2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

Study title: Segment I Study in Rats

Key study findings: This 2-generation study evaluated the effect of iloperidone on male and female gonadal function, mating behavior and fertility, as well as on the prenatal and postnatal growth and development of offspring. Oral (gavage) administration at doses of 0, 4, 12, 36 mg/kg/day to Sprague Dawley male and female rats (32/sex/group) for a period starting 10 weeks prior to mating (males) or 2 weeks prior to mating (females) and continuing through mating, gestation, parturition and lactation, resulted in the following drug-related effects: clinical signs (hypoactivity, ptosis and lacrimation at MD and HD; ptosis at LD), significant decreases in mean body weight of F0 males and females at MD and HD during pre-mating and mating periods, as well as throughout gestation and lactation [e.g., the corrected maternal weight at term (terminal body weight minus gravid uterine weight) was significantly lower at HD and MD by 13% and 7%, respectively], female estrous cycle disturbances (all doses, dose-dependently) and reduction in male reproductive organs' weight (mean absolute prostate weight decreased in all dosed groups; mean absolute and relative testis and epididymis weights decreased at HD). Lower female fertility indices, i.e. 72% and 88% were registered at HD and MD, respectively, vs. 100% in control (statistically significant at HD). A significant negative trend was noted for male fertility, without significant differences between control and any of the treated groups. The pregnancy rate was lower in MD and HD groups (86%, and 60%, respectively, vs. 100% in control), statistically significant at HD. The duration of pregnancy was increased (mean duration of 22, 22.5, and 22.6 days at LD, MD, and HD vs. 21.7 days in control group, statistically significant at MD and HD). Mean numbers of corpora lutea and implantation sites were significantly lower at HD in comparison to control; the reduced implantations were secondary to the reduction of corpora lutea and not due to an increased pre-implantation embryonic lethality since preimplantation loss was not significantly different from control in any of the treated groups. Embryofetal growth was retarded at HD, as indicated by a significantly lower mean fetal weight at term vs. control values. No external or visceral malformations were observed in the treated groups, but visceral variation rates (dilatation of lateral and third brain ventricles, dilatation of heart ventricles) were increased in HD group. There was an increased prenatal and neonatal mortality in F1 generation, as demonstrated by decreased livebirth index (89% and 83% at MD, and HD vs. 99% in control group, statistically significant), increase in stillborn pup number (18 and 17 at MD and HD vs. 2 in control group, statistically significant) and increase in neonatal deaths (mean viability indices, i.e. N alive on postnatal Day 4/ N liveborn = 80% and 24% at MD, and HD vs. 98% in control group, statistically significant). There was no pup lethality after the neonatal period (pups surviving to weaning/pups alive on day 4 post-cull) or after weaning. Mean pup weight was lower in MD and HD groups vs. control, statistically significant at postnatal day 14. There were no differences in developmental landmarks or in neurobehavioral development of F1 generation as assessed by activity and learning tests. However, very few HD litters were available for growth and behavioral evaluations because of the low pregnancy rate and neonatal deaths. F1 post-weaning growth and development were

similar in dosed and control groups. Reproductive performance of F1 animals and F2 generation in utero growth and survival were apparently not affected by treatment.
In conclusion, based on the results of this study, a NOEL was not identified, since dose-related estrous cycle disturbances and a decrease in prostate weight of F0 were induced at all dose levels, including the low dose. These effects are not unexpected and are most likely secondary to the pharmacological action of the drug. However, at the low dose (4 mg/kg/day) these effects did not interfere with F0 reproductive capacity, prenatal and postnatal survival, growth and development of F1 generation, or with F1 reproductive capacity and the prenatal growth and survival of the next, F2 generation. Therefore, iloperidone oral dose of 4 mg/kg/day is identified as the NOAEL in the Segment I rat fertility study.

Study no.: [redacted]
Volume # and page #: N.A.
Conducting laboratory and location: [redacted]

Date of study initiation: June 21, 1993
GLP compliance: yes
QA reports: yes
Lot numbers and potency: Batch RC5634 /Purity 99.8% (HPLC)
Vehicle: 2% potato starch in water
Methods

Doses: 0, 4, 12, 36 mg/kg/day
Species/strain: Rat/ — CD® BR (Sprague-Dawley)
Number/sex/group: 32
Route, formulation, volume: Oral gavage, suspension in 2% water solution of potato starch, dosing volume 10, 5, 7.5 and 10 ml/kg for control, LD, MD and HD groups, respectively.
Satellite groups used for toxicokinetics: None
Study design: Males were dosed for 10 weeks prior to mating through termination; females were dosed for 2 weeks prior to mating through termination. Of the 32 females per group, 20 were assigned to C section, and 12 to natural delivery. The group assignments were as follows:

Group	Dosage Level mg/kg/day	No. of Animals Male	No. of Animals Female	C-Section Day 20	Allowed to deliver[a]
1 (Control)	0	32	32	19	13
2 (Low)	4	32	32	18	14
3 (Mid)	12	32	32	18	14
4 (High)	36	32	32	16	16

[a] All unconfirmed females were allowed to deliver. Of the 32 females per group, 20 were assigned to cesarean section and 12 to natural delivery.

