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 (Gavage) Pre and Post-natal Developmental Toxicity Study in the Rat. The objective of the study was to assess the effects of paliperidone (0, 0.08, 0.31 and 1.25 mg/kg/day) on embryonic, fetal and post-natal development of the rat following administration to mated females from Day 6 of gestation throughout lactation to Day 20 post-partum. The F1 generation was allowed to mature and the effects on growth, development, behavior and reproductive performance were assessed. Maternal treatment with paliperidone at 0.31 and 1.25 mg/kg/day resulted in clinical signs of partially closed eyes with decreased activity during the gestation period. At 1.25 mg/kg/day, decreased activity was observed also during the beginning of lactation. The body weight gain was slightly lower at 1.25 mg/kg/day 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. Apparently, instead of maternal toxicity parameters, reduced pup survival at 2.5 mg/kg/day (64% of survival at Day 4 of lactation versus 91% in control) in the paliperidone 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 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.

Two segment III studies were conducted with risperidone in rats during the development of Risperdal. According to the Dr. Freed's review, in the first study, female Wistar rats were administered risperidone in the diet at doses of 0, 0.31, 1.25 and 5.0 mg/kg. In the second study, rispridone was administered to female Wistar rats by gavage at doses of 0, 0.16, 0.63 and 2.5 mg/kg. The one consistent drug-related effect in these two studies was reduced pup survival rate during the first days postpartum. This effect was noted only at the high dose (5.0 mg/kg) in the first study. In the second study, this effect was noted at all dose levels (0.16-2.5 mg/kg). The reason of this discrepancy was unclear, but may be due to the differences in the route of administration between the two studies. However, toxic effects of risperidone are similar to those of paliperidone in the range-finding study.

Special toxicology:

Immunotoxicity study and studies on impurities were conducted. See page 170 of this review for more information.

2.6.6.2 Single-dose toxicity:

Four single-dose toxicity GLP-compliant studies with paliperidone were conducted in mice and rats employing oral and intravenous routes of administration:

1. **Study title:** Single Dose Oral Toxicity Study in the SPF Albino Swiss Mouse (study No. 4892)

Paliperidone was administered orally, by gavage, to mice (5/sex/group) at single dosages of 0, 20, 40, and 80 mg/kg. Parameters studied included mortality, clinical observations, body weight, body weight gain and gross pathology. All animals survived the study. Dose dependent slight to severe sedation and/or ptosis were observed at all dose levels on the date of dosing. These clinical signs had disappeared on the first, second and third day after dosing in the animals treated with 20, 40 and 80 mg/kg, respectively. In the group dosed at 80 mg/kg/day, body weight and body weight gain were slightly and transiently decreased on Day 3. No test article related macroscopic changes were seen at necropsy in any of the treatment groups.

2. **Study title:** Single Dose Intravenous Toxicity Study in the SPF Albino Swiss Mouse (study No. 4893)

Paliperidone was administered intravenously to mice (5/sex/group) at single dosages of 0, 10, 20, and 40 mg/kg. Parameters studied included mortality, clinical observations, body weight, body weight gain and gross pathology. All animals dosed at 10 mg/kg survived the study. 1/5 females dosed at 20 mg/kg, 3/5 males dosed at 40 mg/kg and 1/5 females dosed at 40 mg/kg died within 3 days after dosing. At all dose levels, moderate to severe sedation, ptosis, respiratory difficulties, hyperpnea and/or anemia were seen on the day of dosing. 2/5 females and several mice at 40 mg/kg/day were in an ill condition during the first days but later recovered. Body weight gain was transiently decreased in males dosed at 40 mg/kg. No test article related macroscopic changes were seen at necropsy in any of the treatment groups.

3. **Study title:** The Acute Oral Toxicity of R76477, the Major and Active Metabolite of the Antipsychotic Risperidone in Rats (study No. 2651)

Paliperidone was administered orally, by gavage, to Wistar Wiga rats (5/sex/group) at single dosages of 0, 20, 40, 80 or 160 mg/kg. A single dose of 320 mg/kg was also administered to an additional group of male rats. Parameters studied included mortality, clinical observations, body weight, body weight gain and gross pathology. All deaths occurred within a period of 6 days after administration of test article. 2/5 females administered 40 mg/kg died on Days 3 and 4 after dosing. 1/5 males administered 80 mg/kg died on Day 6 and 2/5 females died on Days 3 and 4 after dosing. At 160 mg/kg, 2/5 males (on Day 5) and all females (on Days 1, 2 and 3) died. All animals administered 320 mg/kg also died. Clinical observations noted at all dose levels included sedation, ptosis, catalepsy, hypotonia, hypothermia, prostration, and tremors. Clonic convulsions occurred in males at 80 mg/kg and higher dose

levels, and in females at 160 mg/kg/day. All surviving animals became normal again within 5 days after administration of paliperidone. A significant decrease in body weight and body weight gain was observed in males at ≥ 20 mg/kg and females at ≥ 80 mg/kg. Pathology observations included petechia and vibices in the glandular part of the stomach at ≥ 40 mg/kg.

4. **Study title:** Single Dose Intravenous Toxicity Study in the Wistar Rat (study No. 4894)

Paliperidone was administered intravenously to rats (5/sex/group) at single dosages of 0, 10, 20, and 40 mg/kg. Parameters studied included mortality, clinical observations, body weight, body weight gain and gross pathology. No test article-related mortalities were seen. Dose-related sedation and ptosis were noted on the day of dosing in all paliperidone-treated groups. Skin damage at the injection site was observed in several animals. A slight, transient decrease in body weight gain was present in males dosed at 40 mg/kg/day. There were no test-article related macroscopic changes except irritation at the administration site in the 40 mg/kg/day group.

2.6.6.3 Repeat-dose toxicity

REPEAT DOSE TOXICITY STUDIES IN DOGS

1. Study title: 2-Week Repeated Dose Intravenous Toxicity Study in the Beagle Dog (Study No. TOX 6193)

The purpose of this study was to assess the potential toxicity of paliperidone (lot: ZR076477EIA041, purity: 99.8%) at dose levels of 0, 0.31, 1.25, 5 mg/kg/day when administered once daily by intravenous route to beagle dogs (3/sex/group) for a period of 2 consecutive weeks. The toxicokinetics was also studied. The study was conducted by Janssen Pharmaceutica, N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium and was initiated on September 18, 2003. This study was conducted in compliance with GLP regulations (OECD) and was quality assured. Formulation: solution of paliperidone in vehicle containing tartaric acid, NaOH and NaCl for intravenous 30-minute infusion. Parameters investigated included mortality, clinical observations, ECG and heart rate, ophthalmic examination, body weight and body weight gain, food consumption, hematology, serum chemistry, urinalysis, organ weights, gross pathology, histopathology and toxicokinetics.

Results: Mortality: There was no mortality in this study. Clinical signs: Dose-dependent sedation, agitation and congested conjunctiva were observed at doses of 0.31 mg/kg and higher. The sedation was slight and occasionally moderate at 0.31 mg/kg/day and moderate and occasionally severe at 1.25 and 5 mg/kg/day. Sedation was present generally up to 6 hours after dosing. The agitation included out of normal biting and out of normal yelping at all dose levels at the time of dosing. At all dose levels ptosis, nasal discharge, lacrimation, tremors, salivation and coughing were seen. The intensity of some of these signs increased with the increasing dose. Soft feces were observed at 1.25 and 5 mg/kg/day. Body weights: Males dosed at 0.31 and 1.25 mg/kg/day, showed a slight

decrease in body weight and body weight gain. Males dosed with 5 mg/kg of paliperidone showed a slight decrease in body weight (-6%) and a moderate decrease in body weight gain. There were no changes in body weight gain in females. Food consumption: At all dose levels food consumption was moderately decreased in males (up to -20%). Ophthalmology: Ophthalmic examination showed photophobia, ptosis, and protrusion of the third eyelid at all dose levels. Conjunctival hyperemia was observed at 1.25 and 5 mg/kg/day. EKG and heart rate: Heart rate was slightly increased at all dose levels (up to 42%). There were no changes in QTc. Hematology: The following parameters were dose-dependently decreased in both sexes: At all dose levels, white blood cells, the number and percentage of reticulocytes, and neutrophils were decreased. These decreases were slight to moderate. Lymphocytes were slightly decreased in the 1.25 and 5 mg/kg/day groups. Red blood cells, hemoglobin and hematocrit were slightly to moderately decreased in the 5 mg/kg/day group. Serum chemistry: A marginal decreases in triglycerides and a marginal increase in cholesterol were noted in both sexes at 1.25 and 5 mg/kg/day. Urinalysis: Dosing male dogs at 5 mg/kg/day resulted in a slightly decreased pH. Organ weights: Dosing male dogs at 1. 25 and 5 mg/kg/day resulted in a slightly decreased weight of the thymus. Gross pathology: No relevant changes were noted. Histopathology: At the end of the 2 week treatment with paliperidone i.v., changes in testes and epididymides were found. 2/3 males form the 5 mg/kg/day group, 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. Toxicokinetics: The TK analysis demonstrated dose-proportional increase in exposure (AUC) in both sexes, hereby confirming the previously observed dose-proportionality in exposures after oral administration of paliperidone. $T_{1/2}$ was estimated as 5.4-to 7.6 h after single dose and 5.8 to 9.4 h after repeated dosing in both sexes. Mean $AUC_{0\text{-}24h}$ values of paliperidone on Day 12 in the 2-week repeat-dose i.v. toxicity study in beagle dogs are shown in the following sponsor's table:

Dose (mg/kg bw/day)		0.31	1.25	5
		Males		
$AUC_{0\text{-}24h}$	(ng.h/mL)	2850	9770	24600
		Females		
$AUC_{0\text{-}24h}$	(ng.h/mL)	2190	6680	26900

[4] bw = body weight

In conclusion, the 2-week repeat-dose study with i.v. administered paliperidone in dogs 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 not established in this study.

2. Study title: Chronic Toxicity Study in Beagle Dogs

No long-term toxicity study with paliperidone was performed in dogs because the sponsor requested a waiver from performing these studies. The sponsor submitted instead a Study No.1789 conducted with risperidone administered as capsules at 0, 0.31, 1.25 and 5 mg/kg/day for 12 month. This study was reviewed by Dr. Lois Freed and her review is available in the Agency files.

According to the sponsor, the bridging of the chronic paliperidone toxicity study in dogs to the existing 12-month dog study with risperidone is sufficient for the registration of paliperidone. The sponsor justified this approach based on the following considerations: (Note: this fragment below is taken directly from the sponsor's NDA nonclinical overview with minor modifications)

"1. Given the extremely high (90-94%) contribution of paliperidone to the active fraction in risperidone-treated dogs, the toxicity profile observed in the 12 month p.o. risperidone study in dogs primarily reflects treatment-related effects caused by paliperidone.

2. The 3-month comparative p.o. repeat-dose toxicity study with paliperidone and risperidone in beagle dogs showed that systemic exposure to paliperidone in paliperidone treated dogs and the exposure to metabolically formed paliperidone in risperidone-treated dogs is similar at equal dose levels. The toxicity profiles of paliperidone and risperidone were qualitatively and quantitatively similar in this study.

In should be noted that in the 12-month dog study with risperidone (dose levels: untreated, 0.31, 1.25 and 5 mg/kg/day), and in the 3-month comparative p.o. (gavage) study with paliperidone (0, 0.31, 1.25 and 5 mg/kg/day) and risperidone (5 mg/kg/day) in dogs different formulations were used, i.e., powder in gelatine capsules in the 12-month study and p.o. solution in the 3-month study. However, the systemic paliperidone exposure was essentially similar in both studies. This comparable exposure is demonstrated by the overlay plots shown in Figures 2 and 3.

Figure 2: Individual Plasma Concentration-Time Profiles of Paliperidone in Dogs Following Repeated Administration of Risperidone Capsules (Day 366, n = 3)[54] versus Risperidone P.O. Solution (Day 85, n = 4) at 5 mg/kg/day[53]

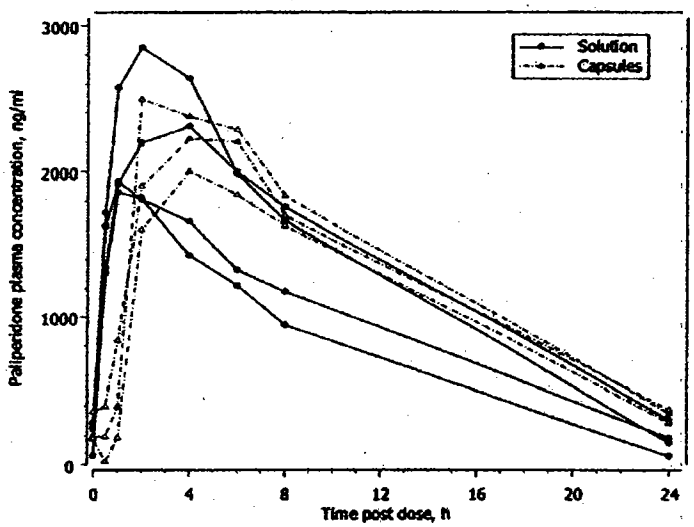
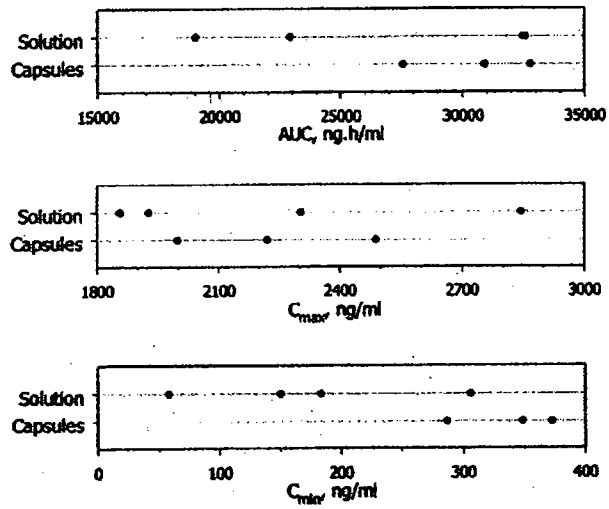


Figure 3: Dot Plot of Individual AUC-, C_{max}-, and Trough Plasma Concentration Values of Paliperidone in Dogs Following Repeated Administration of Risperidone Capsules (Day 366, n = 3)[54] versus Risperidone P.O. Solution (Day 85, n = 4) at 5 mg/kg/day[53]



The bridging of the long-term paliperidone study in dogs to the existing 12-month dog study with risperidone is further supported by the fact that the latter study adequately covers the systemic paliperidone exposure achieved upon administration of paliperidone ER tablets:

- A single-dose pharmacokinetic study in dogs compared the systemic exposure to paliperidone following an immediate release paliperidone p.o. solution (2.12

mg/dog) to the paliperidone exposure after p.o. administration of one experimental 2-mg paliperidone ER tablet (2 mg/dog) (...). Even at the peak time for the paliperidone ER formulation, plasma concentrations following the p.o. solution were higher than those following the paliperidone ER tablet. In one dog (i.e., the dog which showed the longest transit time and had the highest amount of drug released), plasma concentrations at 21 and 24 hours after paliperidone ER administration were similar to concentrations following the p.o. solution.

- In a 3-month repeat-dose p.o. toxicity study in dogs, 15-mg paliperidone ER tablets and paliperidone bulk powder in gelatin capsules were compared. This study confirmed that the systemic exposure following immediate release paliperidone (AUC = 10,855 – 45,906 ng h/ml in individual animals at 60 mg/day) is higher than the exposure to six 15-mg paliperidone ER tablets (AUC = 826-4981 ng h/mL in individual animals at 90 mg/day).
- In the 12-month repeat-dose toxicity study with risperidone in dogs, the systemic exposure to metabolically formed paliperidone at the highest dose level of 5 mg risperidone/kg/day (mean AUC = 30,421 ± 2640 ng h/mL) is approximately 6- to 37-fold higher than the exposure to paliperidone following the administration of six 15-mg paliperidone ER tablets in the 3-month dog study (AUC = 826-4981 ng h/mL in individual animals at 90 mg/day)."

This reviewer agrees with the sponsor's statement regarding similarity of the toxicity profiles of paliperidone or risperidone at equal dose levels (5 mg/kg/day) in comparative studies. However, the sponsor's conclusion regarding similar exposure levels is not quite accurate. In fact, paliperidone C_{max} and AUC_{0-24h} values are 32% and 23% higher, respectively, in paliperidone-treated dogs than in dogs treated with risperidone at equal dose levels on Day 85 of the comparative 3-month study. It is also noted that the TK study was conducted only on 2 dogs/sex/group and that marked variability between individual animals was observed.

3. Study title: Toxicokinetics of Risperidone (R 64766) and of 9-Hydroxy-Risperidone (R 76477) in the Beagle Dog at the Occasion of a Twelve-Month Chronic Oral Toxicity Study of Risperidone at 0.31, 1.25 and 5 mg/kg/day. Tissue Distribution of Risperidone and 9-Hydroxy-Risperidone After Chronic Administration (Study No. FK516).

Mean C_{max} and AUC_{0-24h} values of risperidone and metabolically formed paliperidone on Day 366 of the 12-month repeat-dose p.o. toxicity study in beagle dogs are shown in the following sponsor's table:

Dose (mg/kg bw/day)		0.31	1.25	5	0.31	1.25	5
Analyte		RIS	RIS	RIS	PALI	PALI	PALI
C_{max}	(ng/mL)	117	325	726	251	766	2236
AUC_{0-24h}	(ng.h/mL)	205	761	1954	3252	10704	30421

bw = body weight; RIS = risperidone; PAL = paliperidone

This study was reviewed by Dr. Lois Freed and her review is available in the Agency files.

4. Study title: One-Month Toxicity Study in Beagle Dogs

The purpose of this study was to assess the potential toxicity of paliperidone when administered orally in gelatin capsules to dogs for one month.

Key study findings: Oral administration of paliperidone to dogs for one month resulted in sedation and decubitus at 1.25 and 5 mg/kg/day. Except for this CNS-mediated toxicity, no overt toxicity was observed in this study. Other findings included slight but transient body weight loss during the first 2 weeks of dosing in all dosed groups, slight and transient decrease in hematocrit, hemoglobin, and red blood cells at 5 mg/kg/day, slight increase in haptoglobin at all doses and slight increase in cholesterol and phospholypids at 5 mg/kg/day. All these findings were observed in other studies with risperidone indicating that the toxicity profile of paliperidone and risperidone are similar after oral administration.

Study no.: TOX 2850
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Paharmaceutica, N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: November 17, 1992
GLP compliance: no (pilot study)
QA report: yes ( ) no (x)
Drug, lot #, and % purity: Paliperidone (R76477), lot: FKNA-0054-001-6, [redacted]

Methods

Doses: 0, 0.31, 1.25, 5 mg/kg/day
Species/strain: dog/beagle
Number/sex/group or time point (main study): 2/sex/group
Route, formulation, volume: oral, gelatin capsules containing powder
Satellite groups used for toxicokinetics or recovery: none (TK was conducted on main group)
Age: not provided
Weight: 9.8-10.0 kg

This study was a pilot study. The following parameters were assessed: mortality, clinical observations, ECG and heart rate (Week -2 and 4), body weight (weekly), hematology (Week -2, 2, 4), serum analysis (Week -2, 2, 4), and urinalysis (Week -1 and 5).

Results: There were no deaths in this study. At 1.25 mg/kg/day, slight sedation was noted. A more pronounced sedation was observed at 5 mg/kg/day. Dogs administered 5 mg/kg/day were in decubitus for a few hours after the test article administration. There are no effects on heart rate and ECG parameters in this study. A slight but transient body weight loss was observed during the first 2 weeks of dosing in all dosed groups. At 5 mg/kg/day, slight decrease in hematocrit, hemoglobin, and red blood cells was noted after 2 weeks of dosing, but not at 4 weeks. Serum analysis indicated a slight increase in haptoglobin at all doses and a slight increase in cholesterol and phospholipids at 5

mg/kg/day. There were no effects on urinalysis. The toxicoknetics data from this study are provided in a separate report (see below). Paliperidone administration-related effects compared with the results from a previous 3-month oral toxicity study with risperidone in dogs (No. 1735) are summarized in the following sponsor's table:

Parameter	Dosage groups (mg/kg body weight/day)					
	0.31		1.25		5	
	R 76477	R 64766	R 76477	R 64766	R76477	R 64766
Mortality	-	-	-	-	-	-
Clinical obs. - sedation		+	+	++	+++	+++
E.C.G./heart rate	N	N	N	N	N	N
Body weight gain	decr. +		decr. +		decr. ++	decr. ++
Haematology - haematocrit - haemoglobin - red blood cells				decr. + decr. + decr. +	decr. + decr. + decr. +	decr. ++ decr. ++ decr. ++
Serum analysis -haptoglobin - cholesterol - phospholipids	incr. +	incr. +	incr. +	incr. ++ incr. + incr. ++	incr. + incr. + incr. +	incr. ++ incr. + incr. ++
Urinalysis	N	N	N	N	N	N

Legend: ± trend; + slight; ++ moderate; +++ severe
N = normal

These results indicate that paliperidone administered orally was well tolerated up to the highest tested dose of 5 mg/kg/day. When compared with the toxicity of risperidone as evaluated in a previously conducted 3-month study in dogs (Study No. 1735), it can be concluded that toxicity profile of paliperidone after oral administration is comparable with the oral toxicity profile of risperidone.

5. Study title: Toxicokinetics of 9-Hydroxy-Risperidone (R 76477) in Beagle Dogs at the Occasion of a One-Month Subchronic Oral Pilot Toxicity Study (Exp. No. 2850) of 9-Hydroxy-Risperidone Provided as a Microcrystalline Powder in Gelatin Capsules at 0.31, 1.25 or 5 mg/kg/day (Study No. R 76477/FK1402).

