Key study findings: There was no mortality in this study. Ptosis was seen at all dose levels. Sedation was noted at 2.5 mg/kg/day and above. Food consumption, body weight gain and corrected mean maternal weight gain were slightly to moderately decreased at 2.5 mg/kg/day and above. Even at maternally toxic dose levels, there were no relevant changes at external, visceral and skeletal examination in the fetuses. There were no other pregnancy, litter and fetal changes. The maternal NOAEL was considered to be 0.63 mg/kg/day. The fetal NOAEL was considered to be 10 mg/kg/day.

Study no.: TOX6194
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: September 2, 2003
GLP compliance: GLP regulations according to OECD
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone, lot ZR076477PUA031, purity [redacted]
Methods

Doses: 0, 0.63, 2.5, 10 mg/kg/day
These dose levels were selected based on the results from previously conducted 3-month repeated dose oral toxicity study in rats where the same dose levels were used.
Species/strain: SPF rat/albino Sprague-Dawley
Number/sex/group: 24 females/group
Route, formulation, volume: oral (gavage), aqueous solution with tartaric acid and sodium hydroxide (to pH 5.0), 10 ml/kg body weight
Satellite groups used for toxicokinetics: 3 groups of 6 satellite animals for toxicokinetics
Study design: Paliperidone was administered to female rats from Day 6 to 17 of pregnancy. A similar group of females received the vehicle only according to the same regimen and served as vehicle controls. The females were killed on Day 21 of pregnancy and a necropsy was performed where the females were examined for macroscopic abnormalities, pregnancy status and the numbers of corpora lutea of pregnancy, implantations, resorptions and live and dead fetuses. The fetuses were weighed, sexed and examined for external, visceral and skeletal abnormalities.
Parameters and endpoints evaluated: Females: mortality, clinical observations, body weight gain and corrected maternal weight gain, food consumption, weight of gravid uterus, gross pathology, toxicokinetics. Litter: number of live and dead fetuses per litter, mean litter size, number of early, late and total resorptions, number of implantations, number of corpora lutea of pregnancy, pre-and post-implantation loss, weight and sex ratio of live fetuses, fetal observations (external, soft tissue, skeletal).

Results

Mortality (dams): There were no deaths in this study.

Clinical signs (dams): Females were observed at least once a day for signs of ill health, abnormal behavior or unusual appearance, and clinical signs. At 0.63 mg/kg/day, ptosis was observed during the majority of the dosing period in 23/24 females. At 2.5 mg/kg/day, ptosis (24/24), slight sedation (20/24) and soft feces (22/24) were observed. At 10 mg/kg/day, females exhibited similar clinical signs. However, these signs were more pronounced. In addition to slight sedation observed in all females, 11/24 females exhibited periodically moderate sedation. Soft feces were observed in 18/14 females and red vaginal discharge in 4/24 females on days 14 or 15 of pregnancy. These findings were considered by the sponsor to be without effect on the pregnancy.

Body weight (dams): Body weight gain data were reported for the following periods of pregnancy: Days 0-3, 4-5, 6-9, 10-13, 14-17 and 18-20. At 0.63 mg/kg/day, there were no toxicologically important changes in body weight gain. Body weight gain was reduced during dosing period in females receiving 2.5 mg/kg (between Days 6 and 9 of pregnancy; gain of 14 g versus 21 g in the control group: -33%) or 10 mg/kg (throughout the dosing period but maximally decreased between Days 6 and 9 gain of 12 g versus 21 g in the control group: -43%). During the postdosing period, body weight gain was comparable with that of control at both 2.5 and 10 mg/kg/day. The corrected mean maternal weight gain was reduced in the females receiving 2.5 or 10 mg/kg/day (-22% or -32%, respectively).

Food consumption (dams): Individual food consumption for all females was recorded for the following periods of pregnancy: Days 0-5, 6-9, 10-13, 14-17 and 18-20. There were no effects on food consumption at 0.63 mg/kg/day. At 2.5 mg/kg/day, food consumption was slightly reduced between Days 10 and 13 of pregnancy (-7%). At 10 mg/kg/day, food consumption was slightly reduced from Day 10 of pregnancy until the end of the study (-6%).

Toxicokinetics: On Days 6/7 and 16/17 of pregnancy, blood samples were taken from the orbital venous plexus at 0.5, 1, 2, 4, 8 and 24 hours after dosing from the pregnant female satellite animals of each paliperidone-dosed group. Paliperidone was rapidly absorbed after both single and repeated dose administration in the pregnant rats. Peak levels and AUC-values increased dose-proportionally to slightly more than dose-proportionally over the investigated dose range. The exposure (AUC_{0-24h}) after repeated administration at 10 mg/kg was comparable to that after single dose. $T_{1/2}$ was relatively short and ranged from 2 to 3 hours at all dose levels after both single and repeated dose administration. There was no accumulation of the test article in the plasma after repeated dosing. Mean C_{max} and AUC_{0-24h} values of paliperidone on gestation Day 16 in the embryo-fetal development toxicity study in Sprague-Dawley rats (N=3/dose level) are shown in the following table:

Dose (mg/kg/day)	**0.63**	**2.5**	**10**
C_{max} (ng/ml)	**165**	**663**	**2957**
AUC_{0-24h} (ng.h/ml)	**804**	**3520**	**17500**

Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): On Day 21 of pregnancy the main study animals were sacrificed. Each animal was dissected and examined for evidence of disease or adverse reaction to treatment. All macroscopic pathological changes were recorded. Ovaries were preserved

but not examined. There were no toxicologically important changes in maternal condition observed at necropsy. There were no effects of treatment with paliperidone upon pregnancy as assessed by the number of corpora lutea, implantations, resorptions, live and dead fetuses, the extent of pre- and post-implantation loss, and the weight and sex ratio of the live fetuses.

Offspring (malformations, variations, etc.): There were no treatment related changes in the incidence of major abnormalities observed. There was no increase in the incidence of minor abnormalities in any of the group receiving paliperidone. Occasional findings were in the groups receiving 0.63 or 2.5 mg/kg/day. These findings were considered to be unrelated to the treatment. Findings from this study are summarized in the following sponsor's table:

Johnson & Johnson Pharmaceutical Research & Development,
a division of Janssen Pharmaceutica N.V.
Experiment: TOX - 6194
Oral Developmental Toxicity Study in the Rat
R076477 - OR/GAV - RAT
Dosing period: from day 6 through day 17 of pregnancy

Table 1

Summarized Results
ADULT and LITTER DATA
Day 0 is first day of pregnancy
Printed on : don, 20 jan 2005

