigment were observed at 10 mg/kg/day of paliperidone and risperidone in males and females. Swollen cortical cells of the zona fasciculata were noted in adrenal glands of male rats at all dose levels of paliperidone and risperidone. There were no histopathology changes in pancreas after treatment with paliperidone and risperidone (endocrine pancreas adenomas were seen in carcinogenicity studies in male rats after treatment with risperidone). According to the sponsor, the findings in the dorsolateral prostate, the coagulating glands and female reproductive tract are considered

prolactin related. The increase in accumulation in red blood cells in association with the increase in hemosidrin pigment in the splenic red pulp are, according to the sponsor, due to the α -lytic effect of the test articles. There were no differences in histopathology findings in rats administered paliperidone or risperidone at 10 mg/kg/day.

Other toxicity studies conducted with paliperidone (but not risperidone) included the 2-Week Repeated Dose Intravenous Toxicity Study in the Rat (Study No. TOX 6192) and 3-Month Repeated Dose Oral Toxicity Study in the Rat (Study No. TOX 6343)

The purpose of the i.v. study was to assess the toxicity of paliperidone at dose levels of 0, 0.63, 2.5 and 10 mg/kg/day when administered once daily by intravenous route over 30 minutes to Sprague-Dawley rats for a period of 2 consecutive weeks. Intravenously administered paliperidone in rats revealed no new target organs of toxicity other than those already identified following p.o. administration i.e. mainly CNS and reproductive organs. NOAEL was determined to be 0.63 mg/kg/day for both sexes in this study.

The purpose of the second 3-month study of paliperidone in rats was to assess the potential toxicity of paliperidone when administered daily by the oral route (through the diet) to Sprague-Dawley rats at doses of 0, 1.25, 5 and 20 mg/kg/day. This study was a dose range finding study in order to determine the dose for the carcinogenicity study and was not intended to be in full compliance with GLP regulations. Findings in general were similar to those from other toxicity studies in rats. Histopathological examination revealed prolactin-mediated changes in the female genital tract (ovaries, oviduct, uterus, cervix, vagina), the mammary glands of both sexes and the prostate in rats administered paliperidone at all dose levels. In addition, at 20 mg/kg/day a tendency for an increase in the amount of red blood cells in the splenic red pulp in male rats was noted. Changes in the female reproductive organs at all doses reflected a reduced cyclic activity, with a dose-related increase in pseudopregnancy and are considered prolactin-related. Changes in ovaries included increased incidence of prominent clear-appearing interstitial tissue, increased severity of atretic follicles, and decreased incidence of basophilic corpora lutea. Changes in the uterus included mainly decreased incidence of infiltrating granulocytes. Changes in the vagina included increased frequency of mucified aspect and decreased thickness of the epithelial layer. Histological changes in the mammary gland in dosed male and female rats included (1) female appearance in males (low epithelium with the secretion present in one high dose male rat), and (2) increase in mammary gland glandular development with secretory activity in all female paliperidone-dosed groups, and acinar hyperplasia (multifocal and/or nodular) in females administered 5 or 20 mg/kg/day. Findings in prostate included acute focal or multifocal inflammation of minimal to slight degree. In addition, in 5 and 20 mg/kg male groups, a minimally lower glandular epithelium of the coagulating glands, the seminal vesicles and the ventral prostate was observed. The target organs identified in this study were similar to these from other toxicity studies in rats.

MICE

1. 3-Month Repeated Dose Oral Toxicity Study in the Swiss Mouse (Study No. TOX 5721)
2. 2-Week Repeated Dose Oral Toxicity Study in the Mouse (Study No. TOX 6404)

Summary of results:

The purpose of the 3-Month Repeated Dose Oral Toxicity Study in the Swiss Mouse (Study No. TOX 5721) was to assess the toxicity of paliperidone when administered once daily by the oral route at 0, 0.63, 2.5 and 10 mg/kg/day and to compare its toxicity with the toxicity of risperidone at 10 mg/kg/day. The toxicokinetics was studied as well. This study was a range finding study in order to determine the dose for a carcinogenicity study. Daily oral dosing of paliperidone at 10 mg/kg/day lead to the same observations of ptosis and sedation as seen in mice dosed with risperidone at the same dose. There were slight, but not statistically significant, decreases in body weight and body weight gain in males in this study. However, a marked increase in body weight were noted in all female groups administered paliperidone or risperidone. Several red blood cells-related parameters were increased in both sexes in all paliperidone and risperidone groups. White blood cells and lymphocytes were decreased in males in all groups. Changes in clinical chemistry were of limited toxicological importance. Absolute and relative liver weight was slightly increased in female mice and the absolute and relative adrenals weights were moderately decreased. Mammary gland stimulation was the only paliperidone or risperidone-related gross pathology finding. Histopathology examination indicated several prolactin-related changes characterized as pseudopregnancy in the reproductive tract and mammary gland in all female test article-treated groups. Minimal diffuse hyperplasia was observed in the pituitary (pars intermedia) in both sexes at all dose levels. Findings in paliperidone and risperidone groups were comparable.

The purpose of 2-Week Repeated Dose Oral Toxicity Study in the Mouse (Study No. TOX 6404) was to assess the potential toxicity of paliperidone when administered daily by the oral route (through the diet) to mice at 0, 10, 20, 40, or 80 mg/kg/day. Histopathology revealed a dose-related increase in hypertrophy/hyperplasia of the pars intermedia of the pituitary gland in females at all dose levels (minimal), and in males at 40 and 80 mg/kg/day (minimal or slight). Tissue changes indicative of pseudopregnancy were observed in the female genital tract (ovaries, uterus, vagina) and mammary gland (an increased glandular development and the presence of acinar secretion) in all dosed female groups. The most prominent pseudopregnant appearance was that of the vagina (thin mucified epithelium) and a decrease in recent (basophilic) corpora lutea in the ovaries. In all female dosed groups, the spontaneous disappearance of the transient X zone of the adrenals was accelerated (according to the sponsor, the pseudopregnancy, mimicking pregnancy, has accelerated this generative spontaneous process). The NOAEL was determined to be 10 mg/kg/day for both sexes.

Margins of safety

In the repeat-dose toxicity studies with paliperidone dose selection was mainly driven by CNS effects, severe sedation being considered as dose-limiting toxicity by the sponsor. Test article-related clinical signs were frequently seen already at the lowest dose level tested. Therefore, the NOELs could not be established for most studies. However, the NOAELs were established. The sponsor acknowledged that exposure-based safety margins were generally low compared to the systemic exposure at the MRHD. However, the main toxicity findings are either species-specific or can be easily assessed in the clinic. The following sponsor's table shows exposure-based safety margins comparing the mean AUC_{0-24h} – and C_{max}-values obtained in the animal studies at the NOAEL to the mean AUC_{0-24h}- and C_{max}- value of 869 ng.h/ml and 46 ng/ml, respectively achieved in humans treated with paliperidone ER tablets at the MRHD of 12 mg/day:

Table 2: NOAELs and Exposure-Based Safety Margins in Repeat-Dose Toxicity Studies with Paliperidone

Species	Duration	Route	Sex	NOAEL (mg/kg/day)	NOAEL (mg/m ² /day)	Mean AUC _{0-24h} (ng.h/mL)	AUC _{0-24h} Based Safety Margin	Mean C _{max} (ng/mL)	C _{max} Based Safety Margin	Study ID No.
Mouse	2 weeks	p.o. (diet)	M	10	30	3203	4x	187	4x	18
			F	10	30	2664	3x	159	3x	
Mouse	3 months	p.o. (gavage)	M	< 0.63	< 1.9	n.a.	n.a.	n.a.	n.a.	12
			F	< 0.63	< 1.9	n.a.	n.a.	n.a.	n.a.	
Rat	1 month	p.o. (gavage)	M	0.63	3.8	378	0.4x	98	2x	16, 56
			F	0.63	3.8	350	0.4x	99	2x	
Rat	3 months	p.o. (diet)	M	1.25	7.5	556	0.6x	33.3	0.7x	17
			F	5	30	4910	5x	325	7x	
Rat	3 months	p.o. (gavage)	M	0.63	3.8	595	0.7	136	3x	9, 57
			F	0.63	3.8	346	0.4x	93	2x	
Rat	6 months	p.o. (gavage)	M	0.63	3.8	512	0.6x	212	5x	9
			F	0.63	3.8	965	1.1x	251	5x	
Rat	2 weeks	i.v. (30-minute infusion)	M	0.63	3.8	490	0.5x	n.d.	n.d.	15
			F	0.63	3.8	786	0.9x	n.d.	n.d.	
Dog	1 month	p.o. (capsules)	M	1.25	25	15100	17x	1310	28x	31, 58
			F	1.25	25	15100	17x	1310	28x	
Dog	3 months	p.o. (gavage)	M	0.31	6.2	1747*	2x	153*	3x	19, 59
			F	0.31	6.2	2336*	3x	213*	5x	
Dog	3 months	p.o. (ER tablets in capsules)	M	< 30	< 37	n.a.	n.a.	n.a.	n.a.	20
			F	< 30	< 37	n.a.	n.a.	n.a.	n.a.	
Dog	2 weeks	i.v. (30-minute infusion)	M	< 0.31	6.2	n.a.	n.a.	n.d.	n.d.	26
			F	< 0.31	6.2	n.a.	n.a.	n.d.	n.d.	