The toxicokinetics of paliperidone (9-hydroxy-risperidone) were studied in the beagle dog at the occasion of a one-month subchronic oral pilot toxicity study (Exp. No. 2850). Blood samples were taken at 0, 1, 2, 4, 6, 8 and 24 hours after the first and after the last dose administration. Results: For each dose level, peak plasma concentrations and AUC-values of paliperidone were comparable after single and repeated administration. Exposure tended to increase less than proportionally with the administered dose. Elimination half-lives were on average 6.1 h to 8.5 h after single dosing and 5.2 h to 9.6 h after repeated administration. Mean plasma concentrations and other TK parameters after one-month paliperidone administration are shown in the following reviewer's table:

dose	**0.31** mg/kg/day (N=2)		**1.25** mg/kg/day (N=2)		5 mg/kg/day (N=4)	
day	Day 1	Day 30	Day 1	Day 30	Day 1	Day 30
C_{max} (ng/ml)	504	595	1220	1310	4890± 830	3710±1210

T_{max} (h)	1.5	1.5	2.5	1.5	2.0±1.4	1.5±0.6
$T_{1/2}$ (h)	7.15	7.58	8.49	9.63	6.1±1.5	5.17±0.97
AUC (ng•h/ml)	5510 a	5630 b	15000 a	15100 b	52400±11300 a	36600±9040 b

a: $AUC_{0-\infty}$; b: AUC_{0-24}

According to the sponsor, the exposure, as calculated from the AUC-values, to paliperidone in the present study was on average 2.0 times higher than the exposure to the active moiety in the 3-month risperidone toxicity study. It was also slightly higher than that in the 12-month risperidone toxicity study in dogs.

6. Study title: Three Month Repeated Dose Oral Toxicity Study in the Beagle Dog.

The purpose of this study was to assess the toxicity of paliperidone (R076477) when administered once daily by the oral route (gavage) to beagle dogs for a period of 3 consecutive months. A reference group, in which risperidone (R064766) was administered, 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 nor dietary administration of paliperidone in rodents.

Key study findings: 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 (but not risperidone) at 5 mg/kg/day in the last five weeks of dosing. 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 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 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 are findings in organ weights are the decreased prostate and

increased spleen. 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. The increase in accumulation of red blood cells in the splenic red pulp is due to their α-lytic effect. The oral toxicity profile of paliperidone was comparable with that of risperidone.

Study no.: 4604
Volume #, and page #: electronic submission
Conducting laboratory and location: Department of Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium
Date of study initiation: June 9, 1998 (first day of dosing)
GLP compliance: yes (US FDA GLP)
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone (R076477; 9-OH risperidone), lot ZR076477PFA011, purity [redacted] risperidone (R064766), lot ZR064766PUA181; purity: [redacted]

Methods

Doses: paliperidone: **0, 0.31, 1.25, 5** mg/kg/day; risperidone: **5** mg/kg/day
Species/strain: dog/beagle
Number/sex/group or time point (main study): 4/sex/group
Route, formulation, volume: oral (gavage); aqueous solution of the test article in vehicle (tartaric acid, NaOH 1N ad pH 5, demineralised water); 1 ml/kg body weight/day
Satellite groups used for toxicokinetics or recovery: none
Age: 6 to 8 months old on Day 0
Weight: 9.7 to 9.9 kg
Sampling times: Hematological and clinical chemistry analysis was conducted twice before the administration of the first dose and in Weeks 2, 4, 8 and 13. Urinalysis was conducted prior to the administration of the first dose and in Weeks 4 and 13. Necropsy: male dogs on September 8, 2008, female dogs on September 9, 1998

Observations, times and results:

Mortality: All animals were observed daily. There were no deaths in this study.

Clinical signs: All animals were observed daily from Day -3 onwards. At 0.31 mg/kg/day, all dogs were slightly sedated during the first six days of dosing. At 1.25 mg/kg/day, two dogs were moderately sedated during the first week of dosing and all animals remained slightly sedated for the entire three months. At 5 mg paliperidone/ kg/day, salivation was noted in 8/8 animals during the first day of dosing and tremors in 2/8 dogs during the second day of dosing. Severe sedation was seen during the first six days of dosing in one female and one male. All animals were slightly to moderately sedated for the entire three months. In the animals treated with risperidone at 5

mg/kg/day, sedation was comparable to that in animals administered paliperidone and one animal also had tremors on the second day of dosing. However, the incidence of soft feces was increased only in the dogs dosed with paliperidone at 5 mg/kg but not in dogs administered risperidone at the same dose.

Body weights: Recorded prior to the dosing period and at weekly intervals during the dosing period. Transient, dose dependent decreases (not always statistically significant) in body weight gain were noted during the first three to four weeks of dosing with paliperidone and risperidone in all dose groups. Both body weight and body weight gain was comparable with the vehicle group in all paliperidone and risperidone groups afterwards. During the last month, body weight gain was significantly increased in the paliperidone (but not in the risperidone) 5 mg/kg/day group.

Food consumption: Measured in all dogs at weekly intervals during the dosing period. A slight decrease in food consumption was noted in all dosage groups only during the first week of dosing. Food consumption in the dogs dosed with paliperidone was comparable with food consumption in the dogs dosed with risperidone.

Ophthalmoscopy: An ophthalmological examination (conjunctiva, sclera, cornea, anterior chamber, iris, lens and fundus) was conducted on all dogs prior to the administration of the first dose and towards the end of dosing period. There were no treatment-related eye changes in dogs.

EKG: EKG, heart rate and blood pressure measurements were carried out prior to the administration of the first dose and after approximately one month and three months of dosing. When the test article dosed-groups were compared with the vehicle group, the following significant differences were noted: PQ interval and QT interval were decreased in the 1.25 and 5 mg/kg paliperidone groups, and in the 5 mg/kg risperidone group. Moreover, QTc was increased in all test article-dosed groups after one month (mean group increase when compared to predose values was 9 ms, 23 ms, 23 ms and 39 ms in the 0.31 mg/kg, 1.25 mg/kg, 5 mg/kg paliperidone and 5 mg/kg risperidone groups, respectively) and after 3 months (mean group increase when compared to predose values was 15 ms, 22 ms, 43 ms and 47 ms in the 0.31 mg/kg, 1.25 mg/kg, 5 mg/kg paliperidone and 5 mg/kg risperidone groups, respectively). The differences recorded in QTc at 1.25 and 5 mg/kg were slight and within the range of the historical control data. Heart rate was increased in the 1.25 and 5 mg/kg paliperidone groups and in the 5 mg/kg/day risperidone group after one and three months. After three months the mean group increases were 51%, 69% and 115% above predose mean group values in the 1.25 and 5 mg/kg paliperidone groups and in the 5 mg/kg/day risperidone group, respectively. 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 month of paliperidone or risperidone administration.

Mean heart rate and ECG values at Week -1 prior to initiation of dosing (i.e. baseline) and at Week 4 and 13 of treatment in the 3-month repeat-dose p.o. gavage toxicity study

in beagle dogs (4 males and 4 females/dose level) are shown in the following sponsor's table. Changes against baseline are expressed as percentages (between brackets)

	Vehicle	Paliperidone			Risperidone
Dose (mg/kg bw/day)	-	0.31	1.25	5	5
HR, Week -1 (bpm)	124	125	114	127	100
HR, Week 4 (bpm)	118 (-5%)	152 (+22%)	185** (+62%)	180* (+42%)	176 (+76%)
HR, Week 13 (bpm)	133 (+7%)	153 (+22%)	172* (+51%)	215*** (+69%)	215* (+115%)
QT, Week -1 (msec)	152	150	155	149	157
QT, Week 4 (msec)	149 (-2%)	142 (-5%)	134* (-14%)	139 (-7%)	144 (-8%)
QT, Week 13 (msec)	151 (-1%)	145 (-3%)	139* (-10%)	136* (-9%)	133* (-15%)
QTcB, Week -1 (msec)	216	214	211	213	199
QTcB, Week -4 (msec)	204 (-6%)	223* (+4%)	234** (+11%)	236* (+11%)	238** (+20%)
QTcB, Week 13 (msec)	222 (+3%)	229 (+7%)	233 (+10%)	256*** (+20%)	246* (+24%)
QTcF, Week -1 (msec)	192	189	190	189	183
QTcF, Week 4 (msec)	183 (-5%)	192 (+2%)	194 (+2%)	197* (+4%)	201* (+10%)
QTcF, Week 13 (msec)	195 (+2%)	196 (+4%)	196 (+3%)	207* (+10%)	200 (+9%)
QTcVDW, Week -1 (msec)	195	192	193	191	186
QTcVDW, Week 4 (msec)	188 (-4%)	193 (+1%)	192 (-1%)	194 (+2%)	198 (+6%)
QTcVDW, Week 13 (msec)	197 (+1%)	196 (+2%)	195 (+1%)	198 (+4%)	193 +4%)

- = not dosed; HR = heart rate; bpm = beats per minute; msec = millisecond; QT = QT-interval; QTcB = QTc-Bazett interval; QTcF = QTc-Fridericia interval; QTcVDW = QTc-Van De Water-interval; significance computed by Mann-Whitney U-test (two tailed): * $p< 0.5$; ** $p< 0.01$; *** $p < 0.001$

Hematology: Examinations were conducted in all dogs twice before the administration of the first dose and in Weeks 2, 4, 8 and 13. The following parameters were determined: hematocrit, hemoglobin, red and white blood cell count, red blood cell indices (mean cell volume, mean hemoglobin and mean hemoglobin concentration), thrombocyte count, activated partial thromboplastin time, differential white blood cell count. Treatment with paliperidone and risperidone at 5 mg/kg/day resulted in slight decreases in hematocrit, hemoglobin and red blood cells count. This reviewer notes these changes were noted based on comparison with the vehicle control values but were less obvious when compared to the pretest values. All other changes were slight, not dose related, only temporarily seen and/or the values were within the range of the historical control data.

Clinical chemistry: Examinations were conducted in all dogs twice before administration of the first dose and in Weeks 2, 4, 8 and 13. The following parameters were determined: sodium, potassium, chloride, calcium, inorganic phosphate, total protein, albumin, glucose, cholesterol, triglycerides, phospholipids, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transferase. There were several toxicologically not important changes in some clinical chemistry parameters. These were recorded only temporarily and were slight, not dose related and/or within the range of the historical control data. Cholesterol was slightly increased

in dogs administered paliperidone at 1.25 (up to 18% increase above the mean pretest value) and paliperidone and risperidone at 5 mg/kg/day (up to 26% and 19% increase above the mean pretest value, respectively). It was concluded that administration of paliperidone had no toxicologically important effects on other serum parameters in dogs.

Urinalysis: Examinations were conducted in all dogs prior to administration of the first dose and in Weeks 4 and 13. The following parameters were determined: urobilinogen, pH, proteins, glucose, ketones, bilirubin, occult blood, specific gravity, sediment. Administration of paliperidone or risperidone had no toxicologically important effects on the urinary parameters in dogs.

Gross pathology: Treatment with paliperidone at the dose of 0.31 mg/kg/day or higher for three months resulted in a small prostate in dogs. There were no differences in macroscopical observations between the group dosed with paliperidone and risperidone at 5 mg/kg/day.

Organ weights: The following organs were weighed: lungs, spleen, liver, heart, pancreas, kidneys, brain, thymus, adrenal glands, thyroid glands including parathyroid glands, gonads (testes, ovaries), pituitary gland and prostate. The following significant differences were noted in the paliperidone-treated dogs: lungs (decreases in relative weight in the 1.25 and 5 mg paliperidone-dosed groups), spleen (increases in absolute and relative weight in the 1.25 and 5 mg/kg paliperidone and risperidone groups up to 97% above control value), liver (increase in relative weight in the 5 mg/kg paliperidone group), heart (decreases in relative weight in the 0.31 and 5 mg/kg groups), thyroids (increase in relative weight in the 5 mg/kg group), hypophysis (increase in absolute and relative weight in the 1.25 mg/kg group), prostate (decreases in absolute and relative weight in all test article treated groups up to 50% of control group value). Most of these findings were slight, not dose-related and, according to the sponsor, within acceptable range of the historical data. The most important are findings in the prostate and spleen. This reviewer also notes marked decreases in testes and ovaries in both 5 mg/kg groups. There were no relevant differences in organ weights between the paliperidone and risperidone in 5 mg/kg groups.

Histopathology: Samples of the following tissues from all dogs were preserved in 10% buffered formalin (except eyes and testes), stained with H & E and examined by light microscopy: adrenal glands, aorta, bone (femur, sternum), bone marrow, brain (cerebrum, cerebellum, midbrain), cranial nerve, optic tract, epididymides, esophagus, eye, gall bladder, heart, kidneys, lacrimal gland, large intestine (cecum, colon, rectum), liver, lungs, lymph nodes (bronchial, mesenteric), mammary gland, ovaries, pancreas, parathyroid glands, peripheral nerve, sciatic nerve, pituitary gland, prostate, salivary gland (mandibular, parotid), skeletal muscle, psoas muscle, skin, small intestine (duodenum, jejunum, ileum), spinal cord (cervical, lumbar), spleen, stomach, testes, thymus, thyroid glands, tongue, trachea, urinary bladder, uterus, vagina, and all tissues showing gross changes. Administration of paliperidone at all dose levels and risperidone resulted in changes in the following organs: ovaries, uterus, vagina, prostate and spleen. Ovaries/uterus/vagina: Changes included: decreased atretic and tertiary follicles in the

ovaries; decreased glandular development and increased resting aspect of the uterus, lowered height of the epithelium and the vacuolated/karyorrhetic cells in the epithelium and the presence of mitotic figures in the uterus, decreased thickness of the epithelium, vacuolated cells of the epithelium, and increased resting aspect of the vagina. Prostate: Atrophy with decreased glandular development and increase of clear basal cells were observed in all test article-dosed groups. Spleen: The number of erythrocytes in the red pulp was increased and prominent granulocytes in the red pulp were observed. According to the sponsor, the changes in the female genital tract and prostate are considered to be due to the interference of the test articles with prolactin. The increase in accumulation of red blood cells in the splenic red pulp is due to the α-lytic effect of the test articles.

Endocrinology: On Day 85, blood was colleted before, and 2, 4, 8 and 24 hours after paliperidone or risperidone administration. The circadian profile of serum prolactin levels in dogs of both sexes was evaluated. Paliperidone increased serum prolactin levels in male and female dogs at all dose levels and time points. In male dogs, serum prolactin levels at 0.31 mg/kg/day were similar to those measured after risperidone at 5 mg/kg/day. At higher doses, paliperidone elevated serum prolactin levels slightly more than risperidone at 5 mg/kg/day. In females, prolactin $AUC_{0\text{-}24h}$ values were slightly lower at all doses of paliperidone compared to prolactin $AUC_{0\text{-}24h}$ at a dose of 5 mg/kg/day of risperidone. These results are shown in the following sponsor's table:

Males

Dosage group	Vehicle	R076477 Low 0.31 mg/kg	R076477 Medium 1.25 mg/kg	R076477 High 5 mg/kg	Reference: R064766 5 mg/kg
$AUC_{0\text{-}24h}$ (ng/ml.h)	48	306	604	496	288
Standard error	(0.13)	(174)	(209)	(101)	(82)

Females

Dosage group	Vehicle	R076477 Low 0.31 mg/kg	R076477 Medium 1.25 mg/kg	R076477 High 5 mg/kg	Reference: R064766 5 mg/kg
$AUC_{0\text{-}24h}$ (ng/ml.h)	49	334	408	421	537
Standard error	(1.00)	(76)	(45)	(145)	(91)

Standard error is shown between brackets
Values < 2.0 have been calculated as 2.0 in the calculation of the mean and the AUC

Toxicokinetics: Results of these studies were reported in separate documents: reports R076477/R064766/FK2931 and R076477/R064766/FK2991.

Addendum to the Toxicology Report No. 4604:

7. Study title: Toxicokinetic and Tissue Distribution of Paliperidone (9-Hydroxy-Risperidone, R076477) and of Risperidone (R064766) in the Beagle Dog in a Three-Month Repeated Dose Oral Toxicity Study (Exp. No. 4604) on Aqueous Solutions of

Paliperidone at 0.31, 1.25, and 5 mg/kg/day and on an Aqueous Solution of Risperidone at 5 mg/kg/day (Study No. FK2931).

The aim of this study was to investigate the toxicokinetics and tissue distribution of paliperidone and risperidone in beagle dogs in a 3-month repeated dose toxicity study. Blood samples were taken from the 1st and 2nd male and female dog from each group at 0, 0.5, 1, 2, 4, 6, 8, and 24 hours after dosing on Day 0 and Day 85 for TK. After oral administration, both paliperidone and risperidone were rapidly absorbed from the GI-tract. A dose-proportional increase in AUC values was found on both Day 0 and 85. The elimination half life ($T_{1/2}$) of paliperidone was about 7 hours. The $T_{1/2}$ of risperidone and paliperidone after risperidone administration was 1 and 6 hours, respectively.

Results are summarized in the following reviewer's tables:

TK parameters after paliperidone administration (mean ± SD)						
	Day 0 (N=4)			Day 85 (N=4)		
Dose (mg/kg/day)	0.31	1.25	5.0	0.31	1.25	5.0
C_{max} (ng/ml)	300±98	1077±187	3275±846	183±38	1109±166	3277±376
AUC_{0-24} (ng.h/ml)	3316±1587	10911±2059	34797±9441	2041±505	10752±2612	34656±9045
$T_{1/2}$ (h)	6.7±1.0	6.4±1.1	8.5±1.9	7.7±1.0	7.1±2.1	5.7±0.8

TK parameters after risperidone (5 mg/kg/day) administration (mean ± SD)		
	Day 0	Day 85
C_{max} (ng/ml)		
Risperidone	2233±1456	1950±1241 53% of active moiety
Paliperidone	2906±656	2233±453 60% of active moiety
Risperidone + Paliperidone	4666±1447	3700±1247 100% (active moiety)
AUC_{0-24} (ng.h/ml)		
Risperidone	3825±2064	2944±1839 10% of active moiety
Paliperidone	34037±11209	26756±6859 90% of active moiety
Risperidone + Paliperidone	37980±12220	29744±8077 100% (active moiety)
$T_{1/2}$ (h)		
Risperidone	1.3±0.5	1.0±0.2
Paliperidone	6.4±1.5	5.4±1.2
Risperidone + Paliperidone	6.3±1.4	5.4±1.2

The exposure to active moiety after both single and repeated dose of 5 mg paliperidone/kg/day was comparable to that after risperidone at 5 mg/kg/day. However, the contribution of risperidone to the total pharmacologically active moiety after administration of 5 mg/kg/day risperidone was only about 10%. Exposure values (C_{max} and AUC) of risperidone and paliperidone were lower as compared to data from a one-

month oral toxicity study on paliperidone in dogs at the same dose levels, provided as microcrystalline powder in gelatin capsules, although $T_{1/2}$ data were similar.

One of the main considerations in sponsor's rationale for not performing chronic dog toxicity study with paliperidone and bridging to 12-month repeat-dose toxicity study in dogs was based on the results of a 3-month comparative study in dogs. The sponsor indicated the following:" The 3-month comparative p.o. repeat-dose toxicity study with paliperidone and risperidone in beagle dogs showed that systemic exposure to paliperidone in paliperidone treated dogs and the exposure to metabolically formed paliperidone in risperidone-treated dogs is similar at equal dose levels. The toxicity profiles of paliperidone and risperidone were qualitatively and quantitatively similar in this study".

This reviewer agrees with the sponsor's statement regarding similarity of the toxicity profiles of paliperidone or risperidone at equal dose levels (5 mg/kg/day) in this study. However, the sponsor's conclusion regarding similar exposure levels is not quite accurate. In fact, paliperidone C_{max} and $AUC_{0\text{-}24h}$ values are 32% and 23% higher, respectively, in paliperidone-treated dogs than in dogs treated with risperidone at equal dose levels on Day 85 of this study. It is noted that the TK study was conducted only on 2 dogs/sex/group and that variability between individual animals was significant.

Tissue samples from muscle, lung, kidney, brain, fat and liver were collected at autopsy on Days 91 and 92 about 24 hours after the last dose administration to determine tissue distribution of paliperidone and risperidone. Tissue levels of paliperidone were the highest for the liver, lung, and kidney. According to the sponsor's tables, tissue/plasma concentration ratios of paliperidone after administration of paliperidone at 5 mg/kg/day were 6.67, 4.72 and 6.41 for the lung, kidney and liver, respectively. Tissue/plasma ratios of paliperidone after risperidone administration were similar to those after administration of paliperidone itself.

8. Study title: 3-Month Repeated Dose Oral Toxicity Study in the Beagle Dog.

This study was specifically designed to address the gastrointestinal tolerability of the 15-mg paliperidone ER tablet, the highest dose tested clinically. The administration of paliperidone ER tablets was possible in dogs but is not feasible in rats and mice, because of the dimensions of the tablets that are to large for rodents.

Key study findings: 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, treatment with paliperidone ER tablets demonstrated a relatively low exposure compared to p.o. solutions or capsules in other studies. Due to severe sedation after dosing on Day 0, the dose of the high dose powder group (H2) was lowered from 90 to 60 mg/dog/day from Day 1 to the end of the study. The most important toxicological findings included sedation, tremors, narrowed palpebral fissure, 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, moderate decrease in the weight of ovaries in females, increase in red blood cells, noted as "congestion", in the splenic red pulp in both sexes, delay in sexual maturation and decrease in mammary glandular development in females and delay in prostate development or maturation in male dogs. Clinical signs did not indicate differences in gastrointestinal tolerability between dogs dosed with two formulations of paliperidone. There were no histopathological test article-related findings in the GI tract of dogs.