During the mating period, one male was cohabited with one female from the same group up to a maximum of 21 days or until mating was confirmed. The day of observation of presence of sperm in vaginal lavage was designated as Day 1 of gestation. Pregnant

females were randomly selected for dose group assignment. On gestation day 20, the F0 females scheduled for C-section were sacrificed; fetuses were weighed, sacrificed, and evaluated for external and visceral abnormalities. The F0 females selected for natural delivery were allowed to litter and raise their pups (F1 generation) to weaning (Day 21 post partum). Litters were observed daily for clinical signs, growth and development. Following weaning, selected F1 males and females were allowed to undergo a 7-week growth phase, during which behavioral development was monitored in selected animals. Upon maturation, the F1 animals were mated and allowed to naturally deliver the F2 generation which was terminated on Day 1 post partum.
In addition, HD F0 males were mated with naïve (untreated) females until mating was confirmed; the pregnant females were sacrificed on gestation day 14 and the numbers of corpora lutea, live and dead fetuses were determined.

Parameters and endpoints evaluated:

F0 Parental Generation: Mortality and clinical signs (twice daily); Estrous cycle (all females, daily vaginal lavage, beginning 2 weeks prior to mating through mating or end of breeding); Body weight (weekly for males and non-pregnant females; on gestation days 0, 7, 14 and 20, and on lactation days 0, 4, 7, and 21); Food consumption (weekly for males and females prior to breeding; for delivering females – on lactation days 0-4, 4-7, 7-10, and 10-14; not measured during mating or gestation); Necropsy: F0 males and females were examined grossly; male reproductive organs were weighed and abnormal viscera and reproductive tract organs were preserved in 10% formalin.
F1 fetuses: On gestation day 20, the F0 females scheduled for C-section were sacrificed; numbers of corpora lutea, implantations, resorptions, live and dead fetuses were recorded; fetuses were weighed, examined for external abnormalities and about 50% of fetuses were preserved in Bouin's for visceral examination.
F1 pups: Upon natural delivery, pup weight and viability were recorded on postnatal (lactation) days 0, 4, 7, 14 and 21. Litters were culled to 8 pups on p.n. day 4. Developmental and behavioral evaluations were conducted as listed in the following sponsor's table. The evaluations were performed on all pups beginning on the days listed and continuing until the developmental landmark was positive for the entire litter, or until weaning.

F1 pups – physical and neurobehavioral developmental endpoints

Parameter	Day	Criterion
Pinna unfolding	1	Both pinna detached
Generalized hair growth	7	Density comparable to the dorsal surface of the growth on an adult forepaw
Incisor eruption	7	Upper incisors penetrated gums
Eye opening	11	Both eyes opened
Surface righting	4	Righted from supine position in ≤2 seconds, three out of three trials
Grip reflex	17-21	Gripped wire for 5 seconds

In addition, behavioral evaluations of motor activity (open field on postnatal days 22 and 60) and learning capacity (water maze, 3 weeks after weaning), as well as of sexual maturation were performed on selected pups (1/sex/litter).
F1 Parental and F2 Observations: Following weaning, the F1 pups selected as parental offspring were observed daily for mortality and morbidity; body weight was recorded weekly. Food consumption was not measured. After a 7-week post-weaning growth

phase, the F1 males and females were mated within each group (mating confirmed by vaginal lavage), and pregnant F1 females were weighed on gestation days 0, 7, 14, 20 and on lactation day 0. Upon spontaneous delivery, the F2 pups were weighed, sexed, observed for external abnormalities, terminated and preserved in 10% buffered formalin. F1 parental males and females were sacrificed, gross pathology assessment was performed, and abnormal viscera and reproductive organs were preserved in 10% buffered formalin.
For maternal reproductive and fetal parameters, the litter was selected as the independent sampling unit.

Results

Mortality: 1 MD and 6 HD females were sacrificed following total litter death (no notable clinical observations were recorded). There was no spontaneous mortality.

Clinical signs: Pre-mating and mating, males and females: Hypoactivity, ptosis and lacrimation at MD and HD; ptosis at LD. During gestation, clinical signs were present in all dosed groups.

Body weight:

Body weights of F0 males and females during pre-mating and mating periods:

Prior to dose administration, the mean body weights were similar between the control and treated groups. Mean body weight and body weight gain was significantly lower vs. control in HD and MD males throughout the study; in females, after an initial increase, a significant decrease in mean body weight vs. control was registered at HD and MD (see sponsor's tables below and on the next page).