Observation		Vehicle 0 mg/kg	Low 0.63 mg/kg	Medium 2.5 mg/kg	High 10 mg/kg
ADULT RAT DATA					
Number of dosed females		24	24	24	24
Number of pregnant females/ terminally sacrificed	(2)	24/24	23/24	23/24	23/24
Number of dead or sacrificed females/ dosed females	(1)	0/24	0/24	0/24	0/24
Body weight gain (d0 - d3)	(3)	20	22	19	20
Body weight gain (d4 - d5)	(3)	11	12	13	13
Body weight gain (d6 - d9)	(3)	21	20	14 ***	12 ***
Body weight gain (d10 - d13)	(3)	30	29	27	23 ***
Body weight gain (d14 - d17)	(3)	59	59	55	51 **
Body weight gain (d18 - d20)	(3)	51	57 *	52	53
Weight gravid uterus	(3)	98.0	101.7	99.0	96.6
Corrected mean maternal weight gain	(3)	62.9	62.0	49.2 ***	42.5 ***
Food consumption (d0 - d5)	(3)	142	150	142	142
Food consumption (d6 - d9)	(3)	108	116 *	109	105
Food consumption (d10 - d13)	(3)	121	125	116	113 *
Food consumption (d14 - d17)	(3)	132	135	130	124 *
Food consumption (d18 - d20)	(3)	101	104	97	95
LITTER DATA					
Number of live fetuses/pregnant female	(3)	13.3	13.5	13.7	13.0
Number of dead fetuses/pregnant female	(3)	0.00	0.00	0.00	0.00
Mean litter size	(3)	13.3	13.5	13.7	13.0
Number of early resorptions/pregnant female	(3)	0.92	1.09	0.83	1.17
Number of late resorptions/pregnant female	(3)	0.04	0.00	0.00	0.00
Total number of resorptions/pregnant female	(3)	0.96	1.09	0.83	1.17
Pre-implantation loss (%)	(3)	10.92	8.63	6.61	9.11
Post-implantation loss (%)	(3)	6.90	7.42	5.80	8.34
Number of implantations/pregnant female	(3)	14.3	14.6	14.5	14.2
Number of corpora lutea of pregnancy/pregnant female	(3)	15.6	15.9	15.6	15.9
Weight of live fetuses	(3)	5.6	5.7	5.5	5.6
Sex ratio (% male fetuses)	(3)	56.2	53.3	53.5	57.2
Incidence of malformed fetuses	(1)	1/320	1/310	1/315	0/300
Number of fetuses examined by sectioning		155	150	152	144
Number of fetuses skeletally examined		165	160	163	156

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

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

Reference group = Vehicle
ToxS12Reporter : Version 3.3.1

4.Study title: 13 Day Repeated Dose Oral Toxicity Study in the Pregnant Rabbit (Study No. 4687)

The purpose of this study was to determine the potential toxicity of paliperidone when administered once daily from Day 6 through Day 18 of the presumed pregnancy by oral gavage to female rabbits (5/sex/group). This study was intended as a range finding study for an oral developmental toxicity study. Testing facility: Department of Toxicology, Janssen Research Foundation, 2340 Beerse, Belgium. Study initiation: August 27, 1998. Paliperidone (lot ZR076477PFA011) was administered at 0, 0.63, 2.5, 10 mg/kg/day. Parameters and endpoints evaluated included mortality, clinical observations, body weight and weight gain, food consumption, hematology, serum analysis, gross pathology.

Results: Mortality (dams): There was no mortality in rabbits dosed up to 2.5 mg/kg/day. In the 10 mg/kg/day, one female rabbit was found dead on Day 8. Gross pathology revealed congested lungs, an increase in thoracic and peritoneal fluid, watery and gaseous content of the large and small intestine. These findings are not specific. However, it cannot be excluded that this death was treatment related. Clinical signs (dams): Ptosis and mitosis were seen in all paliperidone-treated groups. Sedation was noted at 2.5 and 10 mg/kg/day. These findings were observed from Days 9-11 of the presumed pregnancy. Rabbits in the 10 mg/kg/day group had small amounts of feces at the end of the treatment. Body weight (dams): A slight decrease in body weight and weight gain was seen in the 0.63 and 2.5 mg/kg/day groups. This effect was more pronounced at 10 mg/kg/day (the mean absolute body weight was 7% less on Day 19 than on Day 0 in this group and 11% less than the mean control value on Day 19). Food consumption (dams): A decrease in food consumption (dose-dependent) was seen in the paliperidone dosed groups, especially in the second half of the dosing period. At 10 mg/kg/day, mean food consumption from the Day 12 to 18 was only 48% of the mean control group value. Hematology: The following findings were noted: hematocrit (decrease at 2.5 mg/kg), mean cell hemoglobin concentration and basophils (increase at 10 mg/kg/day), lymphocytes (decrease at 0.63 mg/kg/day). These findings were statistically significant. However, they were minimal. Clinical chemistry: There were no toxicologically significant findings in rabbits dosed up to 2.5 mg/kg. At 10 mg/kg, potassium, calcium, cholesterol, phosphpolipids and blood urea nitrogen were decreased. Toxicokinetics: not conducted. Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): Only gross pathology was conducted. Findings included inspissated secretion (thickened, condensed material) in the mammary glands of the several rabbits of all paliperidone dosed groups. None of the rabbits was pregnant. Offspring (malformations, variations, etc.): There was no offspring. The results of the 13-day repeated dose oral toxicity study are summarized in the following sponsor's table:

Variables	- dosages in mg/kg body weight/day		
	0.63	2.5	10
Mortality	0/5	0/5	1/5
Clinical observations			
ptosis	++P	+++P	+++P
miosis	+++P	+++P	+++P
sedation	N	+P	++P
small amounts of faeces	N	N	++P
Body weight and weight gain	+D	+D	++D
Food consumption	(+)D	+D	++D
Haematology	N	N	
mean cell haemoglobin conc.			(+)I
basophils			(+)I
Serum analysis	N	N	
potassium			+D
calcium			+D
cholesterol			+D
phospholipids			+D
blood urea nitrogen			+D
Gross pathology			
inspissated secretion mammary glands	++P	++P	++P

[a] Number of mice showing mortality/total number.
N = No test article related effects D = decreased P = present I = increase
(+) = marginal + = slight ++ = moderate +++ = severe

Appears This Way On Original

According to the sponsor, based on the deaths of one rabbit that was considered to be test article-related and other data, doses for the main oral developmental toxicity were selected as 0.31, 1.25 and 5 mg/kg/day.

5.Study title: Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage on Albino Rabbits

The purpose of this study was to investigate the effects of paliperidone on pregnant rabbits and on embryo-fetal development when administered by oral gavage to pregnant rabbits during the period of organogenesis.

Key study findings: Oral administration of paliperidone to pregnant female rabbits during days 6 to 18 of pregnancy revealed maternal toxicity. The maternal toxicity findings included clinical signs of sedation (lethargy) and ptosis at 1.25 mg/kg/day and above, reduced body weight gain at all dose levels, and reduced body weights and food consumption at 5 mg/kg/day. Embryo-fetal effects were observed at 5 mg/kg/day. These included a slight increase in total post-implantation loss, mean number of total resorptions and mean number of dead fetuses. No test article-related teratogenicity was seen (see below for details). There were no other toxic fetal effects. The NOAEL for maternal toxicity was established as 0.31 mg/kg/day (based on lethargy seen in dams at 1.25mg/kg). The NOEL for embryo-fetal toxicity was 1.25 mg/kg/day.