Study no.: TOX6488
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: April 30, 2004
GLP compliance: yes (OECD)
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone (R076477), lot: powder: ZR076477EIA041; 15 mg tablets: ID/control No. 0406659; purity: [redacted]

Methods

Doses:
0 mg/dog/day (6 placebo OROS tablets/dog/day in 3 gelatine capsules)
30 mg/dog/day (2 OROS tablets of 15 mg paliperidone in 1 gelatine capsule)
90 mg/dog/day (6 OROS tablets of 15 mg paliperidone/dog/day in 3 gelatine capsules) (group H1)
90/60 mg/dog/day (30 mg paliperidone powder/dog/day in 3 gelatine capsules) reduced after Day 0 to 60 mg/dog/day (group H2)
Species/strain: dog/beagle
Number/sex/group or time point (main study): 4/sex/group
Route, formulation, volume: oral, gelatine capsules containing OROS® tablets or powder
Satellite groups used for toxicokinetics or recovery: none
Age: 6.5 to 7.5 months
Weight: males: 9.3-9.5 kg; females: 7.2-7.4 kg

Observation, times and results:
Mortality: There was no mortality in this study.
Clinical signs: All animals were observed for clinical signs at least once a day. At 30 mg/dog/day, slight sedation, miosis and slightly congested conjunctivae were noted in both sexes. At 90 mg/dog/day, slight to moderate sedation, decubitus, a slight degree of tremors, miosis and slightly congested conjunctivae were noted in both sexes. Out of normal biting was seen in one female. At 90/60 mg/dog/day, findings were the same but more pronounced or at the higher frequency compared to the 90 mg/dog/day group. In addition, circling movements were noted in one male and out of normal biting was observed in both sexes.
Body weights: Recorded from all animals prior to dosing on Day 0 and at weekly intervals during the study. At 30 and 90 mg/dog/day, minimal and transient (first week)

decreases in body weight and weight gain were observed in females, and in both sexes at 90/60 mg/dog/day.
Food consumption: Measured at weekly intervals. At 30, 90 mg/dog/day and 90/60 mg/dog/day, minimal and transient (first week) decrease was observed in males and females.
Ophthalmoscopy: An ophthalmic examination was performed in all dogs prior to start of dosing and on Day 90. At 30 mg/dog/day, a narrowed palpebral fissure was observed in both sexes. At 90 mg/dog/day, a narrowed palpebral fissure in females and incomplete mydriasis (50% dilated) in one male was noted. At 90/60 mg/dog/day, findings were the same as in the previous group. In addition an epiphora was noted in one female dog.
EKG: EKGs and heart rate measurements were conducted on Day -16 and on Day 90. A slight increase in QTc interval was noted in females in all groups administered test article. In addition, at 90/60 mg/dog/day, a slight increase in heart rate was observed in both sexes.

Mean heart rate and ECG values on Day -16 prior to initiation of dosing (i.e. baseline) and Day 90 of treatment in the 3-month repeat-dose p.o. toxicity study with paliperidone ER tablets and paliperidone bulk powder in beagle dogs are shown in the following sponsor's table. Changes against baseline are expressed as percentages (between brackets)

Dose (mg/day)	Placebo ER Tablets -	Paliperidone ER Tablets 30	Paliperidone ER Tablets 90	Paliperidone Bulk Powder 90/60
Males (n = 4/dose level/formulation)				
HR, Day -16 (bpm)	132	132	128	141
HR, Day 90 (bpm)	119 (-10%)	111 (-16%)	124 (-3%)	150 (+6%)
QT, Day -16 (msec)	153	154	153	149
QT, Day 90 (msec)	191 (+25%)	197 (+28%)	178 (+16%)	162 (+9%)
QTcB, Day -16 (msec)	227	227	222	227
QTcB, Day 90 (msec)	268 (+18%)	266 (+17%)	253 (+14%)	255 (+12%)
QTcF, Day -16 (msec)	199	199	196	197
QTcF, Day 90 (msec)	240 (+21%)	240 (+21%)	225 (+15%)	219 (+11%)
QTcVDW, Day -16 (msec)	200	200	198	199
QTcVDW, Day 90 (msec)	234 (+17%)	235 (+18%)	222 (+12%)	214 (+8%)
Females (n = 4/dose level/formulation)				
HR, Day -16 (bpm)	118	132	122	122
HR, Day 90 (bpm)	94 (-20%)	131 (-1%)	112 (-8%)	144 (+18%)
QT, Day -16 (msec)	163	154	166	156
QT, Day 90 (msec)	178 (+9%)	182 (+18%)	188 (+13%)	180 (+15%)
QTcB, Day -16 (msec)	228	228	228	220
QTcB, Day 90 (msec)	221 (-3%)	268 (+18%)	255 (+12%)	278 (+26%)
QTcF, Day -16 (msec)	204	200	204	196
QTcF, Day 90 (msec)	205 (+1%)	235 (+18%)	230 (+13%)	240 (+22%)
QTcVDW, Day -16 (msec)	205	201	204	198
QTcVDW, Day 90 (msec)	208 (+1%)	229 (+14%)	227 (+11%)	230 (+16%)

- = not dosed; HR = heart rate; bpm = beats per minute; msec = millisecond; QT = QT-interval; QTcB = QTc-Bazett interval; QTcF = QTc-Fridericia interval; QTcVDW = QTc-Van De Water-interval

Hematology: Conducted before the start of dosing (Days -15, -14), after 1 month and at the end of dosing. The following parameters were determined: white blood cell count, red blood cell count, hemoglobin, hematocrit, red blood cell indices (volume, hemoglobin, hemoglobin concentration), normoblasts, activated partial thromboplastin time, reticulocytes, thrombocyte count, differential white blood cell count. At 30 mg/dog/day, a minimal decrease in the number of neutrophils and white blood cells was observed in both sexes and transient and minimal decreases in hemoglobin, hematocrit and red blood cell count were observed in females. At 90 mg/dog/day, findings were similar. In addition, minimal decreases in lymphocytes were noted in both sexes and reticulocytes in males. At 90/60 mg/dog/day findings were similar, with an additional decrease in monocytes in females.
Clinical chemistry: Serum analysis was conducted on the same days as hematology. The following parameters were measured: sodium, potassium, chloride, calcium, inorganic phosphate, total protein, albumin, glucose, cholesterol, triglycerides, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase. At 90 mg/dog/day, a slight increase in cholesterol in males and a slight decrease in potassium in females was noted. At 90/60 mg/dog/day, slight increases in total bilirubin and in cholesterol were seen in the serum of both sexes. A decrease in triglycerides was additionally present.
Urinalysis: Urine collection was done on the same days as blood sampling for hematology and serum analysis. The following parameters were measured: specific gravity, pH, protein, glucose, ketones, occult blood, color, clarity, sediment. There were no changes in the urinalysis parameters in this study.
Gross pathology: A full necropsy was performed on all animals on Days 92 (males) and 93 (females), and all macroscopic changes were recorded. At 30 mg/dog/day, a swollen spleen was observed in one female. At 90 and 90/60 mg/dog/day, a swollen spleen and small thymus was seen in both sexes. In addition, a small thymus was noted at 90/60 mg/dog/day in both sexes.
Organ weights: The following organs were weighed: lymph nodes (popliteal), kidneys, adrenal glands, testes, prostate, liver, spleen, thymus, thyroid gland with parathyroid gland, heart, lung, brain, pituitary gland, ovaries. At 30 mg/dog/day, a moderate increase in spleen weight in both sexes, slight to moderate decrease in the weight of the testes and prostate in males, and a moderate decrease in the weight of ovaries in females was observed. The same changes were seen at 90 mg/dog/day except for the decrease in prostate weight, which was graded pronounced instead of moderate, and a slight decrease in the weight of the thymus in females. The same organ weight changes were present at 90/60 mg/dog/day as at 90 mg/dog/day, except for the moderate decrease in weight of the testes and a slight decrease in thymic weight in male dogs.
Histopathology: The following tissues from all dogs were processed routinely, stained with H & E and examined by light microscopy: adrenal glands, aorta, bone (sternum, femur), bone marrow, brain, optic nerves, epididymides, esophagus, eye, gall bladder, heart, kidneys, lacrimal gland, large intestine (cecum, colon, rectum), liver, lungs, lymph nodes (mesenteric, popliteal), mammary gland, ovaries, pancreas, parathyroid glands, peripheral nerve (sciatic nerve), pituitary gland, prostate, ureter, salivary gland (mandibular, parotid and sublingual), skeletal muscle, skin, small intestine (duodenum,

jejunum, ileum), spinal cord (cervical, thoracic, lumbar), spleen, stomach, testes, thymus, thyroid glands, tongue, trachea, urinary bladder, uterus, vagina, oviducts, cervix, larynx, Peyer's patches, all tissues showing gross changes. At 30 mg/dog/day, an increase in red blood cells, noted as "congestion", in the splenic red pulp way observed in both sexes, a delay in sexual maturation (cervix, ovaries, uterus, vagina) and a decrease in mammary glandular development were noted in females and a delay in prostate and epididymides development or maturation was seen in male dogs. The same changes were seen at 90 and 90/60 mg/dog/day except for the mammary glandular development, which was absent in females at this dose and an additional tendency for an increased thymic involution in both sexes. There were no toxicologically significant findings in the GI tract and other organs or tissues of dogs in this study.

Toxicokinetics: Blood samples were takes on Day 84 from the first and the second male and female dog of each group at 0, 2, 4, 8 and 24 hours. 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, indicating markedly lower bioavailability of paliperidone when compound was delivered as OROS tablets in dogs. Because of the marked variability in exposure data between the individual animals, no conclusion could be drawn with regard to sex related differences and dose-proportionality. These data are shown in the sponsor's table below:

Table: C_{max}- and AUC_{0-24h}-values for the individual animals (on day 84 of the study).

	Paliperidone OROS (30 mg/dog/day)		Paliperidone OROS (90 mg/dog/day)		Paliperidone bulk powder (60 mg/dog/day)	
Males Dog No.	**21**	**22**	**41**	**42**	**61**	**62**
C_{max} (ng/ml)	14.1	540	144	359	4607	2469
AUC_{0-24h} (ng.h/m	197	9968	1589	4981	45906	26610
Females Dog No	**121**	**122**	**141**	**142**	**161**	**162**
C_{max} (ng/ml)	519	878	246	73.6	3347	1120
AUC_{0-24h} (ng.h/m	5611	12349	3091	826	35024	10855

REPEAT DOSE TOXICITY STUDIES IN RATS

9. Study title: 2-Week Repeated Dose Intravenous Toxicity Study in the Rat (Study No. TOX 6192)

The purpose of this study was to assess the potential toxicity of paliperidone (lot: ZR076477EIA041, purity: 99.2%) at dose levels of 0, 0.63, 2.5, 10 mg/kg/day when administered once daily by intravenous route over 30 minutes to Sprague-Dawley rats (10/sex/group) for a period of 2 consecutive weeks. The toxicokinetics was also studied. The study was conducted by Janssen Pharmaceutica, N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium and was initiated on October 9, 2003. This study was conducted in compliance with GLP regulations (OECD) and was quality assured. Formulation: paliperidone in solution containing tartaric acid, NaOH and NaCl for intravenous 30-minute infusion. Parameters investigated included

mortality, clinical observations, ophthalmic examination, body weight and body weight gain, food consumption, hematology, serum chemistry, urinalysis, organ weights, gross pathology, histopathology and toxicokinetics. 6 additional rats/sex/group were used for toxicokinetic analysis conducted after a single dose and after repeated administration.

Results: Mortality: There were no deaths in the study. Clinical signs: Slight sedation was seen at 0.63 mg/kg/day. At 2.5 and 10 mg/kg/day, sedation was slight to moderate. A dose-dependent ptosis was noted (shortly after test article administration up to 5 hours) throughout the study. Body weight and body weight gain: In males dosed with 2.5 and 10 mg/kg of paliperidone, there was a slight dose-related reduction in body weight (up to -8%) and a moderate decrease in body weight gain (-53%). In females, body weight gain was increased only at 0.63 mg/kg (+38%). Food consumption: Food consumption was slightly reduced in males at 10 mg/kg (-7%). In females, food consumption was slightly increased at 0.63 and 2.5 mg/kg (up to +8%). Ophthalmic examination: There were no test article-related changes. Hematology: Serum hemoglobin, hematocrit and red blood cell counts were slightly increased in females at all dose levels (up to +12%, +10%, and +10%, respectively) and minimally increased in males at 2.5 and 10 mg/kg/day. Reticulocytes were slightly decreased at 10 mg/kg/day in both sexes. Serum chemistry: Serum calcium and total protein were was slightly increased in females at 2.5 and 10 mg/kg (up to +6%). In males, serum triglycerides were slightly decreased at these dose levels (up to -33%). Urinalysis: Urinary volume was slightly increased (up to +74%) in males at all dose levels and in females (up to +74%) at 2.5 and 10 mg/kg. Organ weights: Absolute and relative heart weight was increased in males at 10 mg/kg/day and in females at all dose levels (relative weight up to 24%). There were no other relevant changes in organ weights. Gross pathology: Examination indicated stimulation of the mammary gland in females at all dose levels (2/10, 4/10 and 5/10 at 0.63, 2.5 and 10 mg/kg/day, respectively. Histopathology: At the microscopic level, an increase in glandular development and secretory activity of the female mammary glands was evident. These results are shown in the following sponsor's table:

		Females			
Group		V	L	M	H
Treatment (mg/kg/day)		0	0.63	2.5	10.0
Glandular development and secretory activity	Minimal	8	0	0	0
	Slight	2	5	5	3
	Moderate	0	5	4	6
	Marked	0	0	1	1
	Total	10	10	10	10
			***	***	***
Number of rats examined		10	10	10	10

*** p<0.001 with Mann Whitney U Test pairwise comparison.

The vagina and uterus showed signs of pseudo-pregnancy at all dose levels. The findings in the vagina are shown in the following sponsor's table:

		Females			
Group		V	L	M	H
Treatment (mg/kg/day)		0	0.63	2.5	10.0
Mucification in dioestrus	**Slight**	0	6*/**	2	2
Proestrus	**Total**	4	0	3	2
Oestrus	**Total**	2	0	1	0
Metoestrus	**Total**	3	2	2	4
Dioestrus	**Total**	1	8**	4	4
Number of rats examined		10	10	10	10

Mucification: * p<0.05 with Fisher's Exact Test.
**** p< 0.01 with Mann Whitney U Test**
Dioestrus: ** p< 0.01 with Fisher's Exact Test and Mann Whitney U Test

The NOAEL was determined to be 0.63 mg/kg/day for both sexes.

Toxicokinetics: TK analysis indicated a dose proportional increase in exposure (AUC) in both male and female rats. However, females had higher exposures than males at the 0.63 and 10 mg/kg dose levels. Mean $AUC_{0\text{-}24h}$ values of paliperidone on Day 14 in the 2-week repeat-dose i.v. toxicity study in Sprague-Dawley rats are shown in the following sponsor's table:

Dose (mg/kg bw/day)		0.63	2.5	10
		Males (n = 6/dose level)		
$AUC_{0\text{-}24h}$	(ng.h/mL)	490	1690	10400
		Females (n = 6/dose level)		
$AUC_{0\text{-}24h}$	(ng.h/mL)	786	1160	15900

bw = body weight

10. Study title: 6-Month Repeated Dose Oral Toxicity Study in the Rat

The purpose of this study was to determine the potential toxicity of paliperidone when administered once daily by the oral route (gavage) to rats for a period of 6 consecutive months and to compare its toxicity with the toxicity of risperidone. In this study, the toxicokinetics of paliperidone and risperidone were studied as well.

Key study findings: 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 in females at 10 mg/kg/day when compared to the control values. Therefore, it is not clear whether the MTD was achieved for 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, 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 as well as an increased weight of the adrenals 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.

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 at 0.5, 1, 2, 4, 8 and 24 hours after dosing 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 month at 10 mg/kg/day.

Study no.: TOX5708
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: February 25, 2003
GLP compliance: yes (OECD)
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone (9-hydroxy-risperidone, R076477), Batch No. ZR076477PUA031, purity [redacted] risperidone (R064766), Batch No. ZR064766PUA421, purity [redacted]
Methods:

Doses: Paliperidone at 0.63, 2.5 and 10 mg/kg/day; risperidone at 10 mg/kg/day
Species/strain: rat/SPF Sprague-Dawley
Number/sex/group (main study): 20/sex/group
Route, formulation, volume: oral (gavage), solution containing tartaric acid and NaOH, 0.1 ml/10 g body weight/day
Satellite groups used for toxicokinetics or recovery: For the toxicokinetic study part, there were 4 main groups (paliperidone at 0.63, 2.5, and 10 mg/kg/day, risperidone at 10 mg/kg/day) each consisting of 6 males and 6 females. There were no recovery animals.
Age: approximately 6 weeks old
Weight: 135-210 grams
Sampling times: Terminal kill was conducted on September 2-5, 2003 after 6 months of treatment.

Observations, times and results:

Mortality: All animals were observed at least once a day for signs of moribund state or mortality. No drug related mortality occurred during this study.

Clinical signs: All animals were observed for clinical signs at least once a day. During the first month of dosing (Days 0, 1, 8, 15, 22 and 29), time-related observations were recorded in all animals of the main toxicity study prior to daily dosing and at 1, 2, 4, 6 and 24 hours after daily dosing. Later, these observations were conducted once monthly (Days 57, 80, 113, 141 and 169). The following clinical signs were observed in animals administered paliperidone or risperidone: ptosis, soft feces, sedation, hyperreactivity to touch, and vasodilatation. Ptosis was observed in 20/20 males in all groups administered paliperidone or risperidone on the first day of dosing as well as on a few days throughout the study. Ptosis was seen also in 13/20 females administered paliperidone at 0.63 mg/kg/day and in 20/20 females administered higher doses of paliperidone or risperidone. Soft feces were observed in 1/20, 4/20 and 6/20 males administered paliperidone at 2.5 and 10 mg/kg/day and risperidone at 10 mg/kg/day, respectively. Soft feces were also observed in 19/20, 20/20 and 19/20 females administered paliperidone at 2.5 and 10 mg/kg/day and risperidone at 10 mg/kg/day, respectively. Soft feces were noted mainly during the first half of the study on several occasions. Sedation was noted in 9/20, 20/20, 20/20 and 20/20 males administered paliperidone at 0.63, 2.5 and 10 mg/kg/day, and

risperidone at 10 mg/kg/day, respectively. Sedation was also noted in 15/20, 20/20 and 20/20 females administered paliperidone at 2.5 and 10 mg/kg/day, and risperidone at 10 mg/kg/day, respectively. Sedation increased in proportion to the dose from slight and seen only on Day 1 up to 1 or 2 hours after dosing in males administered paliperidone at 0.63 mg/kg/day to moderate and seen up to 6 hours after dosing in animals of both sexes given paliperidone and risperidone at 10 mg/kg. Hyperreactivity to touch was recorded in 2/20 control females, 6/20 females administered paliperidone at 0.63 mg/kg/day, 16/20 females administered paliperidone at 2.5 mg/kg/day, and 2/20 males and 20/20 females administered paliperidone at 10 mg/kg/day. It was also observed in 3/20 males and 19/20 females administered risperidone at 10 mg/kg/day. Vasodilatation was observed in 7/20, 20/20 and 20/20 males administered paliperidone at 0.63, 2.5 and 10 mg/kg/day, respectively, and in 1/20, 19/20, and 20/20 females administered paliperidone at 0.63, 2.5 and 10 mg/kg/day, respectively. It was also observed in 20/20 males and 20/20 females administered risperidone at 10 mg/kg/day. All other findings were considered incidental. Clinical signs observed in males and females are summarized in the following sponsor's tables:

Males					
Dosage Group (mg / kg):	Vehicle X/N	Low:0.63 X/N	Med.:2.5 X/N	High 1:10 X/N	High 2:10 X/N
Subcutaneous tissue mass	1/20	0/20	0/20	1/20	0/20
Alopecia	1/20	0/20	2/20	2/20	0/20
Skin irritation	0/20	1/20	1/20	0/20	0/20
Chromodacryorrhea	1/20	1/20	1/20	3/20	2/20
Ptosis	0/20	20/20 ***	20/20 ***	20/20 ***	20/20 ***
Crusty nose	1/20	0/20	0/20	0/20	0/20
Feces, soft	0/20	0/20	1/20	4/20	6/20 *
Paraphimosis	0/20	0/20	0/20	1/20	0/20
Paralysis	0/20	0/20	0/20	1/20	0/20
Sedation	0/20	9/20 **	20/20 ***	20/20 ***	20/20 ***
Lacrimation	0/20	0/20	0/20	1/20	1/20
Hyperreactive to touch	0/20	0/20	0/20	2/20	3/20
vasodilatation	0/20	7/20 **	20/20 ***	20/20 ***	20/20 ***

Significance level computed with Fisher Exact probability test (two-tailed): * p < .05 ** p < .01 *** p < .001
(Significance computed versus the Vehicle dosage group)
X: Number of positive animals N: Total number of animals
Low and Medium: R076477
High 1: R076477 High 2: R064766

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Females					
Dosage Group (mg / kg):	Vehicle X/N	Low:0.63 X/N	Med.:2.5 X/N	High 1:10 X/N	High 2:10 X/N
Subcutaneous tissue mass	1/20	0/20	0/20	0/20	0/20
Alopecia	1/20	1/20	0/20	1/20	0/20
Chromodacryorrhea	0/20	0/20	0/20	0/20	2/20
Ptosis	0/20	13/20 ***	20/20 ***	20/20 ***	20/20 ***
Eye damage due to blood collection	0/20	0/20	1/20	1/20	1/20
Crusty nose	0/20	0/20	0/20	0/20	1/20
Waste of food	4/20	0/20	1/20	1/20	3/20
Malformed incisors	0/20	1/20	0/20	0/20	0/20
Feces, soft	0/20	0/20	19/20 ***	20/20 ***	19/20 ***
Treatment for abnormal incisors	0/20	1/20	0/20	0/20	0/20
Feces, dark	0/20	0/20	0/20	1/20	0/20
Sedation	0/20	0/20	15/20 ***	20/20 ***	20/20 ***
Hyperreactive to touch	2/20	6/20	16/20 ***	20/20 ***	19/20 ***
vasodilatation	0/20	1/20	19/20 ***	20/20 ***	20/20 ***

Significance level computed with Fisher Exact probability test (two-tailed): * p < .05 ** p < .01 *** p < .001
(Significance computed versus the Vehicle dosage group)
X: Number of positive animals N: Total number of animals
Low and Medium: R076477
High 1: R076477 High 2: R064766

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It can be concluded that the clinical signs observed in rats after administration of paliperidone and risperidone at the same dose level indicate similar toxicity profile.

Body weights: Individual body weights were recorded from all animals of the study prior to start of the dosing period, at weekly intervals during the study, and prior to terminal sacrifice. Body weight and weight gain of males dosed with paliperidone at 0.63 mg/kg/day were slightly lower compared to the control group (96% and 93% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with paliperidone at 0.63 mg/kg/day were slightly increased compared to control group (115% and 129% of control mean value, respectively, on Day 182 of the study). Body weight and weight gain of males dosed with paliperidone at 2.5 mg/kg/day were moderately lower compared to the control group (90% and 84% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with paliperidone at 2.5 mg/kg/day were slightly increased compared to control group (112% and 123% of control mean value, respectively, on Day 182 of the study). Body weight and weight gain of males dosed with paliperidone at 10 mg/kg/day were markedly lower compared to the control group (83% and 75% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with paliperidone at 10 mg/kg/day were comparable to vehicle group values. In rats

dosed with risperidone at 10 mg/kg/day, body weight and body weight gain were also markedly decreased in males compared to the control group (81% and 72% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with risperidone at 10 mg/kg/day were comparable to vehicle group values.