Mean body weights (F0 Males)

F0 GENERATION
MEAN BODY WEIGHTS - grams — MALES

	DOSE LEVEL	GROUP 1 0.0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 12 MG/KG/DAY	GROUP 4 36 MG/KG/D
WEEK 0	MEAN	305.1	307.9	306.2	306.5
	S.D.	14.2	11.4	12.7	16.3
	N	32	32	32	32
WEEK 1	MEAN	354.6	350.6	346.9	329.6**
	S.D.	18.3	14.7	17.7	20.2
	N	32	32	32	32
WEEK 2	MEAN	396.7	390.3	385.5	355.2**
	S.D.	24.5	20.5	21.9	23.6
	N	32	32	32	32
WEEK 3	MEAN	430.7	429.5	417.1	372.7**
	S.D.	34.0	22.1	26.4	31.0
	N	32	32	32	32
WEEK 4	MEAN	462.3	457.9	444.0*	387.3**
	S.D.	29.9	27.4	28.1	33.1
	N	31	32	32	32
WEEK 5	MEAN	489.9	484.9	468.8*	402.5**
	S.D.	33.4	26.2	31.1	32.5
	N	31	32	32	32
WEEK 6	MEAN	514.3	503.8	485.9**	406.3**
	S.D.	36.6	30.0	35.6	34.6
	N	31	32	32	32
WEEK 7	MEAN	531.2	521.9	496.9**	412.9**
	S.D.	38.7	30.7	36.2	37.7
	N	31	32	32	32
WEEK 8	MEAN	549.3	535.9	513.6**	422.8**
	S.D.	41.3	35.8	40.6	38.4
	N	31	32	32	32
WEEK 9	MEAN	564.2	553.8	524.6**	427.7**
	S.D.	43.0	38.1	42.3	40.5
	N	31	32	32	32
WEEK 10	MEAN	579.8	568.8	538.0**	433.1**
	S.D.	44.2	28.6	43.2	39.8
	N	31	32	32	32

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

Mean body weights (F0 Males) - Continued

WEEK 11	MEAN	583.5	570.0	531.1**	436.3**
	S.D.	48.1	36.2	45.0	36.6
	N	31	32	32	32
WEEK 12	MEAN	597.7	580.9	537.9**	441.8**
	S.D.	52.9	32.6	42.9	39.7
	N	31	32	32	32
WEEK 13	MEAN	605.5	589.3	542.9**	448.6**
	S.D.	56.1	31.5	45.5	36.5
	N	31	32	32	32
WEEK 14	MEAN	609.4	593.7	552.5**	443.5**
	S.D.	53.7	30.4	44.2	41.1
	N	31	32	32	32
WEEK 15	MEAN	620.2	603.0	550.1**	458.2**
	S.D.	52.5	30.2	45.2	42.1
	N	31	32	32	32
WEEK 16	MEAN	633.6	607.7	566.3**	466.4**
	S.D.	54.7	29.8	53.7	41.6
	N	20	21	22	32
WEEK 17	MEAN				458.4
	S.D.				41.4
	N				31
WEEK 18	MEAN				457.6
	S.D.				46.9
	N				31

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

Mean body weights (F0 Females)

		MEAN BODY WEIGHTS - grams			FEMALES
	DOSE LEVEL	GROUP 1 0.0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 12 MG/KG/DAY	GROUP 4 36 MG/KG/D
WEEK 8	MEAN	229.4	232.2	229.3	230.9
	S.D.	7.3	7.7	8.6	8.5
	N	32	32	32	32
WEEK 9	MEAN	232.5	244.9**	243.1**	242.6**
	S.D.	11.1	12.4	11.3	9.8
	N	32	32	32	32
WEEK 10	MEAN	237.7	246.7*	242.5	243.5
	S.D.	14.2	13.5	11.7	9.2
	N	32	32	32	32
WEEK 11	MEAN	258.5	260.2	252.6	254.8
	S.D.	16.7	9.1	14.7	10.6
	N	6	11	17	28
WEEK 12	MEAN	281.0	287.5	264.3	259.5
	S.D.	30.6	6.4	21.2	13.7
	N	5	2	4	15
WEEK 13	MEAN	352.0	302.5	261.3**	251.0**
	S.D.	35.8	17.7	21.8	22.4
	N	3	2	3	7
WEEK 14	MEAN		302.0	292.3	259.7
	S.D.		-	47.8	23.7
	N		1	3	7
WEEK 15	MEAN		303.0	271.5	263.4
	S.D.		-	38.4	25.1
	N		1	2	7
WEEK 16	MEAN		293.0	269.0	268.4
	S.D.		-	28.9	18.8
	N		1	2	7

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.

Body weights of F0 Dams during gestation and lactation

Mean body weights and body weight gain values of pregnant and lactating females are presented in the sponsor's tables on the next page. Significantly lower mean body weights in comparison to control were registered at MD and HD throughout gestation (on gestation days 7, 14, and 20) and lactation (as measured on postnatal days 0, 4, 7 and 14; on day 21, the changes were not statistically significant).

Mean body weight of pregnant females at term (gestation day 20, at Caesarean section) was significantly lower at HD and MD vs. control by 16% and 9%, respectively; the

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