Study no.: JRF4708
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]
Date of study initiation: October 14, 1998

GLP compliance: yes (OECD)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477), lot ZR076477PFA011, purity: not provided

Methods

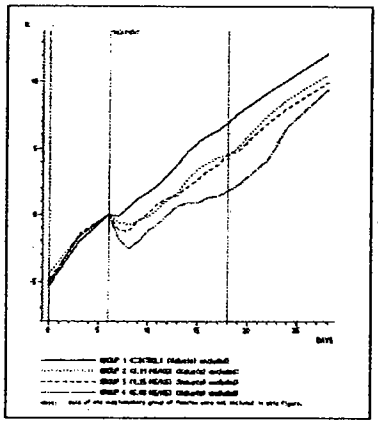
Doses: 0, 0.31, 1.25 and 5 mg/kg/day
Species/strain: albino rabbits/New Zealand White
Number/sex/group: 16 females/group
Route, formulation, volume: Oral (gavage), aqueous solution of paliperidone,
Satellite groups used for toxicokinetics: none; 2 females per each main study group were used for TK analysis.
Study design: 64 virgin females were artificially inseminated in order to obtain 4 groups of 16 pregnant females. From Day 6 to Day 18 of gestation females of the treatment groups received daily oral administration of paliperidone or vehicle (control group). On Day 28 of gestation a caesarian section was performed and the contents of the uterus assessed. All fetuses were further processed for visceral and skeletal examination. During the skeletal staining process, the skeletons of a number of fetuses fell apart and were as a consequence unreadable. The occurrence was randomly distributed among the dose groups and also within the affected litters there was a variable incidence and severity of disintegrated fetuses noted. Due to this technical problem the number of complete litters per dose group was below 12 in the dose groups 2, 3 and 4. Therefore, supplementary females were added to these dose groups with the purpose to increase the number of complete litters per treatment group.

Parameters and endpoints evaluated: Dams: mortality/viability, clinical signs, body weights, food consumption, toxicokinetics. Necropsy: External, thoracic and abdominal examinations were performed for the detection of macroscopic abnormalities. Each ovary and uterine horn of animals surviving to Day 28 of gestation was dissected and examined to determine: the number of corpora lutea (ovaries in situ), the weight of the gravid uterus, the number and distribution of live and dead fetuses, the number and distribution of embryo-fetal deaths, the number of implantation site scars (empty implantations), the weight of each live fetus and corresponding placenta, the sex of each fetus (during further fetal examination), externally visible macroscopic fetal abnormalities. Fetal pathology: All fetuses were dissected and examined for both visceral and skeletal anomalies, with the exception of the heads. From half of the fetuses the heads were removed for visceral examinations, and the other half of the heads were subjected to skeletal examinations.

Results:

Mortality (dams): Observed twice daily. No test substance-related mortality occurred in this study. 3 rabbits died due to gavage errors.

Clinical signs (dams): Observed at least once daily. Clinical signs attributable to the test compound were noted at 1.25 and 5.0 mg/kg/day. At 1.25, lethargy was seen in the majority of the animals for 11 Days. At 5 mg/kg/day, a lethargy and ptosis was noted in the majority of animals. In addition, miosis, reduced amounts of feces, diarrhea, reduced water consumption, ptosis, piloerection and quick breathing were observed occasionally.
Body weight (dams): Recorded on Days 0 and 3, daily from Day 6 to Day 18 and on Days 19, 22, 24 and 28 of gestation. Body weights were slightly reduced at the highest dose level only (on gestation Day 18: -7%). Body weight gain and corrected body weight (after subtracting the uterus weight) were noted to be decreased during the treatment period at all treatment levels in comparison with the control group. Changes in body weight gain of females are shown in the following sponsor's figure:



Food consumption (dams): Determined during Days 0-3, 3-6, 6-9, 9-12, 12-15, 15-19, 19-22, 22-24 and 24-28 of gestation. When compared with the control group, pregnant females treated with paliperidone at 5.0 mg/kg/day showed a reduction in food consumption during the treatment period (-29%).
Toxicokinetics: see a review below
Terminal and necroscopic evaluations: C-section data (implantation sites, pre- and post-implantation loss, etc.): No differences in the number of corpora lutea, pre-implantation loss, and the number of implantations were noted. When comparing this with the control group, a slight increase in total post-implantation loss was recorded for the females treated at 5 mg/kg/day (7.7% of implantation sites versus 1.9% in the control). This implantation loss was associated with a slight increase in the number of embryo-fetal resorptions (0.5 versus 0.2 in the control group) and fetal deaths (2 fetuses affected in 2 dams versus none in the control group).
Offspring (malformations, variations, etc.): No differences were detected in litter sizes of dams receiving paliperidone and control dams. Sex ratios were comparable in treated and control groups. Comparable fetal weights were revealed for treated and control groups. Placenta weights of fetuses from treated and control dams were similar. No external findings were noted among the fetuses. No malformations were observed in any of the dosage groups. Skeletal and visceral examinations revealed no indications of adverse effects on fetal skeletal ossification or on morphological developments. The increased incidence of brown masses in the lateral ventricles (28/52, 57/78, 46/60, 48/65 at 0, 0.31, 1.25 and 5 mg/kg, respectively) were at the border line of the historical control data.

These values represent the following percentages: 54%, 73%, 77%, 74%, respectively. The historical control data provided by the sponsor are 33/52 and 30/42 (63% and 71%, respectively). In addition, the incidence of one 13th rib was slightly increased in the 5 mg/kg group: 24/108 (22%) versus 12/98 (12%) in the control group (historical control value was 7/35 = 20% increase). Since these values are similar, the findings were not considered relevant. The results are shown in the following sponsor's table:

Report Title: Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage in Albino Rabbits — **Test Article:** R076477

Effects on Embryo-Fetal Development

Design Similar to ICH 4.1.3? Yes [X] No [ ]
Species/Strain: Rabbit/New Zealand White
Age at First Dose: At least 17 weeks
Date of First Dose: 15 November 1998
Special Features: An extra number of dams (7 each to low and mid dose groups and 6 added to high dose group) added to evaluate suitable number of litters/treatment group.
No Observed Adverse-Effect Level:
F_0 **Females:** Not established (<0.31 mg/kg/day)
F_1 **Litters:** 1.25 mg/kg/day

Duration of Dosing: GD 6 to GD 18
Day of Mating: GD 0
Day of C-Section: GD 28
Route: Oral gavage
Vehicle/Formulation: Aqueous solution of demineralized H_2O, tartaric acid, and NaOH + R076477

Study No.: 4708
Location in CTD: 4.2.3.5.2
GLP Compliance: Yes

Daily Dose (mg/kg)	0 (Control)	0.31	1.25	5.00
No. of Animals	16	23	23	22
Toxicokinetics[a]:				
No. of Animals	0	2	2	2
$AUC_{0\text{-}\infty}$ (ng·h/mL)				
Day GD 6[b]	---	1047	4782	21750
Day GD 18[b,c]	---	8825	20133	54241
C_{max} (ng/mL)				
Day GD 6[b]	---	120	359	1128
Day GD 18[b]	---	852	1586	3510
Noteworthy Findings				
No. Pregnant	13	19	17	18
No. Died or Sacrificed Moribund	0	2	1	3
No. Aborted or with Total Resorption of Litter	0	0	2	1

[a] Toxicokinetics reported separately under study number FK3036; report location in CTD 4.2.3.5.2.
[b] Indicates the day and interval (gestation) of dosing
[c] $AUC_{0\text{-}24\,h}$ for GD 18

GD = gestation day; H_2O = water; --- = no noteworthy findings

(Continued)

Report Title: Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage in Albino Rabbits — **Test Article:** R076477

Effects on Embryo-Fetal Development

Daily Dose (mg/kg)	0 (Control)	0.31	1.25	5.00
Noteworthy Findings (Continued)				
Clinical Observations (GD 6 – 18)[a]				
Alopecia	0/16	1/23	0/23	0/22
Piloerection	0/16	1/23	0/23	5/22
Lethargy	0/16	0/23	22/23	22/22
Fur (red staining)	0/16	0/23	1/23	0/22
Ptosis	0/16	0/23	0/23	22/22
Breathing (quick)	0/16	0/23	0/23	6/22
Breathing (labored)	0/16	0/23	0/23	1/22
Rales	0/16	0/23	0/23	1/22
Skin (pale)	0/16	0/23	0/23	1/22
Salivation	0/16	0/23	0/23	1/22
Skin (scab; eyelid)	0/16	0/23	0/23	1/22
Diarrhea	0/16	0/23	0/23	1/22
Miosis	0/16	0/23	0/23	22/22
Fecal output (reduced)	0/16	0/23	0/23	22/22
Water consumption (reduced)	0/16	0/23	0/23	[b]
Body Weight[c,d,e]				
(GD 6)	3455	0.99	1.00	0.98
(GD 19)	3714	0.97	0.97	0.93**
(GD 28)	3868	0.98	0.98	0.96

[a] Number of animals with observation/total number of animals.
[b] Number of animals with reduced water consumption in Group 4 not specified.
[c] Dunnett-Test based on pooled variance; significant at 5% (*) or 1% (**).
[d] Finding recorded on the day shown. For controls, group means are shown. For treated groups, noteworthy findings are expressed as fractions or multiples of control. Statistical significance is based on the actual data (not on the fraction or multiple of control).
[e] Supplemental animals (those added after study start) are not included in the body weight mean calculations or statistical analysis.