Food consumption: Individual records were made at weekly intervals during the study and at the end of the study. Treatment with paliperidone at 0.63 and 2.5 mg/kg/day did not affect food consumption in male rats. In female rats, food consumption was moderately increased after dosing with paliperidone at 0.63 mg/kg and 2.5 mg/kg. In male rats dosed with paliperidone or risperidone at 10 mg/kg/day, food consumption was slightly decreased compared to the control group. In female rats dosed with palipridone or risperidone at 10 mg/kg/day, food consumption was slightly (paliperidone) or minimally (risperidone) increased compared to the control group. Changes in food consumption were similar in 10 mg/kg/day paliperidone and risperidone groups.

Ophthalmoscopy: An ophthalmologic examination (conjunctiva, sclera, cornea, iris, lens and fundus) were performed at the start of the study and towards the end of the study in the first 10 animals of each sex in both high dose groups and the control group. After induction of mydriasis with atropine, the eyes were examined by a slit lamp biomicroscope. There were no ophthalmological changes in male rats in this study. In female rats administered paliperidone and risperidone at 10 mg/kg/day, cataracts were observed in one out of the 10 examined animals. These and all other findings were considered incidental and not treatment-related.

EKG: not conducted

Hematology: Blood sampling for hematology was performed in Week 13 and prior to necropsy (Week 27). The following parameters were determined: white blood cell count, red blood cell count, hemoglobin, hematocrit, red blood cell indices (mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration), reticulocytes, normoblasts, thrombocyte count, differential white blood cell count, prothrombin time, and activated partial thromboplastin time, using hematology analyzer. The following table is prepared by the reviewer based on the sponsor's summary table:

Dose (mg/kg/day)	**0 (vehicle)**		**0.63 PAL**		**2.5 PAL**		**10 PAL**		**10 RIS**	
Sex : No.of animals	M:20	F:20	M:20	F:20	M:20	F:20	M:20	F:20	M:20	F:20
White blood cells (10^3/µl)	9.9	4.5	1.020	1.244 **	-	1.267 **	-	1.289 **	-	1.267 ***
Red blood cells (10^6/µl)	-	8.21	-	-	-	1.034 *	-	1.034 *	-	1.039 *
Hemoglobin (g/dl)	15.6	15.1	1.071 ***	1.026	1.096 ***	1.053 ***	1.096 ***	1.060 ***	1.103 ***	1.060 ***
Hematocrit (%)	46.8	44.4	1.056 ***	1.027 *	1.079 ***	1.043 **	1.068 ***	1.052 ***	1.077 ***	1.056 ***
Mean cell volume	51.5	-	1.029	-	1.033	-	1.039	-	1.054	-

(fl)			*		***		***		***	
Mean cell hemoglobin (pg)	17.1	18.4	1.047 **	-	1.053 ***	-	1.070 ***	1.027 *	1.082 **	1.022 *
Mean cell hemoglobin conc. (g/dl)	33.3	34.0	1.015 *	-	1.015 **	1.009 *	1.024 **	1.009 *	1.024 **	1.006 *
Neutrophils (10^3/µl)	1.77	0.98	-	-	-	1.449 ***	1.192	1.429 **	1.266 *	1.378 **
Lymphocytes (10^3/µl)	7.52	3.24	-	1.225 *	-	1.198 *	-	1.238 *	-	1.216 **
Monocytes (10^3/µl)	-	0.17	-	1.353 *	-	1.412 **	-	1.235	-	1.294 *
Eosinophils (10^3/µl)	-	0.14	-	1.286 *	-	1.357 ***	-	1.214 *	-	1.286 **

[a] At the end of dosing period. For vehicles, group means are shown. For treated groups, multiples of vehicles are shown. Statistical significance is based on actual data (not on the multiples of vehicle). "-" No noteworthy findings. * $p<0.05$, ** $p<0.01$, **8 $p<0.001$; PAL-paliperidone; RIS-risperidone

The table above shows noteworthy hematology findings at the end of dosing period (after 27 weeks of dosing). In most cases the increases were dose-related. White blood cells were slightly increased in all paliperidone or risperidone-dosed female groups. Red blood cells were minimally increased in females dosed with paliperidone at 2.5 and 10 mg/kg/day and with risperidone at 10 mg/kg/day. Hemoglobin and hematocrit were slightly to moderately increased males and females in all test articles-treated groups. Mean cell volume was slightly to moderately increased in all male test article treatment groups. Mean cell hemoglobin and mean cell hemoglobin concentration were moderately increased in all test article treatment male rat groups and minimally increased in female rat groups administered 2.5 or 10 mg/kg/day paliperidone or 10 mg/kg/day risperidone. Slight increases in neutrophiles, lymphocytes, monocytes and eosinophils were noted in female rats in all test articles-treated groups. Paliperidone and risperidone effects on hematology parameters were very similar.

Clinical chemistry: Blood was collected for serum analysis during Week 13 and during necropsy (Week 27). The following parameters were determined: sodium, potassium, chloride, calcium, inorganic phosphate, total protein, albumin, glucose, cholesterol, triglycerides, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase. In male rats treated with paliperidone at 0.63 mg/kg/day, a minimal decrease in sodium and triglycerides and a slight increase in creatinine were noted, while in female rats, slight decreases in sodium and chloride and a slight increase in potassium, inorganic phosphate and marked increase in triglycerides were noted after 13 weeks of treatment. After 27 weeks of treatment at 0.63 mg/kg/day, the following changes were seen in males: a minimal decrease in sodium and triglycerides and slight increases in creatinine and albumin. In females, a slight increase in calcium, marked increase in potassium, inorganic phosphate and triglycerides and slight decreases in glucose and creatinine were observed. Dosing with paliperidone at 2.5 mg/kg/day resulted in the same changes as observed at 0.63 mg/kg/day. In addition to these changes, a slight decrease in potassium after 13 weeks of dosing, a slight increase in albumin after 13 weeks of dosing, and marked increase in albumin after 27 weeks of dosing were observed in males. In females, increases in calcium, total protein and

albumin were also seen after 13 weeks of dosing together with a decrease in chloride at 27 weeks. When male and female rats were dosed with paliperidone and risperidone at 10 mg/kg/day, the same changes were observed as described above. Additionally, a decrease in glucose after 13 weeks in males and slight increases in total protein and albumin were noted after 27 weeks of dosing in females. In males dosed with risperidone an additional decrease in glucose and calcium and a slight increase in ALT was observed after 27 weeks of dosing. A marginal decrease in creatinine was present in female rats after 13 weeks of dosing with risperidone.

Urinalysis: Urine sampling for urinalysis was performed in Week 13 and prior to necropsy (Week 27). The following parameters were measured: volume, specific gravity, pH, proteins, glucose, ketones, occult blood, sediment. When female rats were dosed for 27 weeks with paliperidone or risperidone up to 10 mg/kg/day, no changes in urinalysis were observed. In male rats dosed with paliperidone at 0.63 or 2.5 mg/kg/day, an increase in pH, a decrease in proteins and in ketones were noted after 13 weeks of dosing and an increase in volume and consequently a decrease in specific gravity, decreases in protein, in occult blood and in ketones were registered at Week 27. In addition to the above mentioned urinary changes, slight increases in volume and slight decreases in specific gravity and occult blood were present after 13 weeks of dosing. Dosing male rats with paliperidone or risperidone at 10 mg/kg/day resulted in the same changes.

Gross pathology: A full necropsy was performed on all animals of the main study. Animals were fasted prior to terminal kill. All macroscopic changes were recorded. Samples of tissues from all rats of the main toxicity study were collected and preserved (see below). When rats were dosed with paliperidone at 0.63, 2.5 or 10 mg/kg/day or with risperidone at 10 mg/kg/day, yellow or dark stippled prostates were seen in male rats, and mammary gland stimulation and uterine changes indicating decreased cyclic activity were observed in female rats.

Organ weights: The following organs of the main study animals were weighed: lungs, spleen, liver, heart, pancreas, kidneys, brain, thymus, adrenal glands, thyroid glands (including parathyroid glands), gonads (testes, ovaries) and popliteal lymph nodes. Dosing male rats with paliperidone at 0.63 mg/kg/day did not result in drug induced organ weight changes, while in female rats an increase in liver weight and in the weight of the gonads were noted. After dosing with paliperidone at 2.5 mg/kg/day, an increased liver weight and weight of the gonads were seen in females. An increased weight of the adrenals was observed in males. When male and female rats were dosed with paliperdione or risperidone at 10 mg/kg/day, the same changes as seen after dosing with paliperidone at 2.5 mg/kg/day were observed.

Histopathology: Samples of the tissues from all rats of the main toxicity study were preserved in 10% buffered formalin (except the eyes and testes), embedded, sectioned, stained with hematoxilin-eosin and examined by light microscopy. The following tissues were examined in animals from all groups: In male rats: adrenal glands, kidneys, mammary gland, prostate (dorsolateral and ventral), salivary glands (parotid, submandibular, sublingual-bilateral), spleen and all gross changes. In female rats: female

genital tract (ovaries, oviducts, uterus, cervix, vagina), mammary gland, salivary glands (parotid, submandibular, sublingual-bilateral), spleen and all gross changes.
The following tissues were examined histologically in all terminal kill animals of the vehicle and high dose groups: adrenal glands (in female rats only), aorta, bone (stifle joint and sternum) and bone marrow with bone marrow sample, brain, esophagus, exorbital lacrimal glands, eyes, genital tract, male (testes, epididymides, seminal vesicles, coagulating glands), Harderian gland(s), heart, kidneys (in females only), large intestine (cecum, colon, rectum), larynx, liver, lungs, lymph nodes (mesenteric, popliteal-bilateral) nose, optic nerve(s), pancreas, parathyroid glands(s), peripheral nerves (sciatic nerves), Peyer's patches, pituitary gland, skeletal muscle, psoas muscle, skin, small intestine (duodenum, jejunum, ileum), spinal cord (cervical, thoracic), stomach (forestomach, glandular stomach), thymus, thyroid glands, tongue, trachea, tracheal bifurcation, ureter(s), urinary bladder.

Neoplastic changes: 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. There were no neoplastic lesions in rats administered risperidone. These tumors were considered incidental findings by the sponsor. However, mammary tumors can result from dosing with a prolactin-stimulating dopamine D_2 antagonists associated with mammary gland stimulation. There were no pancreatic adenomas that were observed in the risperidone-treated male rats in the carcinogenecity study.

Non-neoplastic changes: The following test-article related changes were observed:

Adrenal glands: A minimal diffuse swelling of cells of the adrenocortical zona fasciculata in 3/19 male rats dosed with paliperidone and 4/19 male rats dosed with risperidone at 10 mg/kg/day.
Heart: The sponsor concluded that there are no relevant differences between vehicle and high dose groups. However, this reviewer notes an increased incidence of minimal multifocal, chronic inflammation in the heart of male rats from 5/19 in the control group to 10/19 and 12/19 in the 10 mg/kg/day paliperidone and risperidone groups, respectively (other groups were not examined).
Liver: An increase in incidence of fatty-like vacuolization of the liver in female rats administered paliperidone from 5/19 in control to 9/19 at 10 mg paliperidone/kg/day.
Kidneys: An increased presence of minerals in the pelvis was observed in the 10 mg/kg/day male paliperidone and risperidone groups. This reviewer notes also in increased incidence of the diffuse hyperplasia of transitional epithelium in kidneys from 1/19 in the control to 3/19 in the 10 mg/kg/day paliperidone female group.
Mammary gland: In all female groups, a dose related increase in glandular development associated with the presence of secretion was observed. Minimal focal acinar hyperplasia was observed in one female rat dosed with paliperidone and in one female rat dosed with risperidone at 10 mg/kg/day. In all paliperidone and risperidone-treated male groups, a female appearance, characterized by tubular transformation of the acini graded minimal, was observed in the mammary gland.

Female reproductive tract (ovaries, oviduct, uterus, cervix, vagina): In all dosed female groups, an increased incidence of pseudopregnancy-status was observed that included an increase in ovarian clear appearance of the interstitial tissue, a decrease in glandular development, luminal dilatation and granulocytic infiltrate in the uterus, a decrease in thickness and desquamation, and an increase in mucification of the epithelial vaginal layer. Histological changes were comparable between the 10 mg/kg/day paliperidone and risperidone groups. This reviewer notes also an increase in the incidence of ovarian cysts (1/19 in the control, 5/19 in 2.5 mg/kg/day, 5/19 in 10 mg/kg/day paliperidone and 2/19 in risperidone groups). These changes are likely due to a stimulation of prolactin secretion induced by the dopamine D_2 antagonistic activity of paliperidone and risperidone.
Male reproductive tract (testes, epididymides, prostate, coagulating glands, seminal vesicles): Multifocal inflammation, predominantly consisting of granulocytic infiltrate in the dorsolateral prostatic gland (graded slight to moderate) was increased in relation to the dose in all dosed male groups. A decrease in the focal inflammation predominantly consisting of chronic inflammatory cells and in the presence of inspissated secrete was observed in the ventral prostatic gland of all dosed groups.
Spleen: An increase in amount of red blood cells in the splenic red pulp in most male and female rats in groups dosed with paliperidone and with risperidone at 10 mg/kg/day.

Toxicokinetics: Toxicokinetic parameters were evaluated on Day 0, 77/78 and after Day 178 of the study. Blood samples were taken from the orbital venous plexus from three satellite animals/sex/dose (a subset) and per toxicokinetic sampling point (alternating sampling) at 30 min (subset A), 1 (subset B), 2 (subset A), 4 (subset B), 8 (subset A) and 24 hours (subset B) post-dosing. Paliperidone was rapidly absorbed after both single and repeated dosing. Following oral administration of paliperidone, C_{max}- and AUC values of paliperidone increased fairly dose-proportionally. In males, lower paliperidone plasma levels were attained than in females. Upon treatment with risperidone, the conversion of risperidone to paliperidone was similar in both sexes. On Day 178 of administration, metabolically formed paliperidone contributed approximately 42-54% (C_{max}-values) or 78% (AUC_{0-24h} values) to the active fraction in risperidone-treated rats. At the 10 mg/kg dose level, the systemic exposure to paliperidone in paliperidone-treated male rats was approximately 2.0 times (based on C_{max}-values) or 1.5 times (based on AUC_{0-24h} values) higher than the exposure to metabolically formed paliperidone in risperidone-treated males. In females these ratios were about 4.1 (C_{max}-values) and 2.7 (AUC_{0-24h} values).

Mean C_{max} and AUC_{0-24h} values of paliperidone, risperidone and active fraction on Day 178 of the 6-month repeat-dose p.o. gavage toxicity study are shown in the following sponsor's table:

		Paliperidone				Risperidone	
Males (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	212	812	3717	1863	1572	3435
AUC_{0-24h}	(ng.h/mL)	512	1948	8476	5479	2128	7066[a]
Females (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	251	1387	5303	1279	1795	3074
AUC_{0-24h}	(ng.h/mL)	965	5115	23291	8584	4315[a]	10978[a]

[a] $AUC_{0-\infty}$ (AUC_{0-24h} could not be estimated accurately)

bw = body weight; PALI = paliperidone; RIS = risperidone; AF = active fraction

Other: Endocrinology: Blood collected from all rats at necropsy on Day 178 and 179 was used for prolactin determinations. Prolactin was determined using a rat specific radioimmunoassay. After 6 months repeated daily oral administration of paliperidone and risperidone, no statistically significant effect on prolactin levels could be observed in serum samples collected in rats of both sexes. Prolactin AUC_{0-24h} values did not show a clear dose related change but the effect on prolactin levels was most pronounced in the 10 mg/kg dose groups.

Mean serum prolactin levels about 24 h after sacrifice and mean serum prolactin AUC_{0-24h} values in the 6-month repeat-dose p.o. gavage toxicity study in Sprague-Dawley rats are shown in the following sponsor's table:

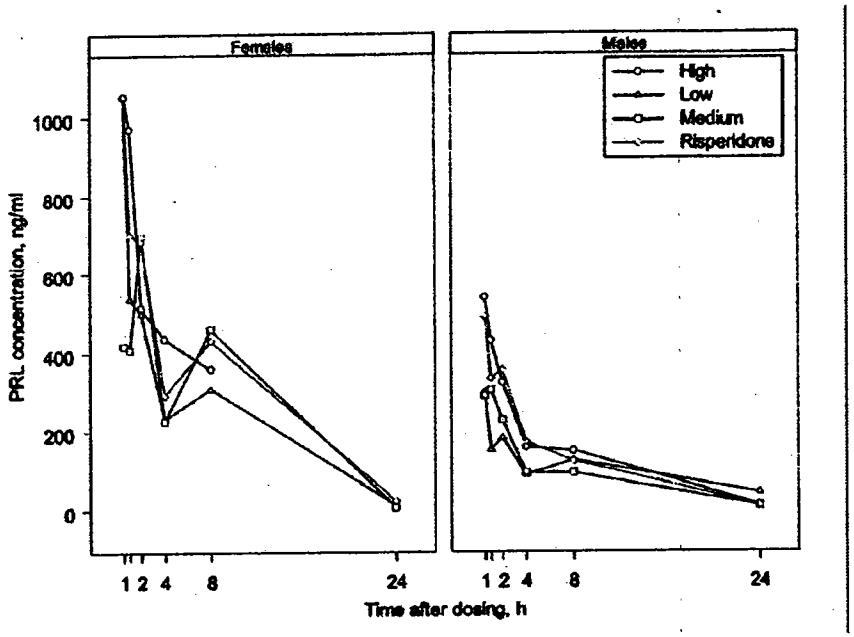
		Control	Paliperidone			Risperidone
			Males[a]			
Dose (mg/kg bw/day		**0**	**0.63**	**2.5**	**10**	**10**
C_{24h}	(ng/mL)	17	20	24	32	42
AUC_{0-24h}	(ng.h/mL)	-	2310	1977	3066	2788
			Females[b]			
Dose (mg/kg bw/day)		**0**	**0.63**	**2.5**	**10**	**10**
C_{24h}	(ng/mL)	44	85	52	36	69
AUC_{0-24h}	(ng.h/mL)	-	5516	7298	7088	7713

[a] C_{24h}: n = 18-19/dose level
[b] AUC_{0-24h}: n = 6/dose level

bw = body weight; - = no data

However, an additional analysis of samples taken at 0.5, 1, 2, 4, 8 and 24 hours after dosing on Day 178, showed a clear increase in prolactin, reaching peak values at 0.5 h and declining gradually over 24 hours.

Mean prolactin plasma concentrations in toxicokinetic samples on Day 178 of the 6-month repeat-dose p.o.gavage toxicity study in Sprague-Dawley rats dosed with paliperidone and risperidone are shown in the following sponsor's figure:



11. Study title: One-Month Toxicity Study in SPF Wistar Rats (Study No. 2849)

The purpose of this pilot (non-GLP) study 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 10 mg/kg/day of risperidone by p.o. gavage for comparative purposes. Out of these animals, 4 males and 4 females per group were used for toxicokinetic analysis. This study was conducted in the Department of Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium. Period of dosing started on October 22, 1992. Parameters studied included: mortality, clinical observations, body weight, food consumption, hematology, serum analysis, urinalysis, organ weights, gross pathology.

Mortality: There was no mortality in this study. Clinical signs: 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 these observed with risperidone. Body weights: Body weight and body weight gain were slightly increased in females at 0.63 mg/kg/day (+8% and +21%, respectively). There were no changes in males at this dose. At 2.5 and 10 mg/kg/day, a slight to moderate decrease was noted in males, while in females, body weight was less affected. In males dosed with either 10 mg/kg/day of paliperidone and risperidone, body weight was moderately decreased (-14% and -19%, respectively). Body weight gain was decreased in males treated with 10 mg/kg of paliperidone (up to -29%) and risperidone (-39%). In females dosed with either 10 mg/kg/day of paliperidone and risperidone, body weight was slightly decreased (-4% and -10%, respectively). Body weight gain was also decreased in females treated with 10 mg/kg/day of paliperidone (up to -14%) and risperidone (-31%). The effect of risperidone was more pronounced as compared to

paliperidone treated groups. Food consumption: Food consumption was increased in females treated at 0.63 mg/kg/day (+14%). Food consumption was 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: 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 (+20%) and a decrease in thrombocytes in male (-22%) and female (-15%) rats treated with paliperidone as well as in males treated with risperidone (-23%). Clinical chemistry: Blood urea nitrogen was slightly increased in males (+30%) 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. Urinalysis: The following 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. Organ weights: a decrease in the weight of ovaries was noted in all paliperidone and risperidone dosed groups. Histopathology was not conducted. All results are summarized in the following sponsor's table:

Parameter	Dosage groups (mg/kg body weight/day)							
	0.63		2.5		10		R 64766 /10	
	M	F	M	F	M	F	M	F
Mortality	-	-	-	-	-	-	-	-
Clinical obs. - sedation - ptosis	 +	 +	 + +	 + +	 + +	 + +	 + +	 + +
Body weight		incr. +	decr. +	decr. ±	decr. ++	decr. ±	decr. ++	decr. +
Food consump.		incr. +					decr. +	decr. ±
Haematology - WBC - WBC formula - neutrophils - lymphocytes - thrombocytes					 incr. + incr. + decr. + decr. +	 incr. ± incr. + decr. + decr. +	 decr. +	
Serum analysis - total protein - BUN - calcium - triglycerides			decr. +	decr. ±	decr. + incr. ++	decr. +	decr. + decr. + decr. +	decr. + decr. ± decr. ±
Urinalysis - creatinine - spec.gravity - bacteria				decr. + decr. +	decr. + decr. + incr. +	decr.+ decr. + incr. +	decr. + decr. + incr. +	decr. + decr. + incr. +
Organ Weights - ovaries		decr. +		decr. +		decr. ++		decr. ++
Gross pathology - mammary gl. stimulation		+		+		++		++

Legend: ± trend; + slight; ++ moderate; +++ severe

In conclusion, the NOAEL for paliperidone was determined to be 0.63 mg/kg/day. Despite the differences in exposure (see TK study below), the toxicological profile after dosing with paliperidone at 10 mg/kg/day was comparable to that observed in rats dosed with risperidone at the same dose.