* means of individual values presented in study report

ID = identification; p.o. = oral; M = male; F = female; n.a. = not applicable; i.v. = intravenous; n.d. = not determined

Genetic toxicology:

Risperidone showed no genotoxic properties in a series of genotoxicity studies conducted to support the registration of risperidone (Risperdal®). Paliperidone was tested in a full battery of genotoxicity studies, including bacterial reverse mutation assays, in vitro

mouse lymphoma assays and in vivo rat micronucleus assay, and showed no genotoxic properties.

The aim of the first study entitled In Vitro Bacterial Reverse Mutation Test with Salmonella typhimurium (Ames test) was to evaluate paliperidone and/or its metabolites for their ability to induce reverse mutations in a gene of histidine-requiring Salmonella typhimurium strain to produce a histidine-independent strain of these bacteria, in the absence and in the presence of a mammalian metabolic activation system. The strains used in this study were able to detect base pair substitutions and frame-shift mutations. Paliperidone did not cause any biologically significant increase in the number of revertant colonies above the solvent control incidence in all of the strains tested either with or without metabolic activation. Therefore, it was concluded that paliperidone was not mutagenic under conditions of this study. This first Ames test was negative at paliperidone concentrations ranging from 5 to 500 µg/plate. However, there was neither precipitation of the test compound nor evidence of cytotoxicity in this study.

Therefore, the sponsor conducted the second Ames study with paliperidone concentrations ranging from 78.13 to 5000 µg/plate, entitled In Vitro Bacterial Reverse Mutation Test with Salmonella typhimurium. Paliperidone did not cause any biologically significant increase in the number of revertant colonies above the vehicle control incidence with all of the strains. At 5000 µg/plate, precipitation was observed. Therefore, it was concluded that paliperidone has no mutagenic properties under this test conditions up to precipitating concentrations of 5000 µg/plate.

Potential genotoxicity of paliperidone was also tested in In Vitro Mammalian Forward Mutation Test with L5178Y Mouse Lymphoma Cells (TK-locus) Using the Microtitre Fluctuation Technique at concentrations ranging from 10 to 150 µg/ml. The purpose of this study was to assess in vitro the mutagenic potential of paliperidone and/or its metabolites by their ability to induce forward mutations at the thymidine kinase locus in mouse lymphoma L5178Y cells, with and without the addition of a mammalian metabolic activation system. No biologically significant induction in mutation frequency was observed either in the absence or in the presence of a metabolic activation system. Therefore, paliperidone had no mutagenic properties towards the L5178Y cells under conditions of this study.

In the second mouse lymphoma assay, entitled R076477: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the Microtitre Fluctuation Technique higher paliperidone concentrations ranging from 37.5 to 570 µg/ml were tested. The objective of this study was to evaluate the mutagenic activity of paliperidone by examining its ability to induce TK mutations in L5178Y cells in the absence and the presence of a rat liver metabolizing system (S-9). In addition to the final report for this study, the sponsor submitted the [REDACTED] Memo dated May 12, 2004. In this memo, [REDACTED] addressed the solubility of paliperidone in the mouse lymphoma assay. It was concluded that the solubility issue could not allow higher concentrations to be tested in this or in an alternative in vitro mammalian cell genotoxicity test. The study consisted of a cytotoxicity range finding experiment followed by three independent experiments. A very weak (1.49 fold) mutagenic response