GD = gestation day; * = $p<0.05$, ** = $p<0.01$

(Continued)

Report Title: Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage in Albino Rabbits **Test Article: R076477**

Effects on Embryo-Fetal Development Daily Dose (mg/kg) Noteworthy Findings (Continued)	0 (Control)	0.31	1.25	5.00
Adjusted Body Weight[a,b]	3443	0.97	0.98	0.96
Corrected Mean Maternal Weight Gain[c]	-12	-94	-72	-92
Food Consumption[d]				
GD 6-9	186	0.96	0.97	0.69**
GD 9-12	177	0.92	0.94	0.85
GD 12-15	168	0.89	0.88	0.74**
GD 15-19	188	0.85	0.89	0.71**
Mean No. Corpora Lutea	11.0	10.6	11.0	10.2
Mean No. Implantations	8.2	8.3	8.1	8.4
Mean % Preimplantation Loss	25.9	21.9	26.7	17.9
Necropsy Observations				
Body cavities: thoracic contains hemorrhagic fluid	0/16	1/23	1/23	0/22
Esophagus: containing part of catheter	0/16	0/23	0/23	1/22
Heart: apex, discoloration	0/16	1/23	1/23	0/22
Heart: irregular surface	0/16	1/23	0/23	0/22
Large intestine: hemorrhage	0/16	0/23	0/23	1/22
Liver: accentuated lobular pattern; foci, yellowish	0/16	0/23	0/23	1/22
Lungs: hemorrhage	0/16	1/23	1/23	0/22
Ovaries: reduced size	0/16	1/23	0.23	0/22
Stomach: irregular surface with red discoloration	0/16	1/23	0/23	0/22
Trachea: contains fluid, reddish	0/16	1/23	1/23	1/22
Urinary bladder: enlarged	0/16	1/23	0/23	0/22
Vagina: discoloration, red	0/16	1/23	0/23	0/22

[a] Adjusted body weight = body weight on day of cesarean sectioning minus the gravid uterine weight.
[b] Dunnett-Test based on pooled variance significant at levels of 5% (*) or 1% (**).
[c] Corrected mean maternal weight gain = adjusted body weight minus body weight at first dose.
[d] Food consumption data presented as mean grams/animal/day for controls; treated rats expressed as fraction or multiple of control value. Statistical significance is based on the actual data (not on the fraction or multiple of control).

GD = gestation day
* = p<0.05, ** = p<0.01

(Continued)

Report Title: Embryotoxicity and Teratogenicity Study with R076477 Administered by Oral Gavage in Albino Rabbits **Test Article: R076477**

Effects on Embryo-Fetal Development Daily Dose (mg/kg)	0 (Control)	0.31	1.25	5.00
Litters: No. of Litters Evaluated	13	19	15	17
No. Live Fetuses	104	155	118	131
Mean No. Live Fetuses	8.0	8.2	7.9	7.7
Mean No. Early Resorptions	0.2	---	0.1	0.2
Mean No. Late Resorptions	---	0.1	0.1	0.3
Mean No. Total Resorptions	0.2	0.1	0.2	0.5
No. Dead Fetuses	0	0	0	2
Mean No. of Dead Fetuses	---	---	---	0.1
Mean % Postimplantation Loss	0.2	0.1	0.2	0.6
Mean Fetal Body Weight (g)	36.5	35.8	36.5	36.1
Fetal Sex Ratios % (Total M/Total F)[a]	40.4/59.6	50.3/49.7	49.2/50.8	54.1/45.9*
Fetal Anomalies:				
Gross External	---	---	---	---
Visceral Anomalies	---	---	---	---
Skeletal Anomalies	---	---	---	---
Total Affected Fetuses (Litters)	---	---	---	---

[a] Fischer's exact test significant at levels of 5% (*) or 1% (**)

M = male; F = female; --- = no noteworthy findings; * = p<0.05, ** = p<0.01

JANSSEN PHARMACEUTICA NV
Department of Toxicology
Experiment: 4708
Oral Developmental Toxicity Study in the Rabbit
R076477 - ORG - Rabbit
Dosing period: from day 6 through day 18 of pregnancy

Table 1A

Summarized results
FETAL EVALUATION

Observation	Vehicle 0 mg/kg N/N1	Low 0.31 mg/kg N/N1	Medium 1.25 mg/kg N/N1	High 5 mg/kg N/N1
A. Affecting the whole body				
no skeletal evaluation due to poor processing	6/104	28/155	16/118	24/132
B. Affecting parts, regions or organs				
1. Cranium and contents				
arachnoid space: filled with brown mass	51/52	71/78 *	51/60 **	54/65 *
lateral ventricle(s): filled with brown mass	28/52	57/78	46/60	48/65
orbital sinus: filled with brown mass	11/52	17/78	20/60	15/65
plaque(s) affecting frontal bones	3/48	7/63	3/48	5/56
plaque(s) affecting nasal bones	1/48	4/63	2/48	4/56
plaque(s) affecting parietal bones	0/48	0/63	2/48	2/56
2. Spine and spinal cord				
cervical vertebra 7: one rudimentary rib	2/98	0/127	1/102	3/108
cervical vertebra 7: rudimentary pair of ribs	0/98	0/127	1/102	0/108
3. Face and sense organs				
4. Neck				
5. Thorax and contents				
ribs: 13th pair	47/98	56/127	45/102	54/108
ribs: one 13th rib	12/98	15/127	9/102	24/108 *
ribs: one rudimentary 13th rib	15/98	15/127	17/102	21/108
ribs: one rudimentary first rib	0/98	1/127	0/102	0/108
ribs: rudimentary 13th pair	4/98	10/127	6/102	5/108
sternum bone(s) asymmetrical	2/98	4/127	0/102	1/108
sternum bone(s) cleaved	3/98	2/127	1/102	1/108
sternum bone(s) dumbbell-shaped	3/98	0/127	1/102	4/108
sternum bone(s) fused	0/98	0/127	0/102	3/108
sternum bone(s): absent	38/98	76/127 **	56/102 *	42/108
sternum bone(s): incomplete ossification	0/98	0/127	1/102	0/108
sternum: rudimentary bone(s)	47/98	52/127	37/102	48/108
6. Abdomen and contents				
7. Pelvis and contents				
pubis: not ossified (absent)	5/98	13/127	6/102	4/108
rudimentary pubis	17/98	23/127	24/102	18/108
8. Urogenital system				
9. Extremities				
only one tarsal bone ossified	2/98	3/127	0/102	3/108

Comparison of the number of fetuses with a particular major abnormality, minor abnormality or variation per litter between the dosed group and the reference group computed by Fisher Exact test. (Right tail probability) Except the observation: no skeletal evaluation due to poor processing.