12. Study title: The Toxicokinetics of 9-Hydroxy-Risperidone (R 76477) and of Risperidone (R 64766) in SPF Wistar Rats at the Occasion of the One-Month Subchronic Oral Pilot Toxicity Study (Exp. No 2849) of Aqueous Solutions of 9-Hydroxy-Risperidone at 0.63, 2.5 or 10 mg/kg/day and of an Aqueous Solution of Risperidone at 10 mg/kg/day (Study No. R 76477/FK1399).

For each dose level of paliperidone, plasma concentrations of paliperidone were comparable in male and female rats after a single as well as after repeated oral administration. Risperidone plasma levels after administration of risperidone were on average 4 times higher in female than in male rats. After repeated administration of paliperidone, peak plasma concentrations and AUC-values tended to increase dose-proportionally. On Day 26 of administration, metabolically formed paliperidone contributed approximately 67% (based on C_{max} values) or 78% (based on AUC values) to the active fraction in risperidone-treated male rats. In females, these contributions were 37% (C_{max}) or 54% (AUC). The exposure to the active moiety was comparable after administration of paliperidone or risperidone in female rats. In male rats, the exposure to the active moiety was about 2 times lower after risperidone than after paliperidone administration. At 10 mg/kg/day, the systemic exposure to paliperidone in paliperidone-treated rats was about 2.8 (F) -3.4 (M) times (C_{max}-values) or 1.9 (F)-2.3 (M) times (AUC-values) higher than the exposure to paliperidone in risperidone-treated animals. Mean C_{max} and AUC_{0-24h} values of paliperidone, risperidone and active fraction on Day 26 of the 1-month repeat-dose p.o. toxicity study in Wistar Wiga rats is shown in the following sponsor's table:

Administration		Paliperidone			Risperidone		
Males (n = 4/dose level)							
Dose (mg/kg bw/day)		0.63	2.5	10		10	
Analyte		PALI	PALI	PALI	PALI	RIS	AF
C_{max}	(ng/mL)	98	445	2849	826	398	1224
AUC_{0-24h}	(ng.h/mL)	378	1742	7182	3101	890	3991
Females (n = 4/dose level)							
Dose (mg/kg bw/day)		0.63	2.5	10		10	
Analyte		PALI	PALI	PALI	PALI	RIS	AF
C_{max}	(ng/mL)	99	860	2100	737	1266	2003
AUC_{0-24h}	(ng.h/mL)	350	2117	7593	4004	3385	7389

bw = body weight; PALI = paliperidone; RIS = risperidone; AF = active fraction

13. Study title: 3 Month Repeated Dose Oral Toxicity Study in the Rat (Study No. TOX 6343)

The purpose of this study was to assess the potential toxicity of paliperidone (Lot No. ZR076477EIA041) when administered daily by the oral route (through the diet) to Sprague-Dawley rats (10/sex/group; weight range from 143 to 224 g) for a period of 3 consecutive months at doses of 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. The study was conducted by Johnson & Johnson Pharmaceutical Research and Development, Global Preclinical Development, Beerse site, Turnhotseweg 30, 2340 Beerse, Belgium. The experimental starting date was January 27, 2004. The following parameters were recorded during the study: mortality, clinical observations, body weight and weight gain, food consumption, test article intake, hematology, serum and urine examination, endocrinology (prolactin), organ weights, gross pathology and histopathology. The toxicokinetics of paliperidone were also studied in an additional group of animals (6/sex/group).

Results:

Mortality: There was no test article related mortality noticed in rats of the main toxicity study part up to 20 mg/kg/day. In the TK satellite group, one female rat dosed at 20 mg/kg body weight/day was found dead on Day 7 of the study.

Clinical signs: No relevant test article related clinical signs were observed when rats were dosed for 3 months at 1.25 mg/kg/day. Dosing with paliperidone at 5 mg/kg/day resulted in ptosis in both sexes (2/10 males, 3/10 females). Dosing at 20 mg/kg/day resulted in the same changes as observed after dosing at 5 mg/kg body weight/day. Additionally, occasional sedation (1/10) and waste of food (9/10) was observed in female rats. Ptosis was present in all animals at this dose.

Body weight At 1.25 mg/kg/day, body weight and weight gain were marginally to slightly decreased in male rats and increased in female rats. At 5 mg/kg/day, moderate decreases in body weight and weight gain were observed in males, while increases in body weight and weight gain in female rats were less pronounced compared to those observed at 1.25 mg/kg body weight/day. At 20 mg/kg/day, marked decreases in body weight and weight gain were measured in male rats and moderate decreases in body weight and weight gain were noted in female rats.

Food consumption: At 1.25 mg/kg/day, food consumption was marginally to slightly decreased in male rats and increased in female rats. Test article intake was 1.26 mg/kg/day for males and 1.27 mg/kg/day for females. At 5 mg/kg/day, a slight decrease in food consumption was observed in males. Food consumption of female rats was also occasionally slightly lower compared to food consumption of control rats. Test article intake was comparable to the theoretical intake: 5.02 mg/kg body weight/day for males and 4.97 mg/kg body weight/day for females. At 20 mg/kg/day, food consumption was moderately lower in males and slightly lower in females, compared to the control group. Test article intake was in the range of the theoretical intake in males and slightly higher in females: the mean intake was 20.3 mg/kg body weight/day in males and 21.6 mg/kg body weight/day in females.

Hematology: At 1.25 mg/kg/day, hematological examination showed a marginal increase in hemoglobin and a slight increase in the number of neutrophils in males. At 5 mg/kg/day, similar hematology changes were present as seen after dosing at 1.25 mg/kg/day. Additionally, hemoglobin was also marginally increased in females and a slight increase in hematocrit was noted in both males and females. At 20 mg/kg/day,

similar hematological changes were present as seen after dosing at 5 mg/kg/day. Additionally, slight increases in mean cell hemoglobin and mean cell hemoglobin concentration were observed in males and a marginal increase in the number of red blood cells was noted in females.

Clinical chemistry: At 1.25 mg/kg/day, biochemical examination showed a slight increase in triglycerides and a slight decrease in creatinine in females. At 5 mg/kg/day, similar serum changes were present as seen after dosing at 1.25 mg/kg body weight/day. Additionally, marginal increases in albumin and total protein and a slight decrease in glucose were observed in males and a marginal decrease in total bilirubin was seen in females. At 20 mg/kg/day, similar serum changes were present as seen after dosing at 5 mg/kg body weight/day. An additional slight increase in urea nitrogen and a slight decrease in glucose were noted in females while marginal decreases in sodium, potassium and chloride and a slight decrease in inorganic phosphate and a slight increase in cholesterol were observed in males.

Urinalysis: There were no treatment related changes in urinalysis.

Organ weights: At 1.25, 5 and 20 mg/kg/day, no toxicologically important organ weight changes were seen in male and female rats except a slight decrease in absolute ovarian weight measured in females administered 20 mg/kg/day. Decreases observed (mainly in male rats) in absolute organ weights with accompanied increases in relative organ weights were likely related to the decrease in body weight of the dosed animals. All other changes were not dose-related or not correlated with relevant histological changes.

Gross pathology: At 1.25 mg/kg/day, no gross pathological changes were seen at necropsy in male and female rats. At 1.25 and 5 mg/kg/day, stimulation of the mammary gland was observed in females. At 20 mg/kg/day, similarly as noted at previous dose levels, stimulation of the mammary glands was observed in females.

Histopathology: Histopathological examination was conducted on tissues from the control and high dose groups using standard procedures. Some tissues were examined from all dose level groups. Examinations 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 also noted. The 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 basophylic corpora lutes. Changes in the uterus included mainly decreased incidence of infiltrating granulocytes. Changes in the vagina included increased frequency mucified aspect and decreased thickness of the epithelial layer. Histological changes in mammary gland in the dosed male and female rats included (1) female appearance in males (low epithelium with the secretion present in one high dose male rats) 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 and with predominantly granulocytes. 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.

Endocrinology: At a dose of 20 mg/kg/day, a slight increase in prolactin level was noted in male rats. There were no increases in prolactin levels at lower doses in males. In females, a dose-dependent increase in prolactin level was observed in paliperidone-treated rats. However, mean serum prolactin level was similar in the control and high dose groups. Different from test article treated rats, prolactin levels fluctuated strongly between different time points in control female animals. In female control animals, prolactin levels were high at certain sampling time points which resulted in an AUC_{24h} value which was comparable to the high dose value. However, at early time points, mean prolactin levels in the control group were clearly in the normal biological range while in the test article treated rats, prolactin levels were increased at these time points.

Mean serum prolactin $AUC_{0\text{-}24h}$ in the 3-month dietary repeat-dose toxicity study in Sprague-Dawley rats is shown in the following table:

	Control	Paliperidone		
Males (n = 10/dose level)				
Dose (mg/kg bw/day)[a]	**0**	**1.25**	**5**	**20**
$AUC_{0\text{-}24h}$ (ng.h/mL)	1003	937	911	1248
Females (n = 10/dose level)				
Dose (mg/kg bw/day)	**0**	**1.25**	**5**	**20**
$AUC_{0\text{-}24h}$ (ng.h/mL)	4354	1801	3523	4453

[a] nominal dose levels

bw = body weight

Toxicokinetics: The exposure levels to paliperidone were measured on Days 13/14 and 76/77. Values obtained on both days were comparable. Exposures to paliperidone in males and females increased reasonably dose-proportionally in this study. The data indicated higher exposure levels in female than in male rats. Mean C_{max} and $AUC_{0\text{-}24h}$ values of paliperidone on Day 76/77 in the 3-month dietary repeat-dose toxicity study in Sprague-Dawley rats are shown in the following sponsor's table:

Dose (mg/kg bw/day)[a]		1.25	5	20
		Males (n = 3/dose level)		
C_{max}	(ng/mL)	33.3	130	772
AUC_{0-24h}	(ng.h/mL)	556	1950	12500
		Females (n = 3/dose level)		
C_{max}	(ng/mL)	52.4	325	1496
AUC_{0-24h}	(ng.h/mL)	874	4910	25600

[a] nominal dose levels

bw = body weight

14. Study title: Three-Month Repeated Dose Oral Toxicity Study in the Wistar Rat

The purpose of this study was to assess the potential toxicity of paliperidone when administered once daily by the oral route (gavage) to Wistar rats for a period of 3 months. An additional group was administered risperidone to allow a direct comparison of toxicities.

Key study findings: Ptosis and sedation (up to moderate level) were 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. A slight decrease in white blood cells and thrombocytes was noted at 10 mg/kg/day in males. There were only slight changes in clinical chemistry parameters (see below). 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 histolopathological changes were observed in the adrenals of males, mammary gland of both sexes, prostate, pituitary gland and female reproductive tract at all dose levels. At 10 mg/kg/day of paliperidone or risperidone, male animals showed low epithelium of the coagulating glands and seminal vesicles. In the splenic red pulp, increases in red blood cells and hemosiderin pigment were observed in both sexes. All of these findings were similar for paliperidone and risperidone at 10 mg/kg/day.

Study no.: 4603
Volume #, and page #: electronic submission
Conducting laboratory and location: Department of Toxicology, Janssen Pharmaceutica N.V., 2340 Beerse, Belgium
Date of study initiation: June 2, 1998 (first day of dosing)
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: paliperidone, lot ZR076477PFA011, purity [redacted]
risperidone, lot ZR064766PUA181, purity: [redacted]

Methods

Doses: Paliperidone: 0, 0.63, 2.5 and 10 mg/kg/day. Risperidone: 10 mg/kg/day

Species/strain: rat/Wistar Hannover
Number/sex/group or time point (main study): 20/sex/group
Route, formulation, volume: oral, aqueous solution (tartaric aid, NaOH ad pH=5, demineralized water), 10 ml/kg body weight
Satellite groups used for toxicokinetics or recovery: TK: 4/sex/group; recovery: none
Age: 4 weeks old
Weight: males 119 g; females 103-104 g
Sampling times: Necropsy was conducted September 2-8, 1998

Observations, times and results:

Mortality: All animals were observed at least once a day. No mortalities occurred in this study.

Clinical signs: All animals were observed at least once a day for clinical signs. Paliperidone administration from a dose of 0.63 mg/kg/day resulted in a dose-dependent ptosis and sedation (from slight to moderate) in rats. These effects were observed in 20/20 animals in each group except ptosis at 0.63 mg/kg that was seen in 7/20 male and 3/20 female rats. Animals dosed with paliperidone and risperidone at 10 mg/kg/day were moderately sedated. No differences were seen between the animals dosed with paliperidone and risperidone.

Body weights: Recorded weekly. Body weight and body weight gain were dose-dependently decreased (up to -21% and -32%, respectively) in male rats dosed with paliperidone at 2.5 and 10 mg/kg/day. In females, body weight and body weight gain were slightly decreased (up to -7% and -14%, respectively) at 10 mg/kg of paliperidone. There were no differences between animals dosed with paliperidone or risperidone at 10 mg/kg/day in changes in body weights.

Food consumption: Recorded weekly. Mean food consumption was slightly decreased (-9%) in males administered paliperidone at 2.5 or 10 mg/kg/day. In female rats dosed at 0.63 mg/kg/day, food consumption was slightly increased (+8%) but not affected at higher doses. There were no differences between animals dosed with paliperidone or risperidone at 10 mg/kg/day in changes in food consumption.

Ophthalmoscopy: Examination was performed at the start of the study and towards the end of the study on the first 10 animals of each sex in the high dose group, the reference group and the control group. There were no test articles-related findings.

EKG: not conducted

Hematology: Examinations were performed in all rats after 4 weeks and after 13 weeks. The following parameters were assessed: hematocrit, hemoglobin, red and white blood cell count, red blood indices (mean cell volume, mean cell hemoglobin and mean cell hemoglobin concentration), thrombocyte count, and differential white blood cell count. In

males in Week 4, a slight to moderate increase in hematocrit (up to +10%), hemoglobin (up to +10%) and a slight increase in red blood cells (up to +8%) were noted. In addition, slight decreases in white blood cells, thrombocytes and lymphocytes were noted at 10 mg/kg/day. In females in Week 4, a slight decrease in hematocrit, hemoglobin, red blood cells, white blood cells, lymphocytes and neutrophils was noted at all dose levels. In males in Week 13, a slight to moderate increase in hematocrit (up to +12%), hemoglobin (up to +14%), slight increase in red blood cells (up to +5%), slight increase in mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentration were noted at all dose levels. In addition, a slight decrease in white blood cells and trombocytes was noted at 10 mg/kg/day. In females in Week 13, findings in hematocrit, hemoglobin, red blood cell count, mean cell volume and mean cell hemoglobin were similar (increases), although less pronounced. Hematology findings were similar in paliperidone and risperidone treated animals.

Clinical chemistry: Examinations were performed in all rats after 4 weeks and after 13 weeks. The following parameters were assessed: sodium, potassium, chloride, inorganic phosphate, total protein, albumin, glucose, cholesterol, triglycerides, phospholipids, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase. Dosing paliperidone for three months to male rats resulted in a slight increase in albumin at all dose levels. From a dose of 2.5 mg/kg body weight/day onwards, a slight increase in blood urea nitrogen was seen in both sexes (transient in females). Slight decreases in chloride and glucose in females were seen at all dose levels. When rats were dosed at 10 mg/kg body weight/day, slight increases in cholesterol and phospholipids in males were present. Sodium was minimally decreased in females at all doses. Changes seen in the group dosed with paliperidone at 10 mg/kg/day were comparable with those seen in the group dosed with risperidone at 10 mg/kg/day.

Urinalysis: Examinations were performed in all rats after 4 weeks and after 13 weeks. The following parameters were assessed: volume, urobilinogen, pH, proteins, glucose, ketones, bilirubin, occult blood, specific gravity, sediment. Dosing with paliperidone from a dose of 0.63 mg/kg/day onwards for three months to rats resulted in a slight decrease in specific gravity in males. When paliperidone was dosed at 2.5 mg/kg/day, a decrease in specific gravity and an increase in urinary volume in females were also seen. Additionally, at 10 mg/kg/day, an increase in presence of sperm was present in males. Urinalysis findings were similar in paliperidone and risperidone treated animals.

Gross pathology: A full necropsy was performed on all animals and all macroscopic changes were recorded. There were no significant findings in males. Gross pathology indicated stimulation of the female mammary glands at all dose levels of paliperidone (mainly at 2.5 and 10 mg/kg/day). Similar effects were seen in animals dosed at 10 mg/kg/day with risperidone.

Organ weights: The following organs of all rats were weighed: lungs, spleen, liver, heart, pancreas, kidneys, brain, thymus, adrenal glands, thyroid glands (including parathyroid gland) and gonads (testes, ovaries). The differences in the weight of the lungs, spleen,

liver, heart, pancreas, kidneys, brain, thymus, thyroids and gonads in males, and in the weight of the lungs, spleen, heart, kidneys, brain, thymus (at 0.63 mg/kg), adrenals and thyroids in females were not considered to be test article related by the sponsor since they were slight, not dose related and/or related to the differences in body weight. Dosing paliperidone at 0.63 mg/kg/day or higher dose levels resulted in slight increases in the absolute and relative to body weight of the adrenals (up to +40%) in males and in the absolute and relative to body weight of the liver (up to +20%) in females, and in a slight decrease in the absolute and relative to body weight of the gonads in females (up to -23%). From the dose of 2.5 mg/kg/day onwards, a decrease in the absolute and relative to body weight of the thymus (up to -20%) in females was also noted. Changes in organ weights seen in the animals dosed with paliperidone at 10 mg/kg/day were comparable with those seen in the animals dosed with risperidone at 10 mg/kg/day.

Histopathology: Tissues were trimmed, embedded, sectioned and stained with H&E. A streptovidin-biotin immunohistochemical staining for prolactin was performed on the pituitary gland. Tissues from the high-dose group, the reference group and gross lesions from all animals were examined histologically. The following tissues/organs were examined: adrenal glands, aorta, bone with bone marrow, brain, coagulating glands, epididymides, esophagus, external ear, extraorbital lacrimal gland, eyes, heart, kidneys, large intestine, liver, lungs, lymph nodes (mesenteric), mammary gland, nose, ovaries, pancreas, parathyroid gland, pituitary gland, prostate, salivary gland, seminal vesicles, skeletal muscle, small intestine, spinal cord, spleen, stomach, testes, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina, all tissues showing gross changes. Test article-dependent 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 due to the α-lytic effect of the test articles. There were no

differences in histopathology in rats administered paliperidone or risperidone at 10 mg/kg/day.

Endocrinology: Prolactin levels were determined in blood collected at sacrifice (i.e. about 24 hours after final administration). Mean serum prolactin levels were markedly increased in both sexes at all dose levels. These increases were up to ~11 – and ~ 6 fold the vehicle control levels in males and females, respectively. There was no clear dose-dependence. A similar increase in mean serum prolactin level was seen in animals dosed with risperidone at 10 mg/kg/day. Mean serum prolactin levels at about 24 h after sacrifice in the 3-month repeat-dose p.o. gavage toxicity study in Wistar Hannover rats are shown in the following sponsor's table:

	Control	Paliperidone			Risperidone
Males (n = 6/dose level)					
Dose (mg/kg bw/day)	**0**	**0.63**	**2.5**	**10**	**10**
C_{24h} (ng/mL)	20	158	192	211	193
Females (n = 6/dose level)					
Dose (mg/kg bw/day)	**0**	**0.63**	**2.5**	**10**	**10**
C_{24h} (ng/mL)	60	286	357	356	304

bw = body weight

Toxicokinetics: TK and metabolism studies were performed according to protocol FK2930 (see below)

15. Study title: Toxicokinetics of Paliperidone and of Risperidone in the SPF Wistar Rat in a Three-Month Repeated Dose Oral Toxicity Study (Exp. No. 4603) on Aqueous Solutions of Paliperidone at 0.63, 2.5 or 10 mg/kg/day and of an Aqueous Solution of Risperidone at 10 mg/kg/day (Study No. FK2930)

After administration of paliperidone, the peak plasma concentrations were reached within 2 h after dosing. Paliperidone levels tended to increase dose-proportionally in male rats, to slightly more than dose-proportionally in female rats. The conversion of risperidone to paliperidone was more extensive in males and females. In males, the exposure to metabolically formed paliperidone was 3- (C_{max}) and 2-(AUC_{0-24h}) times higher than those of unchanged risperidone. In females, these values were similar for both compounds. Mean (n=2) C_{max} and AUC_{0-24h} values of paliperidone, risperidone and active moiety on Day 86-87 in the 3-month repeat-dose p.o. gavage toxicity study in Wistar Hannower rats are shown in the following sponsor's table:

		Paliperidone			Risperidone		
Males (n = 4/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	136	764	2635	628	212	840
AUC_{0-24h}	(ng.h/mL)	595	1763	11101	1772	867	2619
Females (n = 4/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	93	610	3441	1132	1279	2411
AUC_{0-24h}	(ng.h/mL)	346	1610	11366	4420	3506	7899

bw = body weight; PALI = paliperidone; RIS = risperidone; AF = active fraction

REPEAT DOSE TOXICITY STUDIES IN MICE

16. Study title: 3-Month Repeated Dose Oral Toxicity Study in the Swiss Mouse

The purpose of this study was to assess the potential toxicity of paliperidone when administered once daily by the oral route for a period of 3 months and to compare its potential toxicity with the potential toxicity of risperidone. The toxicokinetics was studied as well. This study was designed by the sponsor as a range finding study in order to determine the dose for the carcinogenicty study.

Key study findings: 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 weights 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 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.

Study no.: TOX5721
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica, N.V., Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: March 13, 2003
GLP compliance: yes (OECD)
QA report: yes (x) no ( )

Drug, lot #, and % purity: paliperidone (R076477; 9-OH risperidone), lot ZR076477PUA031, purity [redacted]; risperidone (R064766), lot ZR064766PUA401; purity: [redacted]

Methods

Doses: paliperidone: **0**, 0.63, 2.5, 10 mg/kg/day; risperidone: 10 mg/kg/day
Species/strain: mouse/SPF Albino Swiss
Number/sex/group or time point (main study): 10/sex/group
Route, formulation, volume: oral (gavage); aqueous solution of the test article in vehicle (tartaric acid, NaOH 1N up to pH=5, demineralised water); 10 ml/kg body weight/day
Satellite groups used for toxicokinetics or recovery: for toxicokinetics: 36 males and 36 females extra per dosed group; for recovery: none
Age: 6 weeks old on Day 0
Weight: from 21.1 to 35.3 grams
Sampling times: Hematological and clinical chemistry analysis were conducted on Days 88 and 91/92, respectively. Necropsy was performed June 23 and 24, 2003 (Study Days 91 and 92).