was demonstrated at a single, highly toxic dose on one occasion of testing after 3 hour treatment without metabolic activation. Overall, this was not considered biologically relevant. In addition, a mutagenic response was observed in one out of three experiments in the presence of S-9 following 3-hour treatment with 3 concentrations. The increases in mutant frequency were 1.70 to 1.77 fold. However, no increases in mutant frequency were observed following 3-hour treatments in two additional experiments when tested at the same or very similar concentrations. Paliperidone was also tested after 24 hour treatment. The results were clearly negative. However, the top dose tested yielded only 41% of RTG. Therefore, in the opinion of this reviewer, the sponsor should have used higher concentrations in this study. However, it was also taken into consideration that a range finding study indicated extreme toxicity at higher concentrations. Based on overall results and the weight of evidence approach, it can be concluded that paliperidone was not mutagenic in this study.

The battery of genotoxicity tests included also in vivo study entitled R076477: Induction of Micronuclei in the Bone Marrow of Treated Rats. The objective of this study was to evaluate the clastogenicity/aneugenicity in vivo by examining micronuclei in the polychromatic erythrocytes (PCE) of rat bone marrow. In addition, analysis of plasma samples from satellite animals was used to assess in vivo exposure to the test compound. Treatment with paliperidone did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats up to 40 mg/kg p.o., a dose at which clinical signs of toxicity were observed and blood plasma analysis demonstrated systemic exposure. Therefore, paliperidone was not genotoxic in this study. In addition to the final report for study TOX6094, the sponsor submitted the [REDACTED] Memo dated 29 April, 2004. In this memo, [REDACTED] addressed the dose selection for the micronucleus assay. According to this document, in a range finding study, the clinical signs of toxicity and the substantial loss of body temperature observed at 160 mg/kg were considered sufficient evidence that this dose level exceeded the maximum tolerated dose for this test compound. Doses of 80 and 120 mg/kg resulted also in severe clinical signs and loss of body temperature. Therefore, 40 mg/kg was selected as the maximum tolerated dose and was chosen as the maximum dose level for the main micronucleus test. During the review of the IND 65850, the sponsor was asked by the Agency to ensure that the micronucleus study was conducted at the highest possible dose. Based on subsequently reviewed information, the Agency agreed that the highest tolerated dose in the paliperidone rat micronucleus assay was 40 mg/kg/day. Therefore, there was no need to repeat the micronucleus assay (see Dr. Sonia Tabacova's Addendum to pharmacology/toxicology memorandum of March 29, 2005, dated August 3, 2005, Serial No. 119 for further details).

Carcinogenicity:

No mouse or rat carcinogenicity studies with p.o. paliperidone were conducted. The sponsor requested a waiver because the carcinogenetic potential of paliperidone in rodents was characterized in rat and mouse carcinogenicty studies with risperidone. The sponsor's rationale for this approach is discussed on page 144 of this review followed by

conclusions from Dr. Freed's review of carcinogenicity studies with risperidone in mice and rats.

Reproductive toxicology:

Paliperidone was tested in a series of reproduction toxicity studies including male and female rat fertility and early embryonic developmental toxicity studies, rat and rabbit embryo-fetal developmental toxicity studies (including a rabbit dose-ranging study), a combined pre- and postnatal dose-ranging developmental toxicity and juvenile toxicity study in rats, and pre- and postnatal developmental toxicity study in rats.

The objective of Male Fertility Study in the Rat was to investigate any potential effects of paliperidone on male fertility in rats administered paliperidone (0, 0.16, 0.63 and 2.5 mg/kg/day) by p.o. gavage for 63 days prior to pairing, during pairing with untreated females and until termination in Week 13. 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 Weeks 1 to 5. Partially closed eyes were recorded from Weeks 2 to 13. Absolute epididymides weights were 6% lower than those of controls. In rats dosed at 2.5 mg/kg/day, clinical observations were similar as those at 0.63 mg/kg, and were recorded from Weeks 1 to 13 (subdued behavior or decreased activity) and Weeks 2 to 13 (both eyes partially closed). Absolute terminal body weights were moderately decreased (up to 6% lower than control). Food utilization was slightly reduced in Weeks 5 to 9 and overall. Absolute epididymides weights were 7% lower than those of controls. This finding was clearly not associated with any functional impairment and was considered not to be toxicologically significant. There were no effects on pre-coital interval. There were no effects on male fertility at any of the dose levels tested. There were no other test article related changes. Due to the lack of effects on male fertility, sperm parameters were not tested.