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

Malformations are underlined
N = Number of fetuses with a particular major abnormality, minor abnormality or variation
N1 = Number of fetuses screened for that abnormality

6. Study title: Toxicokinetics of Paliperidone (9-Hydroxy-Risperidone, R076477) in Pregnant SPF Albino Rabbits in an Oral Segment II Reproduction Toxicity Study [redacted] 246915) on Aqueous Solutions of R076477 at 0.31, 1.25, and 5 mg/kg/day.

The toxicokinetic parameters of paliperidone were studied in rabbits dosed orally with paliperidone at 0.31, 1.25, and 5 mg/kg/day in the Study No. 4708 ([redacted] 246915) (see above). The first 2 females of each dose group were subjected to blood sampling for toxicokinetic analysis. Blood was taken at the following time points: Pre-dosing and at 1, 2, 4, 8 and 24 hours after dosing on Day 6 (after the first dose) and on Day 18 (after 13th dose) of gestation. Mean (N=2) pharmacokinetic parameters of paliperidone in pregnant rabbits on Day 6 and Day 18 of gestation are shown in the following table:

	0.31 mg/kg/day		1.25 mg/kg/day		5 mg/kg/day	
	Day 6	Day 18	Day 6	Day 18	Day 6	Day 18
C_{max} (ng/ml)	120	852	359	1586	1128	3510
T_{max}	1.0	1.5	4.5	1.5	1.0	3.0
$T_{1/2}$	4.9	13	6.4	3.9	12	18
AUC_{0-24h} (ng.h/ml)	1015	8825	4344	20133	15790	54241
AUC_{0-24h} (ng.h/ml)	1047	-	4782	-	21750	-

Exposure levels were higher after repeated dose administration than after a single dose administration. The elimination half-life ($T_{1/2}$) after a single oral dose ranged form 4.9 to 12 h and was comparable to that after repeated dose administration, which ranged from 3.9 to 18 hours. On Day 6 of gestation, the exposure increased approximately in proportion to the dose; On Day 18, AUC values increased significantly less than dose proportionally. On Day 18 of gestation, the 16.1-fold increase in dose resulted in a 6.8-fold increase in AUC_{0-24H} values.

Prenatal and postnatal development

7. Study title: Oral (Gavage) Pre- and Post-natal Developmental Toxicity and Juvenile Toxicity Dose Range Finding Study in the Rat (TOX 6710). This study was previously submitted to the IND 65,850 (Serial No.176) and was reviewed by Sonia Tabacova Ph.D. Dr. Tabacova's review of 4/14/2006 is available in the Agency files. The following conclusions and recommendations are taken directly from Dr. Tabacova's review:

The preliminary juvenile toxicity study of paliperidone in rats is inadequate to support the registration of paliperidone in pediatric patients. There is no definintive juvenile toxicity study of paliperidone.
- The definitive juvenile rat toxicity study of risperidone cannot be used as a surrogate for a juvenile rat study of paliperidone, because of the apparent differences in paliperidone and risperidone toxicity manifested in the preliminary juvenile toxicity study (e.g., mortality in paliperidone but not in risperidone study).
-The sponsor needs to perform a definitive juvenile toxicity study with paliperidone in order to support the registration of paliperidone in pediatric patients.

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

The objective of the study was to assess the effects of paliperidone 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 inclusive. The F1 generation was allowed to mature and the effects on growth, development, behavior and reproductive performance were assessed.

Key study findings: 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, the decreased activity was observed also during the beginning of lactation. A body weight gain was slightly lower at 1.25 mg/kg/day following the first day of dosing during the gestation. There were no other test-article related findings. The NOAEL for maternal treatment with paliperidone was 1.25 mg/kg/day, the highest dose tested. The same dose was the NOAEL for pup development, fertility, mating performance, or gestation of the F1 generation. The MTD was not achieved in this study.

Study no.: TOX6737 [redacted] Study no. JAB0084)
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]
Date of study initiation: October 11, 2004 (first dosing)
GLP compliance: yes (UK GLP and OECD)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477; 9-hydroxy-risperidone), Batch ZR076477EIA041, purity [redacted]

Methods

Doses: 0, 0.08, 0.31 and 1.25 mg/kg/day
Basis of dose selection: The dose levels were selected by the sponsor based on results from a combined pre-and postnatal toxicity and juvenile toxicity range finding study (No. TOX6710), in which mated female rats were dosed with paliperidone by oral gavage from Day 6 of gestation to Day 7 of lactation at levels of 0, 0.08, 0.16, 0.63 and 2.5 mg/kg/day. There were signs of sedation of the dams in all treated groups. The number of pups born alive was not affected. At Day 4 of lactation, the percentage pup survival was 91%, 96%, 99%, 98% and 64% at 0, 0.08, 0.16, 0.63 and 2.5 mg/kg/day, respectively. Based on this information, dose levels of 0.08, 031 and 1.25 mg/kg/day were selected.

Note: The dose selection is questionable for this study. Apparently, instead of maternal toxicity parameters, reduced pup survival at 2.5 mg/kg/day in the dose range-finding study (No. TOX6710) was used to justify selection of 1.25 mg/kg/day as the top dose for this study. This reviewer notes that there was no reason to decrease the top dose of 2.5 mg/kg/day because it clearly did not exceed

the MTD based on maternal parameters, for example maternal body weights. At 2.5 mg/kg/day in the dose range-finding study (No. TOX6710), 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.

Species/strain: rat/[redacted]:CD (SD) IGS R VAF PLUS
Number/sex/group: 25/sex/group
Route, formulation, volume: Oral, solution in vehicle (UHP water, tartaric acid and NaOH 0.1 M up to pH = 5±0.1), 5 mL/kg body weight.
Satellite groups used for toxicokinetics: none
Study design: Three groups of 25 time-mated female rats (F0) were dosed with paliperidone at three dose levels once daily by oral gavage, from Day 6 of gestation to Day 20 of lactation, inclusive. A group of 25 similar females dosed with the vehicle served as controls. The maternal females were necropsied on Day 21 of lactation. Approximately one week after the start of weaning, the F1 generation, 20 male and 20 female offspring were randomly selected (at least one from each of the weaned litters). The F1 generation was allowed to mature untreated and the effects of paliperidone were assessed.
Parameters and endpoints evaluated:
Maternal: Clinical observations (examined daily), mortalities (examined twice daily), body weights (recorded on Days 6, 7, 8, 9, 12, 15 and 20 of gestation and Days 1, 4, 7, 14 and 21 of lactation), food consumption (recorded daily to Day 6 of gestation, and then from Days 6 to 9, 9 to 12, 12 to 15 and 15 to 20 of gestation and over Days 1 to 4, 4 to 7, 7 to 10 and 10 to 14 of lactation), parturition (when possible, the time of onset and completion of parturition was recorded), lactation, necropsy observations, pregnancy status, number of corpora lutea, number and intrauterine position of implantations.
F1: Litter size, sex, clinical observations, body weight, malformations, litter developmental and behavioral assessments (learning and memory in the Morris water maze test, locomotor activity using a rotarod, auditory function), sexual development and reproductive ability, necropsy observations.