Observations, times and results:

Mortality: There was no treatment related mortality. Three main group mice (1 in control, 2 in 10 mg/kg paliperidone groups) died due to gavage errors.
Clinical signs: All animals were observed at least once a day for clinical signs. Slight sedation was observed at 0.63 mg/kg/day on the first day of dosing and at 2.5 mg/kg during the first 5 weeks of dosing. At 10 mg/kg/day of paliperidone and risperidone, sedation was moderate to severe up to first 3 days of dosing and slight for the reminder of the treatment. Ptosis was recorded (up to 6 hours after test article administration) at all dose levels during this study. The same observations of ptosis and sedation were noted after treatment with paliperidone and risperidone at 10 mg/kg/day.
Body weights: Body weights were recorded on Day 0 and at weekly intervals during the study. Body weight was slightly decreased in males at all dose levels (up to -6%). Body weight gain was also reduced (markedly, up to -61%) in males administered 10 mg/kg/day. Changes in body weight gain observed in males after treatment with paliperidone at 10 mg/kg/day were greater than these after administration of risperidone at the same dose (in males: maximum decreases in body weight gain were -61% and -25% in the paliperidone and risperidone groups, respectively). Females showed a moderate increase in body weight (up to 16%) and marked increase in body weight gain (up to 114%). In females, increases in body weights in the risperidone group were similar or slightly greater to these in the paliperidone group.
Food consumption: Food consumption was recorded weekly. There were minimal and slight increases in food consumption in all treatment groups in this study.
Ophthalmoscopy: not conducted
EKG: not conducted
Hematology: Blood sampling for hematology was performed towards the end of the study (Day 88). The following parameters were determined: white blood cell count, red blood cell count, hemoglobin, hematocrit, red blood cell indices (mean cell volume, mean

cell hemoglobin, mean cell hemoglobin concentration), normobasts, reticulocytes, thrombocyte count, differential white blood cell count. Slight to moderate increases in hemoglobin (up to +20%) and hematocrit (up to +12%) were observed at all paliperidone dose levels in both sexes. Red blood cell counts were increased at all dose levels in females (up to 12%). Mean red blood cell volume was slightly increased in all male groups. Mean cell hemoglobin was slightly increased in animals of both sexes treated with paliperidone at 2.5 or 10 mg/kg/day. White blood cells, lymphocytes, monocytes, eosinophiles were slightly to moderately decreased in males dosed with paliperidone. Changes in hematology induced by paliperidone and risperidone were similar.

Clinical chemistry: Blood sampling for serum analysis was performed at the end of the study (Days 91/92). The following parameters were determined: sodium, potassium, triglycerides, blood urea nitrogen, chloride, calcium, inorganic phosphate, total protein, albumin, glucose, cholesterol, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase. There were no adverse effects at a paliperidone dose of 0.63 mg/kg/day in males. Female mice at this dose showed marginally increased total protein, slightly increased potassium and alanine aminotransferase and slightly decreased alkaline phosphatase. Dosing at 2.5 mg/kg/day caused a slight increase in inorganic phosphate, marginal increase in total protein and a marginal decrease in glucose in males. In females, a slight increase in total protein, a slight increase in potassium, inorganic phosphate and alanine aminotransferase and a slight decrease in alkaline phosphatase were noted. At 10 mg/kg/day, the same changes were observed. In addition, slight increases in serum calcium, inorganic phosphorus and blood urea nitrogen were noted in female rats and total protein was slightly increased in both sexes. Findings in the risperidone group were similar.

Urinalysis: not conducted

Gross pathology: A full necropsy was performed on all animals (including mice found dead during the study) and all macroscopic changes were recorded. Mammary gland stimulation at 10 mg/kg was the only paliperidone (in females) or risperidone (in males and females)- related gross pathology finding.

Organ weights: The following organs of the main study animals were weighed: lungs, spleen, liver, heart, pancreas, kidneys, brain, thymus, adrenal glands, gonads (testes, ovaries). Absolute (up to +42%) and relative liver weight was slightly increased in female mice and the absolute (-23%) and relative adrenals weights were moderately decreased. Qualitatively similar changes were seen at all doses, although they were more pronounced with the increasing dose. In addition, slightly increased absolute and relative weights of the kidneys were observed in males.

Histopathology: Samples of the tissues from the vehicle and high dose groups of the main toxicity study were preserved in 10% buffered formalin, embedded, sectioned, stained with hematoxilin-eosin and examined by light microscopy. The following tissues were examined: adrenal glands, aorta, bone, bone marrow, brain, esophagus, exorbital lacrimal glands, eyes with harderian glands, genital tract, female (ovaries, oviducts, uterus, cervix,

vagina), genital tract, male (testes, epididymides, prostate, seminal vesicles, coagulating glands), gall bladder, heart, kidneys, large intestine (cecum, colon, rectum), liver, lungs, lymph nodes (mesenteric), lymph nodes (submandibular), mammary gland, nose, pancreas, parathyroid gland, peripheral nerves (sciatic nerves), Peyers's patches, pituitary gland, salivary glands (parotid, submandibular), skeletal muscle, skin, small intestine, spinal cord, spleen, stomach, thymus, thyroid gland, trachea, urinary bladder, all tissues showing gross changes. Liver, mammary gland and pituitary gland were examined in all male and female dose groups. Cervix, ovaries, oviducts, uterus and vagina were examined in all female groups. Findings were in general related to the increased prolactin levels. Minimal diffuse hyperplasia was observed in the pituitary (pars intermedia) in 1/10, 5/10, 6/10, 8/10 and 10/10 male rats and in 0/10, 5/8, 10/10, 10/10 and 10/10 female rats administered paliperidone at 0, 0.63, 2.5 and 10 mg/kg/day and risperidone at 10 mg/kg/day, respectively. Mammary gland glandular development was seen at all dose levels in all (10/10) females. The severity of this finding increased with the increasing dose. Secretion (graded minimal) was present in the mammary gland of 3/10 and 2/10 female rats administered 10 mg/kg/day paliperidone and risperidone, respectively. The incidence of basophilic corpora lutea in ovaries was decreasing with increasing dose of paliperidone from 8/10 in the vehicle group to 3/10, 2/10, 0/10 and 2/10 in the 0.63, 2.5, 10 mg/kg/day paliperidone groups and 10 mg/kg/day risperidone group, respectively. There was also an increase in the eosinophilic corpora lutea. There were no changes in the spleen in male rats. Minimal hyperplasia was noted in 0/10, 3/3, 2/6, 1/10 and 2/10 female rats administered paliperidone at 0, 0.63, 2.5 and 10 mg/kg/day and risperidone at 10 mg/kg/day, respectively. There were no changes in bone marrow in females. In males, a slight increase in the incidence of prominent granulopoesis and in the severity of bone marrow cellularity was noted. In the uterus, the incidence of infiltrating granulocytes and vacuolated (karyorrhetic) epithelium and in the vagina cornification and infiltrating granulocytes was decreased dose dependently in all test articles groups. The incidence of mucified aspect of the vagina was increased with the increasing dose. Female genital tract showed pseudopregnancy appearance in all test article groups. There were no changes in the pancreas.

Toxicokinetics: On Days 45 and 87 blood samples were collected at 0.5, 1, 2, 4, 8 and 24 h after dosing from satellite animals. These samples were analyzed for paliperidone and risperidone. Mean C_{max} and $AUC_{0\text{-}24h}$ values of paliperidone, risperidone and active fraction on Day 87 of the 3-month repeat-dose p.o. toxicity study in mice are shown in the following sponsor's table:

Administration		Paliperidone			Risperidone		
Males (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	89	279	1269	502	303	783
AUC_{0-24h}	(ng.h/mL)	354	1170	5079	2148	526	2674
Females (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	52	258	1241	440	296	735
AUC_{0-24h}	(ng.h/mL)	284	931	4232	1720	457	2177

bw = body weight; PALI = paliperidone; RIS = risperidone; AF = active fraction

After dosing with risperidone, the active moiety levels were ~1.6 to 2.1-fold lower relative to those achieved after dosing with paliperidone at the same dose level. For both paliperidone and risperidone, the plasma levels were slightly higher in males than in females.

17. Study title: 2-Week Repeated Dose Oral Toxicity Study in the Mouse (Study No. TOX 6404)

The purpose of this study was to assess the potential toxicity of paliperidone when administered daily by the oral route (through the diet) to mice for a period of 2 consecutive weeks. This study was conducted by Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium, and was initiated on March 19, 2004. Mice (5/sex/group, 6 weeks old) were treated with paliperidone (Batch ZR076477EIA041) at 0, 10, 20, 40, or 80 mg/kg/day. In addition, toxicokinetic analysis was conducted on satellite animals. The following parameters were evaluated: mortality, clinical observations, body weight and body weight gain, food consumption, test article intake, hematology, serum analysis, organ weights, gross pathology, histopathology.

Results:
Mortality: There was no mortality in male mice up to 40 mg/kg and in female mice up to 20 mg/kg/day. At 40 mg/kg/day, 1/5 females was sacrificed on Day 5. At 80 mg/kg/day, 1/5 males was found dead on Day 5 and 2/5 females were sacrificed (Days 5-6). According to the sponsor, these deaths were caused by a prolonged decrease in general activity that resulted in emaciation and dehydration. In the TK portion of the study, 1 male and 1 female mouse dosed at 80 mg/kg/day were found dead on Day 6.
Clinical signs: Narrowing of the palpebral fissure was seen at all dose levels in nearly all mice. General activity was slightly decreased at 20 mg/kg/day and higher doses. In addition, poor condition and rough haircoat were seen in one male and one female dosed at 40 mg/kg/day. At 80 mg/kg/day, poor condition was seen in 3 females (in 2 prior to sacrifice) and cold extremities in one female (prior to sacrifice). Body weights: A moderate and transient decrease in body weight gain was observed in Week 1 in all males administered paliperidone at 10 or 20 mg/kg/day. At 40 or 80 mg/kg/day, a moderate decrease in body weight (up to 90% of control level) and a marked decrease in body weight gain were noted in males. In females given 40 or 80 mg/kg/day, a slight decrease in body weight and a moderate but transient decrease in body weight gain, were observed. Food consumption and test article intake: There were no changes in food

consumption at 10 mg/kg/day. A moderate decrease in food consumption was noted in male mice dosed at 20, 40 and 80 mg/kg/day (up to -21%) and in female mice dosed at 20 mg/kg/day (-34%). At 40 and 80 mg/kg/day, female mice showed a marked decrease in food consumption (up to -46%). Test article intake was close to theoretical values at 10 mg/kg/day. However, at higher doses, test article intake was lower in both sexes. In males, intake was 16.0, 34.0, and 66.3 mg/kg/day at 20, 40, and 80 mg/kg/day, respectively. In females, intake was 15.7, 27.9, and 57.1 mg/kg/day at 20, 40, and 80 mg/kg/day, respectively. Hematology: Hematology findings were as follows: a slight decrease in monocytes (up to -56%) in both sexes, and a slight decrease in neutrophils in females (up to -50%) at all dose levels; a slight increase in thrombocytes (up to +54%) in females dosed at 20 to 80 mg/kg/day; At 80 mg/kg/day, in addition to changes observed at lower dose levels, decrease in lymphocytes (-46%) and white blood cells (-44%) was noted in females. In addition, the decrease in monocytes was more pronounced in males. In females, minimal decreases in hemoglobin, red blood cells and hematocrit were also observed. Clinical chemistry: Clinical chemistry testing showed marked glucose decrease (up to -42%) in both sexes at all dose levels. Moderate decreases in total bilirubin and alkaline phosphatase were observed in females at all dose levels. Organ weights: No relevant changes were observed in males. In females, absolute and relative adrenals weights were minimally decreased at all dose levels. Gross pathology: There were no relevant changes. Histopathology: Histopathology revealed a dose-related increase in hypertrophy/hyperplasia of the pars intermedia of the pituitary gland in females at all dose levels (minimal, present in 3/5, ¾, 4/5 and 4/4 females dosed at 10, 20, 40 and 80 mg/kg/day, respectively), and in males at 40 and 80 mg/kg/day (minimal in 4/5 and 2/5 males dosed at 40 and 80 mg/kg/day, respectively; slight in 2 males dosed at 80 mg/kg/day). 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.

Toxicokinetics:

The exposure to paliperidone after dietary administration (based on AUC) increased dose-proportionally over the 10 to 80 mg/kg dose range. The exposure in males was slightly higher (~20%) than in females. Mean C_{max} and AUC_{0-24h} values of paliperidone on Days 13-14 in the 2-week dietary repeat-dose study in mice are shown in the following sponsor's table:

Dose (mg/kg bw[a]/day)[b]	10	20	40	80
	Males (n = 3/dose level)			
C_{max} (ng/mL)	187	366	699	1347
AUC_{0-24h} (ng.h/mL)	3203	6350	12449	25840
	Females (n = 3/dose level)			
C_{max} (ng/mL)	159	306	578	1012
AUC_{0-24h} (ng.h/mL)	2664	5395	10101	21193

[a] body weight
[b] nominal dose levels

2.6.6.4 Genetic toxicology

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

The aim of his study 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.

Key findings: 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.

Study no.: 4555
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica N.V., Department of Toxicology, Turnhoutseweg 30, B-2340 Beerse, Belgium
Date of study initiation: June 8, 1998
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477), Batch ZR076477PFA011, purity: not provided

Methods

Strains/species/cell line: Salmonella typhimurium strains TA1535, TA1537, TA102, TA98 and TA100
Doses used in definitive study: 5, 10, 25, 50, 100, 250 and 500 µg/plate
Basis of dose selection: Before performing the main reverse mutation tests, the non-inhibitory concentration level was determined and used for the dose selection.
Negative controls: Solvent: dimethylsulfoxide (DMSO)
Positive controls: The following positive controls were used in this study:

Compound	solvent	Without or with S 9	Strain
2-nitrofluorene	DMSO	without	TA98
Sodium azide	water	without	TA1535, TA100

9-aminoacridine	DMSO	without	TA1537
2-aminoanthracene	DMSO	with	All strains
4-nitroquinoline-N-oxide	DMSO	without	TA102

Incubation and sampling times: Paliperidone was tested at seven concentrations (see above). The following solutions were successively added to 2 ml histidine-biotine supplemented top agar: 0.1 ml of an overnight bacterial culture of the tester strain, 0.1 ml of a dilution of paliperidone and either 0.2 or 0.5 ml S9 mix (Aroclor 1254 induced rat liver enzymes - S9 fraction and an energy producing system containing NADP and glucose-6-phosphate) for the activation portion, or 0.2 or 0.5 ml phosphate buffer for the non-activation portion. Solvent controls (DMSO) were plated for each strain with and without metabolic activation. The agar plates with bacterial culture of tester strains with or without S9 mix were incubated in the dark at 37°C for 2 days.

Results

Study validity: All concentration levels of paliperidone, solvent controls and positive controls were plated in triplicate. Plates were counted automatically, except plates exhibiting precipitate or contamination that were counted manually. Sterility checks, genotypes of bacterial strains and bacterial titer were according to the established criteria. The number of spontaneous and solvent control revertant colonies for the strain in the absence and presence of rat liver S9-mix falls within the range of the conducting laboratory historical data. The positive controls showed a significant increase in the number of revertant colonies indicating their mutagenic activity. The repeat study confirmed the results obtained in the first study. On the basis of these findings, the study was considered to be acceptable for the evaluation of the mutagenic potential of paliperidone. The sponsor concluded that this test satisfied the criteria for a valid test. However, this test did not reveal precipitation of the test compound, or evidence of cytotoxicity. Therefore, the second test was carried out by the sponsor in order to explore higher concentrations of paliperidone (see below).

Study outcome: Based on the lack of biologically significant increase of the reversion rate, it can be concluded that paliperidone, in the presence and in the absence of a rat liver metabolic activation system, has no mutagenic properties towards the Salmonella typhimurium strains at concentrations ranging from 5 to 500 µg/plate under conditions of this study.

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

The aim of his study 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.

Key findings: Paliperidone did not cause any biologically significant increase in the number of revertant colonies above the vehicle control incidence with all of the strains. Therefore, it was concluded that paliperidone has no mutagenic properties under this test conditions up to precipitating concentrations of 5000 µg/plate.

Study no.: TOX6095
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica N.V., Global Preclinical Development, Beerse site, Department of Toxicology/Pathology, Turnhoutseweg 30, B-2340 Beerse, Belgium
Date of study initiation: October 09, 2003
GLP compliance: GLP of OECD
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477), Batch ZR076477EIA021, purity: [redacted]

Methods

Strains/species/cell line: Salmonella typhimurium strains TA1535, TA1537, TA102, TA98 and TA 100
Doses used in definitive study: 78.13, 156.25, 312.5, 625, 1250, 2500 and 5000 µg/plate (all three main studies)
Basis of dose selection: Two range finding studies
Negative controls: Solvent: dimethylsulfoxide (DMSO)
Positive controls: Positive controls were used in this study according to the table given below:

Compound	solvent	Without or with S 9	Strain
2-nitrofluorene	DMSO	without	TA98
Sodium azide	water	without	TA1535, TA100
9-aminoacridine	DMSO	without	TA1537
2-aminoanthracene	DMSO	with	All strains
4-nitroquinoline-N-oxide	DMSO	without	TA102

Incubation and sampling times: Paliperidone was tested in the first, second and third definitive study without and with S9-mix (Aroclor 1254 induced rat liver enzymes - S9 fraction and an energy producing system containing NADP and glucose-6-phosphate) at concentration levels listed above. All concentration levels of paliperidone, vehicle controls and positive controls were plated in triplicate. All tests were performed in the absence as well as in the presence of S9-mix. The following solutions were successively added to 2 ml histidine-biotine supplemented top agar: 0.1 ml of an overnight bacterial culture of the tester strain, 0.1 ml of a dilution of paliperidone and either 0.5 ml of S9-mix containing 40 µl S9/ml (first study) or 0.5 ml of S9-mix containing 100 µl S9/ml (second and third study) for the activation portion, or 0.5 ml phosphate buffer (first, second and third study) for the non-activation portion. The content of the tube was then

mixed and poured onto minimal glucose agar Petri dishes. The agar plates were incubated in the dark at 37°C for 2 days.

Results

Study validity: All concentrations of paliperidone, solvent controls and positive controls were tested in triplicates. All plates were counted manually. Sterility checks, genotypes of bacterial strains and bacterial titer were according to the established criteria. The number of spontaneous and solvent control revertant colonies for the strain in the absence and presence of rat liver S9-mix falls within the range of the conducting laboratory historical data. The positive controls showed a significant increase in the number of revertant colonies indicating their mutagenic activity. The second and third study confirmed the results obtained in the first study. On the basis of these findings, the study was considered to be acceptable for the evaluation of the mutagenic potential of paliperidone. It was concluded that this test satisfied the criteria for a valid test.

Study outcome: At the concentrations tested up to 5000 µg/plate, paliperidone did not reveal a biologically significant increase in the number of revertant colonies in the absence or in the presence of S9-mix. With all the strains in the absence and the presence of S9-mix, no bacteriostatic effects visualized by a decrease in the number of revertant colonies, thinning of the background lawn or occurrence of pinpoints was observed at the concentrations tested. Precipitation of paliperidone into agar was found at the top concentration of 5000 µg/plate in the absence or the presence of S9-mix. In conclusion, paliperidone had no mutagenic properties under conditions of this study.

3. Study title: In Vitro Mammalian Forward Mutation Test with L5178Y Mouse Lymphoma Cells (TK-locus) Using the Microtitre Fluctuation Technique.

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.

Key findings: No biologically significant induction in mutation frequency was observed neither in the absence nor in the presence of a metabolic activation system. Therefore, paliperidone had no mutagenic properties towards the L5178Y cells under conditions of this study.

Study no.: 4556
Volume #, and page #: electronic submission
Conducting laboratory and location: Janssen Pharmaceutica N. V., Department of Toxicology, Turnhoutseweg 30, B-2340 Beerse, Belgium
Date of study initiation: September 24, 1998
GLP compliance: yes
QA reports: yes (x) no ( )

Drug, lot #, and % purity: Paliperidone (R076477), Batch ZR076477PFA011, purity: [redacted]

Methods

Strains/species/cell line: L5178Y mouse lymphoma cells
Doses used in definitive study: 10, 25, 50, 75, 100 and 150 µg/ml
Basis of dose selection: The highest soluble concentration was determined in the range finding study. In this study, paliperidone was used at concentrations of 0.5, 1, 2.5, 5, 10, 25, 50, 75, 150 and 300 µg/ml culture medium. Cytotoxicity was observed in cultures treated at 300 µg paliperidone/ml. Based on precipitation of paliperidone into the culture medium at a concentration of 300 µg/ml, 150 µg/ml was selected as the highest paliperidone concentration for the main study.
Negative controls: Solvent: dimethylsulfoxide (DMSO)
Positive controls: Methylmethanesulfonate (MMS) was used as positive control for the non-activation portion of the test and N-nitrosodimethylamine (DMN) for the activation portion of the test.
Incubation and sampling times: Cells were exposed for 3 and 24 hours to each selected concentration of paliperidone in buffered culture medium in the absence or presence of the metabolic activation system comprised of Aroclor 1254 induced rat liver enzymes (S9 fraction) and an energy producing system containing NADP and glucose-6-phosphate. Negative and positive controls were included. Following the exposure, the treatment solutions were removed. After an overnight recovery period, the treated cells were sub-cultured to maintain a log phase growth for 2 days to allow for phenotypic expression of the mutants. After an expression period, cells were cultured in TFT selective medium for 10 days, and then counted.