The objective of the Oral Female Fertility Study in the Rat was to investigate any potential effects of paliperidone (0, 0.16, 0.63 and 2.5 mg/kg/day) on female fertility and reproductive performance. Female rats were dosed for 14 days prior to pairing, during pairing (with undosed males) and up to Day 7 of pregnancy. The dose of 0.16 mg/kg was the NOAEL for fertility and reproductive capacity for female rats. At 0.63 mg/kg/day, maternal toxicity was slight in females as evidenced by ptosis, slightly decreased body weight gain during pregnancy, and decreased maternal corrected weight gain. During the pre-pairing period, increased body weight gain and food consumption was noted. The pre-coital interval was increased from 3 (control) to 11 days, likely due to a 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 and fertility rates and pregnancy parameters remained unaffected by treatment with paliperidone at this dose. In females receiving 2.5 mg/kg/day, ptosis, lacrimation, increases in food consumption during the first week of treatment, and a slight reduction in food intake during pregnancy were noted. Body weight and body weight gain were significantly increased during the first week of the treatment but they returned to control levels at the

end of the pre-pairing period due to decreased body weight gain during the second week of the treatment. During pregnancy, body weight gain was decreased in females administered 0.63 and 2.5 mg/kg/day. Moreover, the corrected maternal weight gain was decreased at these dose levels. 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 post-implantation loss (23% versus 14% in control group and 14% versus 8% in control group, respectively) resulting in decreases in the number of implantations (-13%) and live fetuses (-16%) as expressed per pregnant female, and lower weights of the gravid uterus.

Embryo-fetal development was investigated in the Oral Developmental Toxicity Study in the Rat. The purpose of this study was to assess the potential effects of paliperidone (0, 0.63, 2.5 and 10 mg/kg/day) on maternal condition and embryo-fetal development in rats administered paliperidone p.o. from gestation Day 6 through 17. Ptosis was seen at all dose levels. Sedation was noted at 2.5 mg/kg/day and above. Food consumption, body weight gain and corrected mean maternal weight gain were slightly to moderately decreased at 2.5 mg/kg/day and above. Even at maternally toxic dose levels, there were no relevant changes at external, visceral and skeletal examination in the fetuses. There were no other pregnancy, litter and fetal changes. The maternal NOAEL was considered to be 0.63 mg/kg/day. The fetal NOAEL was considered to be 10 mg/kg/day.

A dose range-finding study, entitled 13 Day Repeated Dose Oral Toxicity Study in the Pregnant Rabbit was performed. The purpose of this study was to assess the potential toxicity of paliperidone (0, 0.63, 2.5 and 10 mg/kg/day) when administered once daily from Day 6 through Day 18 of the presumed pregnancy by oral gavage to female rabbits. Dose-related sedation, ptosis and miosis were observed at all dose levels. Body weight, body weight gain and food consumption were dose-dependently decreased at all dose levels. Gross pathology findings included inspissated secretion in the mammary glands of the several rabbits of all paliperidone dosed groups. None of the rabbits was pregnant. According to the sponsor, based on the death of one rabbit that was considered to be test article-related and other data, doses for the main oral developmental toxicity in rabbits were selected as 0.31, 1.25 and 5 mg/kg/day.

In the Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage on Albino Rabbits, the effects of paliperidone (0.31, 1.25 and 5 mg/kg/day) on pregnant rabbits and on embryo-fetal development when administered by oral gavage to pregnant rabbits during the period of organogenesis were assessed. Administration during Days 6 to 18 of pregnancy revealed maternal toxicity. The maternal toxicity findings included clinical signs of sedation (lethargy) and ptosis at 1.25 mg/kg/day and above, reduced body weight gain at all dose levels, and reduced body weights and food consumption at 5 mg/kg/day. Slight post-implantation loss increase was observed at 5 mg/kg/day associated with a slight increase in the number of embryonic/fetal resorptions and fetal death. According to the sponsor, these findings are similar to those obtained in a previously conducted rabbit embryo-fetal developmental study with risperidone. No test article-related teratogenicity was seen. There were no other toxic fetal effects. The NOAEL for maternal toxicity was established as 0.31 mg/kg/day (based on lethargy seen