Results

F_0 in-life: Mortality: There were no maternal deaths during the gestation period. On the Day 2 of lactation one high dose female was sacrificed following total litter death. There was no milk in the stomach of the pups. This finding was considered incidental. There were no macroscopic findings in this female at necropsy. Clinical observations: Sedation (both eyes partially closed) was observed in females for up to six hours after dosing at 0.31 and 1.25 mg/kg/day during the gestation and lactation periods. Decreased activity was observed in all females at 0.31 and 1.25 mg/kg/day during the gestation period. This finding was recorded during lactation only in females administered 1.25 mg/kg/day until Day 3 of lactation. Maternal body weight and body weight gain: Group mean absolute body weight was similar in all groups until the end of the study. A slight but statistically significant reduction in group mean body weight gain was observed at 1.25 mg/kg

following the first day of dosing (Day 6 of gestation) until Day 7 (mean gain value of 2 g versus 5 g in the control group). After Day 7 of the gestation, mean gains were similar to controls. Food consumption: There were no treatment related changes during the gestation period. Minimal decreases (-6%) were noted in females at 1.25 mg/kg/day between Days 4 to 7 of lactation. Gestation and parturition: There were 23/25, 25/25, 25/25 and 22/25 females that produced live litters in the control, 0.08, 0.31 and 1.25 mg/kg/day groups, respectively. There were no treatment effects on the duration of gestation or on the live birth index. One female given 1.25 mg/kg/day failed to litter and had 2 resorption sites in the uterus.
F_0 necropsy: There were no test article related macroscopic necropsy findings. As indicated above, two early resorptions were observed in the horn of the uterus of one female given 1.25 mg/kg/day. Due to isolated incidence of this finding, it was considered not to be related to the treatment.
F_1 physical development: There was no effect of maternal treatment with paliperidone, on the number of pups born, on the live birth index, on litter survival to weaning and on sex ratio of the born pups. There was also no treatment effect on the incidence of clinical signs, group mean absolute pup body weight, and group mean body weight gain. There were no toxicologically significant changes in the litter development, as assessed by percentage of litters with ears open on Day 3 and eyes open on Day 15 of age, and the acquisition of the righting reflex (Day 5), startle response (Day 15) and pupillary light reflex (Day 21), when compared to control values. There were no macroscopic findings at necropsy of F1 males and females that were considered to be related to F0 treatment with paliperidone.
F_1 behavioral evaluation: There were no effect of maternal treatment with paliperidone on the locomotor coordination in males and females of F1 generation in rotarod test, on the auditory acuity as assessed by the Preyer response, and on learning and memory in the Morris-maze learning test (conducted at 48 days of age).
F_1 reproduction: There were no toxicologically significant effects of treatment with paliperidone on sexual development of males and females (as assessed by the mean day of balanopreputial separation for males and the mean day of vaginal perforation for females), on the time taken by the F1 generation to mate or the number of copulation plugs observed, and on the copulation or fertility indices.
F_2 findings: There were no toxicologically significant effects of treatment of F0 with paliperidone on the pregnancy parameters of F1 as assessed by the numbers of corpora lutea, implantations and live fetuses, and the extent of pre-implantation loss. No other F2 parameters were evaluated.

2.6.6.7 Local tolerance

A 3 month repeat dose toxicity study in beagle dogs was conducted where the animals were treated p.o. with 15-mg paliperidone ER tablets. Its purpose was to evaluate the local tolerability of paliperidone ER tablets in the gastrointestinal tract. Clinical signs and histopathology examination did not demonstrate any differences in gastrointestinal tolerability between dogs dosed with 15 mg paliperidone ER tablets or paliperidone bulk powder. There was no evidence of gastrointestinal lesions in this study (for a detailed review see page 97 of this document).

Special toxicology studies:

IMMUNOTOXICITY

Study title: Assessment of Immunomodulating Effects of Paliperidone by Means of a Plaque Forming Cell Assay After Repeated Dose (4 Weeks) Oral Administration in Rats (Study No. TOX6965)

The objective of this study was to assess the potential immunomodulating effects of paliperidone in rats following administration of paliperidone by oral gavage once daily for 28 days. Sprague-Dawley rats (8/sex/group) were treated at 0, 0.63, 2.5 and 10 mg/kg/day. All animals were immunized with sheep red blood cells (SRBC) shortly before the end of the study to assess potential changes in the primary T-cell-dependent antibody response using Plaque-Forming Cell (PFC) assay. The spleen of immunized animals was collected and weighed. A part of each spleen was further analyzed in the PFC assay. The vehicle group and high dose groups included a subgroup of 8 males and 8 females that were not immunized with SRBC. At necropsy, lymphoid organs were examined histopathologically.

Results: Clinical signs of sedation and ptosis were observed at 2.5 and 10 mg/kg/day. Reduced body weight gain was noted in males mainly during the first two weeks of dosing. In females, higher body weight gain (up to +17%) and higher body weights (up to +8%) were observed at 0.63 and 2.5 mg/kg/day. Increased food consumption was observed in females at all dose levels, but mainly at 0.63 and 2.5 mg/kg (up to +24%). These results are consistent with findings in other toxicity studies. SBRC immunization resulted in increased relative splenic weight in vehicle control animals (+32% in males; +22% in females). In paliperidone treated males, SBRC immunization resulted in a dose-dependent decrease in relative splenic weight (up to -11%) at all dose levels. In contrast, in females a slight increase (up to +10%) in relative splenic weight was seen at all dose levels. There were no treatment-related microscopic changes. Treatment with paliperidone did not affect the functionality of the primary T-cell-dependent antibody response in the spleen of rats.

STUDIES ON IMPURITIES:

[redacted] is the only impurity consistently appearing at levels above 0.05% (qualification threshold) in the paliperidone drug substance. It is a process-related synthesis impurity. This impurity is also a degradation product in paliperidone drug product. It is also found in the body as the [redacted] of paliperidone. [redacted] was found in urine of male healthy volunteers, female Wistar rats (but not male rats) and dogs at concentrations of [redacted] of the dose administered, respectively. [redacted] is the [redacted] function of paliperidone. Chemical structure is shown in the following figure:

Chemical Structure of [redacted]

According to the sponsor, the presence of this impurity will be controlled at a specified concentration of [redacted] (w/w) in the paliperidone drug substance and drug product. [redacted] is the only compound that exceeds the threshold for toxicological qualification of impurities in drug substance and the toxicological qualification of impurities or degradation products in drug products. Several toxicity studies with paliperidone were conducted with batch ZR076477PFA011 containing [redacted] relative to paliperidone. These studies are listed in the table below:

Table 24: Overview of Toxicity Studies Conducted with Batch ZR076477PFA011

Study	Study Number	Dose Levels of Paliperidone
Single dose p.o. toxicity study in mice	Ref. 1	0-20-40-80 mg/kg bw
Single dose i.v. toxicity study in mice	Ref. 2	0-10-20-40 mg/kg bw
Three-month p.o. gavage toxicity study in rats	Ref. 10	0-0.63-2.5-10 mg/kg bw/day
Three-month p.o. gavage toxicity study in dogs	Ref. 16	0-0.31-1.25-5 mg/kg bw/day
Embryo-fetal developmental toxicity study in rabbits	Ref. 37	0-0.31-1.25-5 mg/kg bw/day
Ames reverse mutation test in *S. typhimurium*	Ref. 22	up to 500 µg/plate
In vitro mouse lymphoma assay	Ref. 24	up to 150 µg/mL

Other toxicity studies with paliperidone were conducted with batch ZR076477EIA021 containing [redacted] relative to paliperidone. These studies are listed in the table below:

Table 25: Overview of Genotoxicity Studies Conducted with Batch ZR076477EIA021

Study	Study Number	Dose Levels of Paliperidone
Ames reverse mutation test in *S. typhimurium*	Ref. 23	up to 5000 µg/plate
In vitro mouse lymphoma assay	Ref. 25	up to 570 µg/mL
In vivo rat micronucleus assay	Ref. 27	0-2.5-10-40 mg/kg

At the highest dose levels tested in the 3-month repeat dose toxicity studies with p.o. gavage administration (10 mg/kg/day in rats, 5 mg/kg/day in dogs) the actual amount of [redacted] in rats and [redacted] in dogs. According to the sponsor, in humans impurity [redacted] will be controlled at [redacted] The MRHD is 12 mg/day (0.24 mg/kg for a 50-kg patient). Therefore, humans treated at this dose level will receive [redacted] Since this impurity was present in rats and dogs at

[redacted] respectively, this impurity was qualified in animal toxicity studies.