Results

Study validity: Cells were plated in 96-well plated in duplicates. After cultivation of the cells for a period of time enough to allow the formation of colonies, the colonies were counted. The calculations, performed by a computer using validated software, determined the mutant frequency per survivor. In case of a mutagenic response, the colonies were divided into small colonies and large colonies, based on their size. A test article was considered as mutagenic only if the test was valid, a mutant frequency was above two times the negative control mutant frequency, a concentration-related increase in mutant frequency was observed, and the results could be reproduced in an independent repeat study. The number of spontaneous and solvent control mutant frequencies in the absence and presence of rat liver S9-mix was within the range of the conducting laboratory's historical data. The positive controls showed a significant increase in the mutation frequency, indicating their mutagenic activity. The second study confirmed the results obtained in the first study. On the basis of these findings, the study was considered to be acceptable for the evaluation of the mutagenic potential of paliperidone. It was concluded that this assay satisfied the criteria for a valid test.

Study outcome: Cytotoxicity (a gradual reduction in total growth) was observed only after 3 hours of treatment in the absence of a metabolic activation system at concentrations of paliperidone of 75 µl/ml and higher. After 3 hour of treatment in the presence of metabolic activation and after 24 hours of treatment, the total growth determinations at all paliperidone concentrations were comparable to the solvent control. Due to precipitation of the test article into the culture medium, the tests cold not be performed at the limit of toxicity. The plating efficiencies for all paliperidone concentrations and test conditions were comparable to the solvent control. At 3 hours exposure, either with or without metabolic activation, no biologically significant increase in mutant frequencies was observed with any of the paliperidone concentrations tested. No test article-related induction in mutation frequency was observed at any of the paliperidone concentrations tested at 24 hours without metabolic activation. In conclusion, paliperidone had no mutagenic properties towards the L5178Y cells under conditions of this study.

4. Study title: R076477: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the Microtitre Fluctuation Technique.

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).

Key findings: The study consisted of a cytotoxicity range finding experiment followed by three independent experiments. A very week (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 41% RTG. Therefore, in the opinion of this reviewer, the sponsor should have used higher concentrations in this study. Based on overall results and the weight of evidence approach, it can be concluded that paliperidone is not mutagenic in this study.

Study no.: TOX 6093 ([redacted] Study no.: 1073/76)
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]

Date of study initiation: July 11, 2003
GLP compliance: yes (OECD, UK)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477), Batch ZR076477EIA021, purity: [redacted]

Methods

Strains/species/cell line: L5178Y mouse lymphoma cells
Doses used in definitive study: In the first experiment, seven doses ranging from 37.5 to 570 µg/ml were tested; In the second experiment, seven doses ranging from 75 to 570 µg/ml were tested; In the third experiment, eleven doses ranging from 75 to 570 µg/ml were tested.
Basis of dose selection: Doses were selected based on the cytotoxicity range-finding experiments conducted with 3 hours treatment in the absence and in the presence of S9 with six paliperidone concentrations ranging from 9.375 to 300 µg/ml and with 24 hours treatment in the absence of S9 with nine paliperidone concentrations ranging from 1.172 to 300 µg/ml. The maximum concentration was limited by solubility in the primary solvent dimethylsulphoxide (DMSO). Cells survived at all concentrations of paliperidone treatment for 3 hours but extreme toxicity was observed at the top 3 doses tested for 24 hours. As no evidence of marked toxicity or precipitation was observed following 3 hour treatment in the range-finding study, a further solubility assessment was performed. Paliperidone was found to be soluble in DMSO following heating to 80-85 °C.
Negative controls: DMSO
Positive controls: 4-nitroquinoline 1-oxide (without S9) and benzo(a)pyrene (with S9)
Incubation and sampling times: The study consisted of a cytotoxicity range-finding experiment followed by three independent experiments, each conducted in the presence and absence of metabolic activation system S9. A 3 hour incubation period was used for all experiments performed in the presence of S9. In the absence of S9, the range-finding study and experiment 2 were performed using 3 and 24 hours treatment incubation period, and experiments 1 and 3 were performed using 3 hours treatment incubation.

Results

Study validity: In the first experiment (3 hours with and without S9), the top two doses tested in the absence of S9 (500 and 570 µg/ml) were later rejected from analysis due to excessive toxicity and heterogeneity. The top doses analyzed in the absence (400 µg/ml) and the presence of S9 (570 µg/ml), yielded 41% and 26% relative total growth (RTG), respectively. In the second experiment (3 hours with and without S9; 24 hours without S9), the top two doses tested for 3 hours treatment in the absence and presence of S9 (500 and 570 µg/ml) were later rejected from analysis due to excessive toxicity (<10% RTG). The lowest and highest doses analyzed in the presence of S9 (75 and 450 µg/ml) were also rejected from analysis due to excessive heterogeneity. The top doses analyzed 450 µg/ml in the absence and 400 µg/ml the presence of S9, yielded 49% and 41% relative total growth (RTG), respectively. In the 24 hours treatment in the absence of S9, the top dose tested (100 µg/ml) yielded RTG of 41%. Due to the dose-response profiles observed in the absence and presence of S9 in the second experiment, where no doses yielding 10-20% RTG were achieved, and due to the nature of the results observed in the presence of S9 in experiments in the first and second and 2, a third, confirmatory experiment was performed. In the third experiment (3 hours with and without S9), the top doses were rejected from analysis due to excessive toxicity. One intermediate dose was also rejected due to excessive heterogeneity. The highest doses selected for analysis, 420 µg/ml in the

absence of S9 and 440 µg/ml in the presence of S9, yielded 14% and 15% RTG, respectively. In summary, in all experiments, appropriate cytotoxicity was demonstrated.

Negative and positive controls were included in each mutation experiment. Mutant frequencies in control cultures were within a historical control range. Clear increases in mutation frequencies were induced by positive control compounds. Marked increases of both small and large colony mutants were observed with the positive controls. At the doses of paliperidone where statistically significant increases in mutant frequency occurred, the observed increases in both small and large colony mutant frequencies were not large, and there were no marked increases in the proportion of small colonies. On the basis of these findings, the study was considered to be acceptable for the evaluation of the mutagenic potential of paliperidone. It was concluded that this assay satisfied the criteria for a valid test.

Study outcome: In the absence of S9, statistically significant increase in mutant frequency was observed following 3 hour treatment at the highest dose of 420 µg/ml tested in the third experiment. However, the increase in the mutant frequency was small (1.49 fold) compared to concurrent controls. The sponsor concluded that a very weak mutagenic response was therefore demonstrated at a single, highly toxic dose on only one occasion of testing. Overall, this was not considered biologically relevant.

In the presence of S9, statistically significant increases in mutant frequency were observed following 3 hour treatment at 400-570 µg/ml tested in the first experiment at doses yielding 26-58% RTG. These increases in the mutant frequency were not large (1.70 to 1.77 - fold) compared to concurrent controls and did not increase with the increasing dose. No statistically significant increases in mutant frequency were observed at the same concentrations in the second and third experiment. The sponsor concluded that a weak mutagenic response was therefore observed in one out of three experiments but was not reproducible between experiments; therefore the criteria for a positive response were not fulfilled.

In the absence of S-9 following 24 hour treatment there were no test article related changes in the mutant frequency. However, the top dose selected by the sponsor was only (100 µg/ml). At this dose, the RTG was 41% and there was no precipitation. Apparently, the sponsor selected the top dose based on the range finding experiment in which extreme toxicity was observed following 24 hour treatment at three highest doses tested (75, 150 and 300 µg/ml).

The test article was considered by the sponsor to be mutagenic if all of the following criteria were met: (1) the assay was valid, (2) the mutant frequency at one or more doses was significantly greater than that of the negative control, and (3) there was a significant dose-relationship as indicated by the linear trend analysis. According to the sponsor, the criteria for a positive response were not fulfilled. It was concluded that paliperidone was not mutagenic in the absence and presence of metabolic activation system in this study. The results are shown in the following sponsor's tables:

Experiment 1 (3-hour treatment)

Treatment (µg/mL)	-S-9 %RS	RTO	MF§		Treatment (µg/mL)	+S-9 %RS	RTO	MF§	
0	100.00	1.89	125.87		0	100.00	1.80	110.73	
37.5	103.87	0.91	108.99	NS	37.5	89.60	0.97	97.82	NS
75	101.09	0.80	114.56	NS	75	104.82	0.91	100.98	NS
150	98.01	0.79	131.97	NS	150	116.31	0.76	125.14	NS
300	92.92	0.62	161.48	NS	300	85.13	0.69	157.61	NS
400P	61.57	0.41	139.57	NS	400P	75.52	0.58	188.32	*
500P SS	23.26	(0.12)	(210.29)		500P	65.30	0.45	194.87	*
570P SS,X	9.89	(0.01)	(300.58)		570P	55.27	0.26	196.34	*
Linear trend			*		Linear trend			***	
NQO					BP				
0.15	73.45	0.91	626.76		2	74.98	0.44	1233.36	
0.2	56.42	0.35	998.06		3	40.82	0.16	2745.36	

Experiment 2 (3-hour treatment)

Treatment (µg/mL)	-S-9 %RS	RTO	MF§		Treatment (µg/mL)	+S-9 %RS	RTO	MF§	
0	100.00	1.00	100.00		0	100.00	1.00	90.53	
75	96.67	0.89	102.31	NS	75 SS	83.65	(1.26)	(86.72)	
150	79.25	0.55	140.10	NS	150	92.10	0.77	126.80	NS
300	68.82	0.29	122.97	NS	300	105.03	0.55	109.51	NS
400P	68.29	0.42	114.99	NS	400P	92.30	0.41	115.51	NS
450P	67.85	0.49	108.88	NS	450P SS,X	98.19	(0.04)	(326.63)	
500P X	67.57	0.01	360.97		500P X	94.31	0.06	175.01	
570P X	71.25	0.00	800.00		570P X	76.98	0.02	350.13	
Linear trend			NS		Linear trend			NS	
NQO					BP				
0.15	66.60	0.52	568.51		2	121.31	0.92	483.73	
0.2	59.90	0.40	660.38		3	53.92	0.49	951.52	

§ 5-TFT resistant mutants/10^6 viable cells 2 days after treatment
P Precipitate observed at time of treatment
%RS Percent relative survival adjusted by post treatment cell counts
SS Treatment excluded from analysis due to excessive heterogeneity
Data in parentheses indicates marked heterogeneity observed
X Treatment excluded from final test statistics due to excessive toxicity
NS Not significant
* Comparison of each treatment with control: Dunnett's test (one-sided), significant at 5% level
*, **, *** Test for linear trend: χ^2 (one-sided), significant at 5%, 1% and 0.1% level respectively

Experiment 2 (24-hour treatment)

Treatment (µg/mL)	-S-9			
	%RS	RTG	MF§	
0	100.00	1.00	117.07	
5	114.59	1.21	122.10	NS
10	90.43	1.30	128.44	NS
20	72.46	1.12	133.57	NS
40	58.65	1.03	107.06	NS
50	56.47	0.99	114.55	NS
60	38.30	1.07	90.96	NS
70	19.09	0.68	91.89	NS
80	12.80	0.49	124.14	NS
100	8.19	0.41	126.91	NS
Linear trend			NS	
NQO				
0.02	67.53	1.58	262.90	
0.04	56.94	1.84	495.00	

Experiment 3 (3 hour treatment)

Treatment (µg/mL)#	-S-9				Treatment (µg/mL)#	+S-9			
	%RS	RTG	MF§			%RS	RTG	MF§	
0	100.00	1.00	113.63		0	100.00	1.00	126.65	
75	72.89	0.81	131.98	NS	75	91.89	0.97	130.27	NS
150	96.59	0.74	116.31	NS	150 SS	102.71	0.92	(87.23)	
300	68.92	0.69	136.69	NS	300	87.33	0.50	107.04	NS
400P	58.06	0.18	154.34	NS	400P	85.57	0.18	122.46	NS
420P	44.68	0.14	169.84	*	420P	92.92	0.16	120.96	NS
440P X	46.00	0.09	200.32		440P	79.19	0.15	130.85	NS
460P X	45.68	0.04	174.93		460P X	78.83	(0.06)	(232.44)	
480P X	46.36	0.02	264.65		480P X	65.80	0.03	244.24	
500P X	19.67	0.01	139.81		500P X	79.86	0.05	168.41	
525P S	7.83				525P X	63.19	0.02	164.14	
Linear trend			**		Linear trend			NS	
NQO					BP				
0.15	51.29	0.55	728.52		2	90.93	0.39	665.60	
0.2	41.44	0.52	830.35		3	47.78	0.20	1788.16	

§ 5-TFT resistant mutants/10^6 viable cells 2 days after treatment
P Precipitate observed at time of treatment of cultures
%RS Percent relative survival adjusted by post treatment cell counts
$ Not plated for viability / 5-TFT resistance
SS Treatment excluded from analysis due to excessive heterogeneity
Data in parenthesis indicates marked heterogeneity observed
X Treatment excluded from final test statistics due to excessive toxicity
NS Not significant
* Comparison of each treatment with control: Dunnett's test (one-sided), significant at 5% level
*, **, *** Test for linear trend: χ^2 (one-sided), significant at 5%, 1% and 0.1% level respectively
Treatments at 570 µg/mL were too toxic to be plated for mutation assessment, and are not included
Final

[redacted] **Memo:**

In addition to the final report for study TOX6093, the sponsor submitted the Memo dated May 12, 2004. In this memo, [redacted] addressed a solubility of paliperidone in the mouse lymphoma assay. It was concluded that the solubility issue could not allow higher concentrations to be tested in an alternative in vitro mammalian cell genotoxicity test.

5. Study title: 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.

Key findings: Treatment with paliperidone did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats up to 40 mg/kg, a dose at which clinical signs of toxicity were observed and blood plasma analysis demonstrated systemic exposure.

Study no.: TOX6094 ([redacted] Study no.: 1073/77)
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]
Date of study initiation: July 23, 2003
GLP compliance: yes (GLP of the United Kingdom and OECD)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477), Batch ZR076477E1A021, purity: [redacted]

Methods

Strains/species: main study: male Han Wistar [redacted]:WI (Clx:BRL/Han) IGS BR rats
Doses used in definitive study: 2.5, 10 and 40 mg/kg
Basis of dose selection: An initial range finding study was performed using groups of 3 male and 3 female rats at doses covering the range 40 to 225 mg/kg to determine a maximum acceptable dose. Doses of 80 to 225 mg/kg induced prolonged hypothermia and severe clinical signs and these doses were considered to be too high for testing in the micronucleus test. The dose of 40 mg/kg/day was selected as the maximum dose for the main test because clinical signs of toxicity and mild hypothermia were observed at this dose level. As no substantial difference in toxicity was observed between males and females in the range-finding study, the main study was conducted using male rats only.
Negative controls: The negative (vehicle) control was tartaric acid, dematerialized water and NaOH to pH 5.0 administered by gavage.
Positive controls: Cyclophosphamide (CPA) was administered orally by gavage as a single dose at 20 mg/kg to a group of 6 male rats that were killed after 24 hours.
Incubation and sampling times: Animals were dosed with the test article, vehicle or positive control as follows:

Treatment (mg/kg)	Number of animals dosed	Number of animals sampled	
		24 hours after administration	48 hours after administration
vehicle	12 M	6	6
paliperidone 2.5	6 M	6	-
paliperidone 10	6 M	6	-

paliperidone 40	12 M	6	6
positive control CPA (20)	6 M	6	-

Satellite animals in groups of 6 (highest dose) or 3 (other doses) were included in the main study for evaluation of exposure to the test article.

Results

Study validity: In this study, paliperidone was administered as a single dose orally by gavage. Animals were sampled 24 or 48 hours after administration. A single femur from each animal was removed. Slides were prepared according to standard procedures. The relative proportions of PCE and NCE was determined until a total of at least 1000 cells per animal had been analyzed. Counting continued until at least 2000 PCE per animal had been observed. After completion of microscopic analysis and decoding of the data, the ratio of PCE/NCE for each animal and the mean for each group was calculated to see if there was any decrease that could be taken as evidence of bone marrow toxicity. The assay was considered valid if the following criteria are met: (1) The incidence of micronucleated PCE in the vehicle control group is consistent with the distribution of micronucleated PCE in the historical control data; (2) At least 5 animals are analyzed; (3) The positive control induced a statistically significant increase in the frequency of micronucleated PCE. Based on this information, it was concluded that this test satisfied the criteria for a valid test.

Study outcome: No clinical signs were observed in any animal dosed with the vehicle or positive control. The following clinical signs of toxicity were observed in animals treated with paliperidone.

dose (mg/kg)	number of animals	deaths	observations
paliperidone 2.5	6 M	0	Day 1: lethargy (6M), palpebral closure (6M), bradypnoea (6M) Day 2: normal (6M)
paliperidone 10	6 M	0	Day 1: lethargy (6M), palpebral closure (6M), bradypnoea (6M) Day 2: slight weight loss (6M)
paliperidone 40	12 M	0	Day 1: lethargy (12M), palpebral closure (12M), bradypnoea (12M), soft feces (2M) Day 2: weight loss (12M) Day 3: normal (6M)

Negative (vehicle) control rats exhibited normal group mean ratios of PCE to normochromatic erythrocytes (NCE). The distribution of micronucleated PCE within the vehicle control group was consistent with historical negative control data. Positive control animals exhibited increased numbers of PCE such that the micronucleus frequency in the positive control group was significantly greater than in concurrent controls. Toxicokinetic analysis confirmed that all paliperidone treated rats were systemically exposed to paliperidone. Rats dosed with paliperidone at all doses exhibited group mean ratios of PCE to NCE and frequencies of micronucleated PCE that were

similar to the values for the vehicle control group and were consistent with historical negative control data. The results are summarized in the following sponsor's table:

24 hour data

Treatment group (mg/kg)	Kill Time (hours)	Sex	Mean Ratio PCE/NCE	Group mean frequency of micronucleated PCE (per 1000 cells) per treatment group (sd)
Vehicle Control	24	M	0.98	0.25 ± 0.27
R076477 (2.5)	24	M	0.95	0.25 ± 0.27
R076477 (10)	24	M	0.85	0.33 ± 0.41
R076477 (40)	24	M	1.01	0.17 ± 0.26
Positive control, CPA (20)	24	M	0.83	14.58 ± 7.05

sd Standard deviation
M Male

48 hour data

Treatment group (mg/kg)	Kill Time (hours)	Sex	Mean Ratio PCE/NCE	Group mean frequency of micronucleated PCE (per 1000 cells) per treatment group (sd)
Vehicle Control	48	M	0.94	0.33 ± 0.41
R076477 (40)	48	M	0.91	0.33 ± 0.26

sd Standard deviation
M Male

It was concluded that paliperidone did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats treated up to 40 mg/kg, a dose at which clinical signs of toxicity were observed and blood plasma analysis demonstrated systemic exposure.

[redacted] **Memo:**

In addition to the final report for study TOX6094, the sponsor submitted the Memo dated 29 April, 2004. In this memo, [redacted] addressed a 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.

Note: 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's Sonia Tabacova Addendum to

pharmacology/toxicology memorandum of March 29, 2005, August 3, 2005, Serial No. 119 for further details).

2.6.6.4 Carcinogenicity

No standard carcinogenicity studies with p.o. paliperidone were performed because the sponsor requested a waiver from these studies based on considerations that 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 carcionogenicity 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.

The rationale for this approach provided by the sponsor is based on the following logic: (Note: this fragment below is taken directly from the sponsor's submission)

"Immediate release risperidone (Risperdal) has been approved up to dose levels of 8 mg/person twice daily. The preclinical safety information in the marketing application of Risperdal formulations therefore is adequate to support this maximum dose level of p.o. risperidone.

In humans the p.o. administration of immediate release risperidone (Risperdal) produces a systemic exposure to its active metabolite paliperidone of an average 70% of the active fraction. This paliperidone exposure in humans is therefore adequately supported by the preclinical safety information in the marketing application of Risperdal formulations.

Human systemic exposure to paliperidone and each of the individual enantiomers at steady state following administration of paliperidone ER tablets at the highest tested daily dose level of 15 mg/person does not exceed the level of paliperidone and enantiomer exposure observed after administration of the highest approved dose of Risperdal (i.e., 8 mg/person twice daily).

Based on the above considerations, the effects of the systemic exposure to paliperidone and its two enantiomers after administration of paliperidone ER tablets in humans are adequately covered by the nonclinical toxicity data used to support the registration of Risperdal® together with the new data specifically generated to support the marketing application of paliperidone ER tablets. In particular it should be noted that the systemic paliperidone exposure after paliperidone ER administration is not only quantitatively covered by the paliperidone exposure after risperidone administration (as argued above), but is also qualitatively similar as can be derived from the following data:

- No new metabolites are observed in humans following p.o. administration of paliperidone as compared with risperidone.
- The range of enantiometric ratios of paliperidone in humans following paliperidone ER tablet administration is within the range of enantiomeric ratios observed after risperidone administration.

The above statement is also supported by the following additional nonclinical toxicity data:

- The toxicological profile of risperidone and paliperidone was similar at equal dose levels in the 1-month repeat-dose toxicity study in Wistar Wiga rats, the 3-month gavage study in Wistar Hannover rats, the 6-month study in Sprague-Dawley rats, and the 3-month study in albino Swiss (CD1) mice.
- The pre-neoplastic profile of paliperidone (0, 0.63, 2.5 and 10 mg/kg/day) and risperidone (10 mg/kg/day) was similar as evaluated in the 3-month repeat-dose toxicity study in albino Swiss (CD1) mice and the 6-month repeat-dose toxicity study in Sprague-Dawley rats. In fact, no unexpected treatment-related pre-neoplastic lesions were observed that would indicate a need for carcinogenicity testing of either paliperidone or risperidone:

  - In agreement with the dopamine D_2-antagonistic activity of paliperidone and risperidone, female mice treated with either compound showed a dose-related increase in diffuse hyperplasia of the pars intermedia of the pituitary gland. This response was also seen in males at the highest dose levels of paliperidone (10 mg/kg/day) as well as in risperidone-treated males (10 mg/kg/day).

  - As expected for PRL enhancing dopamine D_2-antagonists, 1 out of 20 females at 10 mg/kg/day of paliperidone and 1 out of 20 females at 10 mg/kg/day of risperidone showed minimal focal acinar hyperplasia of the mammary gland in the 6-month rat study. Acinar hyperplasia was occasionally observed at 5 and 20 mg/kg/day of paliperidone in the 3-month dietary rat study as well.

- Paliperidone did not reveal genotoxic properties."

The following carcinogenicity studies with risperidone were resubmitted within present NDA submission:

1. Study title: Carcinogenicity Study in Swiss Mice (Study No. 1927)
2. Study title: Toxicokinetics of Risperidone (R 64766) and of 9-Hydroxy-Risperidone (R 76477) in the Albino Swiss Mouse at the End of an Eighteen- to Twenty-Four-Month Carcinogenicity Study of Risperidone (Admixed with the Food) at 0.63, 2.5 or 10 mg/kg/day. (Study No. R 64766/FK1028)
3. Study title: Carcinogenicity Study in Wistar Rats (Study No. 1928)
4. Study title: Toxicokinetics of Risperidone (R 64766) and of 9-Hydroxy-Risperidone (R 76477) in the SPF Wistar Rat at the End of a Twenty-Four-to Thirty-Month Carcinogenicity Study of Risperidone (Admixed with the Food) at 0.63, 2.5 or 10 mg/kg/day. (Study No. R 64766/FK1137)

These studies were reviewed previously by Dr. Lois Freed. Her full review is available in the Agency files.

Conclusions from Dr. Freed's review are presented below:

Carcinogenicity study in mice:

{Note: Risperidone was administered orally to mice (50/sex/group) in the diet at doses of 0, 0.63 (LD), 2.5 (MD) and 10 mg/kg/day (HD) for 18 months}.

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) It was not possible to confirm levels of plasma exposure for risperidone or 9-hydroxy-risperidone because of:
(a) food wastage in nearly all groups which made calculation of food consumption, and thereby, actual dose difficult.
(b) the possible lack of a sufficiently reliable assay system to confirm diet risperidone concentrations or stability.
(c) the failure to control the interval between removal of the medicated diet and blood collection for plasma drug analysis.

Comparing plasma drug levels obtained in humans with those measured in mice would give a conservative estimate of relative risk since, in all probability, peak plasma levels in mice were higher than reported. In mice, plasma drug levels were undetectable at the LD (0.63 mg/kg). At the MD (2.5 mg/kg), risperidone was detectable in males only. Plasma levels of risperidone in mice at the MD (males only) were 2.5 fold lower than plasma risperidone levels in humans at 10-16 mg/day. At the HD (10 mg/kg) in mice, plasma risperidone levels were only slightly higher (15%) than in humans at 10-16 mg/day. Compared to MD mice, plasma 9-hydroxy-risperidone levels were 4-6 fold and 7-10 fold higher in humans at 10 and 16 mg/day, respectively. Compared to HD mice, plasma 9-hydroxy-risperidone levels were 1.2 – 1.5 fold and 2-2.5 fold higher in humans at 10 and 16 mg/day.

3) It does not appear that the MTD was achieved in male mice. Doses were selected on the basis of data collected during a 3-mo dose-range finding study. In that study, no consistent effects were noted on body weight at the HD (20 mg/kg), nor were there any marked drug-related effects on hematology or clinical chemistry parameters. Changes in organ/tissue weights were noted; however, no histopathology was performed in order to verify toxicity. No analysis of plasma drug levels was conducted in order to document plasma drug exposure. In the 18-mo carcinogenicity study, the HD was lowered to 10 mg/kg. No drug-related effects were noted on mortality, body weight, or hematological parameters. Serum glucose was reduced at the MD (13 %) and HD (26 %). [This was not a consistent finding; during the dose-range finding study, serum glucose was not affected in males at 20 mg/kg.] At the HD, changes were noted in the weight of various organs (10-27 %; e.g., spleen, liver, heart) and histopathological changes were noted in various organs/tissues, particularly at the HD. However, there were no drug-related increases in tumors in males. It is not clear that the MTD was achieved in female mice. Although not statistically significant, there was a trend for mortality rate to be higher in MDF and HDF than in the other groups (64-68 vs. 50-52%). Body weight was elevated in a non-dose-

related fashion at all doses (4-18%). [In the dose-range finding study, the elevation in body weight at the HD (20 mg/kg) was 6-13% compared to control.] Dose-related changes were noted in serum glucose (10-21%, compared to 25% at the HD in the dose-range finding study), consistent with findings in males. The increase in serum cholesterol and phospholipid noted in the dose-range finding study was not observed in the carcinogenicity study; however, the changes in the dose-range finding study were not dose-related. Changes were noted in weight of liver (non-dose related increase) and ovary (decrease; 38% for relative weight at MD and HD). Primary changes noted in histopathology were increased incidence of mammary gland development (hyperplasia, secretion, inflammatory cell infiltration), pituitary gland (hyperplasia), and uterus and vagina (changes indicative of restive state). No histopathology was performed in the dose-range finding study. These data suggest that the HD in the carcinogenicity should have been at least equal to the HD used in the dose-range finding study; however, if the trend for mortality rate to be higher in MDF and HDF is real, then the HD used may be justified.

4) There was an increase in the incidence of mammary gland neoplasms (specifically, adenocarcinomas) and pituitary gland adenomas in risperidone treated females, with greatest response at MD and HD (doses 12-18 and 50-70 fold higher than the maximum proposed human dose). These neoplasms are consistent with chronic hyperprolactinemia, which has been demonstrated in mice after both acute and chronic dosing (0.63-10 mg/kg, p.o.). A dose-related trend in primary lung tumors (primarily benign) was noted in females; however, incidences were well within historical control values.

Carcinogenicity study in rats:

{Note: Risperidone was administered orally to rats (50/sex/group) in the diet at doses of 0, 0.63, 2.5 and 10 mg/kg/day for 25 months}.

1) The theoretical HD used in the study was 30-45 fold higher than the proposed maximum therapeutic dose in humans (16 mg/day).

2) The mortality rates in MDM and HDM (78 and 74%, respectively) were close to the maximum recommended rate.

3) It was not possible to confirm plasma drug exposure because the interval between removal of the medicated diet and blood collection was not controlled. Data from a previous study, in which does of 0.16-10 mg/kg were administered to Wistar rats (satellite group, n=2) by gavage for 3 mo, could not be used for comparison because plasma levels of risperidone and 9-hydroxy-risperidone were up to 30-fold higher than levels reported in dietary studies at comparable doses.
Comparing plasma drug levels obtained in humans with those measured in rats would give a conservative estimate of relative risk since, in all probability, peak plasma levels in rats were higher than reported. Plasma risperidone levels in humans (10-16 mg/day) were 2.5-3 fold higher than in LD rats, similar to those in MD rats, and 3-4 fold lower than those in HD rats. At 10 mg/day, plasma levels of 9-hydroxy-risperidone in humans were

6-7 fold higher than in LD rats, 2-4 fold higher than in MD rats, and slightly lower (6-28%) than in HD rats.

4) The HD exceeded the MTD in both males and females based on the reduced body weight in males (LD: 11%, MD: 14%, HD: 27%) and in females (23% .....)

5) Drug-related changes in the incidence of certain neoplasms were noted in both males and females:
a) In males, the incidence of mammary gland adenocarcinomas was increased in MDM and HDM, but significantly only in HDM. The incidence of mammary gland neoplasms in total was increased in MDM and HDM. There were dose-related trends in the incidence of pancreatic (endocrine) adenomas and soft tissue fibrosarcoma (fatal).
b) In females, the incidence of mammary gland adenocarcinomas was increased in MDF and HDF. However, there was no drug-related increase in overall number of mammary gland neoplasms. The incidence of total neoplasms of the cervix, uterus, and vagina was reduced at all doses.
c) The incidences of pancreatic adenomas and soft tissue fibrosarcomas in MDM and HDM are above the level of historical control. The incidence of soft tissue fibrosarcoma was only 2/50 for both dose groups versus 0-1/50 for historical control. This small increase may or may not have any real significance.

6) Increases in various mammary gland and pituitary neoplasms, benign and malignant, are consistent with chronic hyperprolactinemia. Hyperprolactinemia commonly results from chronic neuroleptic administration and was demonstrated in rats after acute and chronic dosing and in humans after acute dosing with risperidone. The sponsor indicated that the observed dose-related trend in pancreatic adenomas in male rats was also prolactin related. To the reviewer's knowledge, prolactin receptors have been identified in a number of organs/tissues (e.g., choroid plexus, liver, kidneys, mammary gland, mammary tumor, adrenal, ovary, testis, prostate, seminal vesicles and uterus), but not in endocrine pancreas. The sponsor, at the Agency's request, submitted documentation (4/13/93, Vol 1-2).
Together, these studies suggest, but do not directly demonstrate, pancreatic islet cell responsiveness (e.g., altered morphology) to increased serum prolactin.
Another issue is the relevance of these preclinical findings to humans. Epidemiological studies have suggested that the observation of mammary gland changes in animals treated chronically with neuroleptics is not relevant to humans. This conclusion is based on the lack of an observed increase in breast neoplasms in a large number of patients treated chronically with neuroleptics. Also, unlike rodents in which a relationship between hyperprolactinemia and mammary gland neoplasms has been clearly demonstrated, a role for PRL in human breast cancer has not been established. The possibility, however, that differences between rodents and humans may be explained, at least in part, by differences in serum prolactin levels has not been systematically explored. That is, are serum prolactin levels elevated in humans to the extent and duration associated with increased mammary gland neoplasms in rodent studies. The relevance of observed pituitary gland and pancreatic neoplasms in animals treated with neuroleptics (e.g., risperidone) to

humans has not been determined. Conclusions about hyperprolactinemia and breast cancer are not necessarily generalizable to neoplasms in other organ/tissues.

Analysis of serum prolactin levels indicated that there was a dose-related increase in the % of patients with increased serum prolactin (20-50%2). There was also an increase in absolute serum prolactin levels (58-100%) in those patients. By comparison, a 20% increase in serum prolactin levels were noted in haloperidol-treated patients, and 14% of haloperidol-treated patients were affected.

Although limited carcinogenicity data are available for neuroleptics, 2-yr studies have been conducted in rats using, among others, sulpiride, chlorpromazine, and penfluridol [cf " [redacted] Review of toxicological data (submission of 1/13/82)", Barry N Rosloff, Ph.D (3/4/82); "Pharmacologist review of two year rat carcinogenicity studies", Joseph F. Contrera, Ph.D. (4/6/81)]. The incidence of pancreatic (endocrine) adenoma was increased after dosing with all three of these neuroleptics. Except for one study of penfluridol ([redacted] No. 929) in which no increase was observed, the increased incidence (%) of pancreatic islet adenoma was greater with sulpiride, chlorpromazine, and penfluridol (total pancreatic tumors) than with risperidone (12-, 7-, 3 to 12-, and 1.6-fold, respectively, at the HD). At least in the case of penfluridol, this observation prevented further development in the U.S. Increases in pituitary gland neoplasia were noted in rodents treated with haloperidol (mice only), sulpiride (rat), and risperidone (mice). No consistent effect was noted with chlorpromazine.

In summary, it is clear that both pancreatic islet adenoma and pituitary gland neoplasia are observed with other neuroleptics and that the magnitude of the effect is not greater with risperidone than with other neuroleptics (based on limited data). In addition, data from published studies suggest that these types of neoplasia are related to hyperprolactinemia."

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

1. Study title: Male Fertility Study in the Rat

The objective of this study was to investigate any potential effects of paliperidone on male fertility in rats administered paliperidone by p.o. gavage for 63 days prior to pairing, during pairing with untreated females, and until termination in Week 13.

Key study findings: The objective of this study was to investigate any potential effects of paliperidone on male fertility. There were no test article related findings at dose level of 0.16 mg/kg/day. In rats dosed at 0.63 mg/kg/day, clinical observations of subdued or decreased activity were noted from Week 1 to 5. Partially closed eyes were recorded from Week 2 to 13. Epididymides weights were 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 Week 1 to 13 (subdued behavior or decreased activity) and Week 2

to 13 (both eyes partially closed). Body weights were moderately decreased (up to 6% lower than control). Food utilization was slightly reduced in Weeks 5 to 9 and overall. Epididymides weights were 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 precoital interval. There were no effects on male fertility at any of the dose levels tested. There were no other test article related changes.

Study no.: TOX6967 (RR1052)
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]
Date of study initiation: February 9, 2005
GLP compliance: yes (UK GLP, OECD GLP)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone, lot ZR076477EIA041, purity [redacted]

Methods

Doses: 0, 0.16, 0.63 and 2.5 mg/kg/day
The dose selection for this study was based on information from previously conducted toxicity studies with paliperidone. In a 3-month repeated dose toxicity study in Wistar rats and a 6-month oral toxicity study in Sprague-Dawley rats, paliperidone was administered at dose levels of 0.63, 2.5 and 10 mg/kg/day. Dose-related sedation and decreases in body weight and body weight gain were observed in males in these studies. This reviewer notes that body weight and weight gain of males dosed with paliperidone at 2.5 mg/kg/day for 6 month were only moderately lower compared to the control group (90% and 84% of mean control value, respectively, on Day 182 of the study). Body weight and weight gain of females dosed with paliperidone at 2.5 mg/kg/day were slightly increased compared to control group (112% and 123% of control mean value, respectively, on Day 182 of the study). At all levels males showed prolactin-mediated inflammation of the dorso-lateral prostate. In addition, an increased accumulation of red blood cells in the splenic red pulp at 10 mg/kg/day was also observed. Therefore, in opinion of this reviewer, there was no clear justification for selecting such a low top dose for fertillity study based on previous toxicity studies in rats. However, the dose selection was also based on the results of two oral fertility studies in Wistar rats with risperidone. In the first study, there were many toxic effects at 5 mg/kg/day (decreased body weight and body weight gain, marked decrease in the copulation rate and increase in the pre-coital interval) and some at lower doses. In the second study males showed a decrease in body weight and body weight gain at 2.5 mg/kg/day. Other parameters remained unchanged. According to the sponsor, testing higher doses of paliperidone in male fertility study was deemed not feasible due to prolactin-mediated decrease in mating behavior resulting in a marked reduction of the copulation rate as demonstrated at 5 mg/kg/day in a combined male and female fertility study in rats with risperidone conducted to support Risperdal.

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

Results

Mortality: No mortality occurred during the study.
Clinical signs: There were no test-article related findings at 0.16 mg/kg/day. At 0.63 mg/kg/day, subdued or decreased activity was recorded in all (24/24) males from Weeks 1 to 5 and partially closed eyes were recorded in all males from Weeks 2 to 13. At 2.5 mg/kg/day, subdued or decreased activity was recorded in all (24/24) males from Weeks 1 to 13 and partially closed eyes were recorded in all males from Weeks 2 to 13.
Body weight: Body weights were up to 6% lower than control at 2.5 mg/kg/day, although the differences from control did not achieve statistical significance at all weeks.
Food consumption: There were no effects on food consumption at any dose. Food utilization was slightly reduced in Weeks 5-9 and overall at 2.5 mg/kg/day (Weeks 1-9: 91% of control level).
Toxicokinetics: not conducted
Necropsy: There were no macroscopic pathology findings at any dose. Absolute epididymides weights were 6% and 7% lower than those of controls at 0.63 and 2.5 mg/kg/day, respectively. There were no effects on testes weights.
Fertility parameters: There were no significant effects on pre-coital interval, successful matings, pregnancy data and litter data. The majority of males in all groups mated and the mating was successful judged on the presence of live uterine implantations in the females. There were no effects on male fertility at any dose levels tested.

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

Key study findings: The objective of this study was to investigate any potential effects of paliperidone on female fertility and reproductive performance. Maternal toxicity was slight in females receiving 0.63 mg/kg/day as evidenced by ptosis, slightly decreased body weight gain during pregnancy, and decreased maternal corrected weight gain. During the preparing period, increased body weight gain and food consumption 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. In females receiving 2.5 mg/kg/day, ptosis, lacrimation, increases in body weight gain and food consumption during the first week of treatment, and a slight reduction in food intake were noted. 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 numbers of implantations (-13%) and live fetuses (-16%) as expressed per pregnant female, and lower weights of the gravid uterus. The dose of 0.16 mg/kg was the NOAEL for fertility and reproductive capacity for female rats based on incereased percoital interval (11 versus 3 days) and decreased corrected maternal weight (-20%) at 0.63 mg/kg/day.

Study no.: TOX6348
Volume #, and page #: electronic submission
Conducting laboratory and location: Global Preclinical Development, Beerse site, Turnhoutseweg 30, 2340 Beerse, Belgium
Date of study initiation: February 3, 2004
GLP compliance: GLP regulations according to OECD
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone, lot ZR076477EIA041, purity [redacted]

Methods

Doses: 0, 0.16, 0.63 and 2.5 mg/kg/day
The dose selection for this study was based on information from previously conducted 3-month repeated dose toxicity study in Wistar rats and a 6-month oral toxicity study in Sprague Dawley rats, as well as based on the results of two oral fertility studies performed in Wistar rats with risperidone (see the review of Male Fertility Study in the Rat for further details)
Species/strain: SPF rats/Sprague Dawley ([redacted]:CD (SD) rats)
Number/sex/group: 24 females/group
Route, formulation, volume: oral (gavage), aqueous solution with tartaric acid and NaOH, volume: 10 ml/kg body weight.
Satellite groups used for toxicokinetics: none
Study design: Female rats were dosed orally with paliperidone for 14 days prior to mating, during the mating with undosed males and up to Day 7 of pregnancy. Female rats were sacrificed on Day 14 of pregnancy for evaluation of pregnancy status and determination of the fertility rate.

Parameters and endpoints evaluated: mortality, clinical observations, body weight, body weight gain, food consumption, weight of gravid uterus, gross pathology, fertility rate, copulation rate, pre-coital interval, number of corpora lutea of pregnancy, number of implantations, number of resorptions, number of embryos, pre-and post-implantation loss.

Results

Mortality: No mortality occurred during the study.
Clinical signs: All females were observed at least once a day for clinical signs. There were no adverse clinical signs in rats receiving 0.16 mg/kg/day. Ptosis was observed in 21/24 and 24/24 during the pre-pairing period and 17/23 and 23/23 during pregnancy in females receiving 0.63 or 2.5 mg/kg/day, respectively. Excessive lacrimation was observed in 15/24 females receiving 2.5 mg/kg/day during the first few days of paliperidone administration.
Body weight: All females were weighed initially, twice at weekly intervals during the preparing period and on Days 0, 8 and 14 of pregnancy. All groups receiving paliperidone exhibited slight increase in body weight gain during the first week of treatment when compared to control. In animals dosed at 2.5 mg/kg/day, body weight and body weight gain were significantly increased (+4% and +200%, respectively) during the first week of the treatment but the absolute body weight returned to control levels at the end of the pre-pairing period due to decreased body weight gain in the second week. During pregnancy, body weight gain was decreased in females treated at 0.63 and 2.5 mg/kg/day. Moreover, a statistically lower corrected mean maternal body weight gain was noted at 0.63 mg/kg/day (-20%) and at 2.5 mg/kg/day (-27%). These findings indicate that the selected high dose was adequate.
Food consumption: Non-dosage related increase in food consumption was noted in all groups receiving paliperidone during the first week of treatment. During the pregnancy, food intake was comparable with the control. During the post-dosing period food consumption was slightly decreased in female rats receiving 0.63 and 2.5 mg/kg/day.
Toxicokinetics: not conducted
Necropsy: On Day 14 of presumed pregnancy, animals were killed and examined for evidence of disease or adverse reaction to the treatment. All macroscopic pathological changes were recorded. There were no treatment related macroscopic changes at necropsy in any dosage group.
Fertility parameters: The female genital tract was dissected out and weight of gravid uterus, number of corpora lutea of pregnancy, number of implantations, number of resorptions, number of embryos, pre-and post-implantation loss were recorded. Pseudopregnancies were observed by vaginal cytology in all (24/24 for each group) females administered 0.16, 0.63 and 2.5 mg/kg/day. They were considered test article related and probably a consequence of prolactin mediated effects. Prolongation of the pre-coital interval was observed in groups receiving 0.63 or 2.5 mg/kg/day (11 days and 10 days for these groups, respectively). The median pre-coital interval for the control group was 3 days. In the 0.16 mg/kg/day group, in 8/24 females it was longer than 7 days, although the median value for the group was also 3 days. The copulation index was unaffected by treatment with paliperidone. The fertility indices also showed no effect of

treatment. The weight of the gravid uterus was decreased in females dosed at 2.5 mg/kg/day due to the reduced number of implantations in this group. At 2.5 mg/kg/day, there was an increased pre-implantation loss (23% versus 14% in the control group) and post implantation loss (14% versus 8% in the control group), resulting in fewer implantations/pregnant female (13.6% versus 15.6% in the control group) and a statistically significant lower number of live embryos/pregnant female (-16%). Mean litter size was also smaller (14.6% versus 12.4% in the control group). There were no changes in these parameters at 0.16 or 0.63 mg/kg/day.

The results form this study result are summarized in the following sponsor's table:

Observation		Vehicle 0 mg/kg	Low 0.16 mg/kg	Medium 0.63 mg/kg	High 2.5 mg/kg
FEMALE DATA					
Number of pregnant females/ terminally sacrificed	(2)	24/24	23/24	19/23 *	22/23
Copulation rate	(2)	24/24	24/24	23/24	23/24
Fertility rate	(2)	24/24	23/24	19/23 *	22/23
Body weight gain (d0 - d7)	(3)	35	32	29	23 **
Body weight gain (d8 - d13)	(3)	35	33	29 *	29 *
Weight gravid uterus	(3)	12.8	12.9	12.2	10.4 *
Corrected mean maternal weight gain	(3)	57.2	52.0	45.7 *	41.5 **
Food consumption (d0 - d7)	(3)	192	198	197	188
Food consumption (d8 - d13)	(3)	159	160	150	149 *
LITTER DATA					
Number of live embryos/pregnant female	(3)	14.6	15.3	14.7	12.3 *
Mean litter size	(3)	14.6	15.3	14.7	12.4 *
Number of early resorptions/pregnant female	(3)	1.00	1.30	1.16	1.23
Number of late resorptions/pregnant female	(3)	0.00	0.00	0.00	0.00
Total number of resorptions/pregnant female	(3)	1.00	1.30	1.16	1.23
Pre-implantation loss (%)	(3)	13.72	13.98	14.11	22.89
Post-implantation loss (%)	(3)	7.78	8.20	9.62	14.14
Number of implantations/pregnant female	(3)	15.6	16.7	15.9	13.6
Number of corpora lutea of pregnancy/pregnant female	(3)	17.9	19.8 *	18.6	17.9

Embryofetal development

3. Study title: Oral Developmental Toxicity Study in the Rat

The purpose of this study was to investigate the potential effects of paliperidone on maternal condition and embryo-fetal development in rats administered paliperidone p.o. from gestation Day 6 through 17.