[redacted] is also a degradation product in paliperidone drug product. The following studies were conducted with [redacted] forced degraded [redacted] paliperidone ER tablets stored under extreme stress conditions at 40°C and 75% relative humidity for 29 weeks. Based on the information obtained from Dr. [redacted] under those conditions the amount of [redacted] remained constant at [redacted] level in the drug product. Therefore, there is no need for qualification of this impurity since the qualification threshold is 0.5% or 200 µg TDI, whichever is lower. However, the sponsor conducted the following studies with forced-degraded formulations:

1. Study title: 2-Week Comparative Repeat-Dose Toxicity Study with Formulations Derived from Paliperidone ER Tablets Administered to Beagle Dogs p.o. in Gelatin Capsules.

The purpose of this study was to determine the potential toxicity of forced degraded tablets of paliperidone and compare this to the toxicity of reference tablets when administered once daily by the oral route (via capsules) to beagle dogs for a period of 2 consecutive weeks.

Study no.: 5655
Volume #, and page #: electronic submission
Conducting laboratory and location: [redacted]
Date of study initiation: November 7, 2002
GLP compliance: yes (OECD)
QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone (R076477): (1) Forced degraded tablets of R076477 (lot No. bulk drug: MV0201008), which were stored at 40 °C and 75% relative humidity for 29 weeks (further written as R076477*); (2) Reference tablets of R076477 (lot No. bulk drug: MV0201008), which were stored at room teemperatue for 36 weeks (further written as R076477); purity: not provided
Formulation/vehicle: gelatine capsules filled with R076477* or R076477/gelatine capsules with placebo formulations

Methods
Doses: 0, 0.31 and 1.25 mg/kg/day
Study design: A reference formulation and a degraded formulation of paliperidone derived from tablets stored at 40 °C and 75% relative humidity for 29 weeks were administered orally via capsules to beagle dogs (3/sex/group) at doses of 0.31 and 1.25 mg/kg body weight/day for a period of two weeks. A vehicle group received a placebo formulation in capsules. The following parameters were recorded during the study: mortality, clinical and eye observations, ECG and heart rate, body weight and weight gain, food consumption, blood, serum and urine examination, organ weights, gross pathology and histopathology.

Results: The results are summarized in the following sponsor's table:

SUMMARY TABLE

		Doses in mg/kg body weight/day			
PARAMETERS	**vehicle**	**0.31**	**0.31***	**1.25**	**1.25***
Mortality[a]	0/6	0/6	0/6	0/6	0/6
Clinical observations[a]					
Soft feces	2/6	1/6	2/6	5/6	3/6
Tremors	0/6	6/6	6/6	6/6	6/6
Sedation:	0/6	6/6	6/6	6/6	6/6
- deep set eyes	0/6	5/6	6/6	6/6	6/6
- appearance of third eyelid	0/6	2/6	6/6	6/6	5/6
- decreased general activity	0/6	6/6	6/6	6/6	6/6
Congested conjunctiva	0/6	5/6	6/6	6/6	6/6
Decreased appetite	0/6	4/6	4/6	5/6	5/6
Coughing	0/6	3/6	2/6	4/6	1/6
Sneezing	0/6	1/6	2/6	1/6	3/6
Out of normal licking	0/6	0/6	2/6	1/6	1/6
ECG and heart rate	N				
PC interval		(+)D	(+)D	+D	+D
QT interval		(+)D	(+)D	+D	+D
Heart rate (b.p.m.)		(+)I	(+)I	+I	+I
Opthalmologic observations[a]	N	N			
Slight protrusion of the third eyelid			1/6	3/6	3/6
Incomplete mydriasis				4/6	4/6
Body weight	N	+trD	+trD	+trD	+trD
Body weight gain	N	+trD	+trD	+trD	+trD
Food consumption	N	++D	++D	++D	++D
Haematology	N				
Heamatocrit		(+)D	(+)D	+D	+D
Haemoglobin		(+)D	(+)D	+D	+D
Red blood cells		(+)D	(+)D	+D	+D
White blood cells		+D	+D	+D	+D
Reticulocytes		(+)D	(+)D	+D	+D
Neutrophils		+D	+D	+D	+D
Lymphocytes		N	+D	+D	+D
Monocytes		+D	+D	+D	+D
Serum analysis	N	N	N		N
Triglycerides				(+)D	
Urinalysis	N	N	N		
pH				(+)D	(+)D

Legend: [a] = number of dogs on total number
N = within normal limitst
D = decrease
+ = slight
tr = transient
A: absolute organ weight
I = increase
(+) = marginal
R: relative organ weight

QA reports: yes (x) no ( )
Drug, lot #, and % purity: Paliperidone, Lot No. 7491-023C obtained by making a granulate from tablets stored at 40 °C and 75% relative humidity for 29 weeks (force degraded tablets). The batch of impurities contained the following impurities: [redacted]

Methods: The force-degraded batch of paliperidone with impurities was tested in Ames test. Five bacterial strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and TA102) were used in this study according to standad protocol.

Results: It was concluded that the force-degraded batch of paliperidone with impurities did not induce mutation in five Salmonella strains under conditions of this study.

2.6.6.8 Discussion and Conclusions

Repeat-dose toxicity: Various treatment-related findings, which were consistently observed in the repeat-dose paliperidone toxicity studies, are thought to be mediated by dopamine D_2-antagonistic activity of paliperidone. Clinical signs of sedation, reduced general activity and palpebral ptosis observed in several studies in mice, rats, rabbits and dogs are considered to be related to D_2 receptor antagonistic action. The same properties are responsible for hyperprolactinemia observed in paliperidone- and risperidone-treated rats and dogs. In repeat-dose toxicity studies, body weight and body weight gain was generally dose-dependently decreased in paliperidone treated male rats and mice. However, in females body weight and body weight gain was generally increased at the low and medium dose levels and slightly decreased or unchanged at the highest dose. Changes in body weight occurred in parallel with changes in food consumption. Increased body weight and body weight gain in female rats and mice are most likely related to the increased prolacin levels. Increased prolactin release is also likely responsible for the following observations in the repeat dose toxicity studies with paliperidone in mice, rats and dogs, as well as in the carcinogenicity studies in rats and mice conducted with risperidone:

Pituitary gland: Increased incidence of prolactin-immuno-positive cells in the anterior pituitary gland of rats was observed in the comparative 3-month repeat-dose toxicity study with paliperidone and risperidone. This observation suggests increased activity of prolactin producing cells. Immunochistochemical staining of the pituitary was not conducted in other studies. Hyperplasia of the pituitary gland (adenohypophysis) was observed in the 3-month repeat-dose toxicity study with paliperidone and risperidone in mice and in carcinogenicity studies with risperidone in mice. A dose-related increase in the incidence of pituitary gland adenomas occurred in female mice dosed with risperidone in the carcinogenicity study. The pituitary gland was not affected in dogs treated with paliperidone or risperidone. No pituitary tumor response was seen in risperidone treated male mice or rats. **Mammary gland:** Increased mammary gland stimulation i.e. enhanced glandular development in female mice and rats and increased secretory activity in female rats, as well as female aspect of the mammary glands in male rats (i.e. tabulo acinar development) was observed in studies with paliperidone and

risperidone. For example, in the 6-month study in rats, female rats showed minimal (multi) focal hyperplasia of the mammary gland at the highest dose level tested (10 mg/kg/day) of paliperidone and risperidone. In addition, increased incidence of mammary gland adenocarcinomas in rats and female mice were observed in the carcinogenicity studies with risperidone. These effects are considered to be mediated by prolonged stimulation of the mammary gland due to hyperprolactinemia. In contrast to the mammary gland stimulation seen in rats and mice, the mammary gland in dogs treated with paliperidone and risperidone showed a resting aspect. Prolactin-mediated mammary carcinogenesis in rodents seen in the risperidone carcinogenicity studies is well known. **Female reproductive organs:** Reduced cyclic activity and resting aspect of the female reproductive organs (ovaries, uterus, vagina) was observed in rats and mice, and a delay in sexual maturity was observed in female dogs after treatment with paliperidone and risperidone. Similar findings were observed in rodents in carcinogenicity studies with risperidone. Pseudopregnency (resting aspect of female genital tract and a stimulation of the mammary gland) is a frequently observed response to treatment with dopamine D_2-receptor antagonists in rodents. **Male reproductive/accessory sex organs:** Low glandular epithelium of the coagulating glands and seminal vesicles of male rats, increased inflammation in the dorsolateral prostate in male rats and atrophy with decreased glandular development of the prostate in male dogs were observed after treatment with paliperidone. There were no effects on prostate in mice. There were no inflammatory changes in prostate in dogs. Treatment-related changes in the male accessory sex organs were also noted in the rat carcinogenicity study with risperidone. According to the sponsor, there is no evidence that prolactin induces inflammation in the human prostate. **Endocrine pancreas:** Increased incidence of pancreas endocrine adenomas in male rats observed in carcinogenicity studies with risperidone was attributed to hyperprolactinemia. There were no findings in the pancreas in studies conducted with paliperidone submitted to this NDA. **Adrenal glands:** Swollen cortical cells of the zona fasciculata of the adrenals were observed in paliperidone- and risperidone-treated male rats in the 3- and 6-month rat gavage toxicity studies. There were no findings in the adrenals in other toxicity studies in rats and in studies in dogs. In carcinogenicity studies with risperidone in rats, an increased incidence of adrenocortical ectasia and congestion was noted. Findings in the adrenals are likely related to increased prolactin levels.

Other treatment-related findings in studies with paliperidone included changes in the red pulp of the spleen and QT-prolongation. **Spleen**: The increase in erythrocyte accumulation in the splenic red pulp of rats and dogs accompanied by an increase in relative spleen weight was observed. This effect is considered by the sponsor to be due to the inhibition of the contraction of the splenic smooth musculature in response to the α_1-adrenergic receptor blocking activity of paliperidone and is related to the method of euthanasia, and of no relevance to humans. Other effects related to α_1-adrenergic receptor blocking activity of the paliperidone in animal studies include hypotesion, sedation and palpebral ptosis seen in many studies. Increase in heart rate in studies with paliperidone is likely α_2-adrenergic receptor-mediated. Slight **QTc interval prolongation** was observed in dogs in the 3-month repeat-dose toxicity study with paliperidone ER tablets and paliperidone bulk powder. In another 3-month repeated dose oral toxicity study in dogs, daily administration of paliperidone and risperidone solution by the oral route (gavage)

resulted also in slight QTc interval increases in all test article-dosed groups after one month and after three months of treatment. Heart rate increased after one and three months. According to the sponsor, administration of paliperidone and risperidone had no influence on blood pressure. However, this reviewer notes slight decreases in the mean group diastolic and systolic blood pressures in all groups, when compared to the predose values and control group after three months of paliperidone or risperidone administration. These data in combination with the safety pharmcology data indicated that paliperidone affected the cardiovascular system in dogs.

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

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

There have been numerous discussions with the sponsor on this point. The Agency agreed that the carcinogenicity could be waived if it were shown that (1) the toxicologic profiles of paliperidone and risperidone were similar, (2) human systemic exposure to paliperidone at therapeutic doses of paliperidone does not exceed that at therapeutic doses of risperidone, (3) the enentiomeric ratio of paliperidone in humans receiving therapeutic doses of paliperidone is similar to that in humans receiving therapeutic doses of risperidone, and (4) no metabolites are formed in humans after therapeutic doses of paliperidone that are not seen after therapeutic doses of risperidone.

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

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

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

There were no treatment related effects on fertility in the male fertility study in rats. In the female rat fertility and early embryonic developmental toxicity study, pseudopregnancies considered as a consequence of prolactin mediated effects were observed. The pre-coital interval was increased. Adverse effects on fertility and reproductive capacities at the highest dose level were evidenced by increases in pre- and post-implantation loss resulting in decreases in the number of implantations and live fetuses as expressed per pregnant female, and lower weights of the gravid uterus. The dose of 0.16 mg/kg was the NOAEL for fertility and reproductive capacity for female rats in this study.

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

Prenatal and postnatal development was also assessed in the oral (pre and post-natal developmental toxicity study in the rat. Maternal treatment with paliperidone resulted in clinical signs of partially closed eyes with decreased activity during the gestation period. Decreased activity was observed also during the beginning of lactation. The body weight gain was slightly lower at the highest dose following the first day of dosing during gestation. However, after 7 days of dosing, mean gains were similar to controls. There were no other test-article related findings. The MTD was not achieved in this study. The NOAEL for maternal treatment with paliperidone was 1.25 mg/kg/day, the highest dose

administered. The same dose was the NOAEL for pup development, fertility, mating performance, or gestation of the F1 generation. Therefore, the dose selection is questionable for this study. This reviewer notes that there was no reason (based on the dose-range finding study) to decrease the top dose of 2.5 mg/kg/day because this dose was not an MTD based on maternal parameters, for example maternal body weights. At 2.5 mg/kg/day in the dose range-finding study, group mean maternal body weight and body weight gain were only slightly decreased (-6% and -8%, respectively). Therefore, the dose selection for the pre and post-natal developmental toxicity study in the rat is inadequate. The sponsor should be asked to repeat this study as a phase IV commitment.

2.6.6.10 Tables and Figures

See individual study reports for tables and figures

2.6.7 TOXICOLOGY TABULATED SUMMARY

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

OVERLL CONCLUSIONS AND RECOMMENDATIONS

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

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

Recommendations: Approval of the application for paliperidone is recommended from the pharmacology/toxicology perspective. It is also recommended that the reproductive toxicology study of pre- and post- natal development in the rat (reproductive toxicology study segment III) be repeated using higher doses during Phase IV.

Suggested labeling: see page 3 of this review

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

none

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

/s/

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9/29/2006 12:30:41 PM
PHARMACOLOGIST

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I concur with all recommendations and major conclusions in Dr. Chalecka-Franaszek's excellent review.