

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.: _____

Volume # and page #: N.A.

Conducting laboratory and location: _____

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		C-Section Day 20 ^a	Allowed to deliver ^a
		Male	Female		
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)

DOSE LEVEL	MEAN S.D. N	FO GENERATION MEAN BODY WEIGHTS - grams			
		GROUP 1 0.0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 12 MG/KG/DAY	GROUP 4 36 MG/KG/DAY
WEEK 0	395.1 14.2 32	397.0 11.4 32	395.2 12.7 32	395.5 16.3 32	
WEEK 1	354.6 18.3 32	350.6 14.7 32	346.9 17.7 32	322.6** 20.2 32	
WEEK 2	396.7 24.5 32	390.3 20.5 32	385.5 21.6 32	353.2** 23.6 32	
WEEK 3	430.7 31.6 32	429.5 22.1 32	417.1 16.1 32	372.7** 31.0 32	
WEEK 4	462.3 29.2 31	457.0 27.4 32	444.0** 28.1 32	387.3** 35.1 32	
WEEK 5	489.9 33.4 31	484.0 28.2 32	468.9** 31.1 32	402.5** 34.3 32	
WEEK 6	514.3 36.6 31	503.0 30.0 32	485.9** 35.6 32	406.3** 34.6 32	
WEEK 7	531.2 38.7 31	521.0 30.7 32	494.9** 36.7 32	412.9** 37.7 32	
WEEK 8	549.3 41.3 31	535.9 35.8 32	512.6** 40.6 32	422.8** 38.4 32	
WEEK 9	544.7 43.0 31	533.0 30.1 32	524.6** 42.4 32	427.7** 40.4 32	
WEEK 10	579.0 44.7 31	568.0 28.6 32	534.0** 43.4 32	433.1** 39.3 32	

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

Mean body weights (F0 Males) - Continued

WEEK	MEAN S.D. N	583.5 48.1 31	570.0 34.3 32	531.1** 43.0 32	434.3** 34.8 32
WEEK 12	MEAN S.D. N	597.7 52.3 31	580.9 31.0 32	537.9** 42.9 32	441.0** 39.7 32
WEEK 13	MEAN S.D. N	605.5 56.1 31	589.3 31.5 32	542.0** 43.2 32	440.0** 38.1 32
WEEK 14	MEAN S.D. N	609.4 53.7 31	583.7 30.4 32	552.5** 44.2 32	443.5** 41.1 32
WEEK 15	MEAN S.D. N	620.2 52.9 31	603.0 30.2 32	559.1** 45.2 32	450.7** 42.1 32
WEEK 16	MEAN S.D. N	633.6 54.7 29	607.7 29.0 21	566.7** 53.7 22	466.4** 41.4 32
WEEK 17	MEAN S.D. N				458.4 41.4 31
WEEK 18	MEAN S.D. N				457.6 40.9 31

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

Mean body weights (F0 Females)

WEEK	DOSE LEVEL	MEAN BODY WEIGHTS - grams			
		GROUP 1 0.0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 12 MG/KG/DAY	GROUP 4 36 MG/KG/DAY
WEEK 8	MEAN S.D. N	229.4 7.3 32	232.7 7.7 32	229.3 8.1 32	230.9 8.2 32
WEEK 9	MEAN S.D. N	232.5 11.1 32	244.9** 12.4 32	243.1** 11.3 32	242.6** 9.6 32
WEEK 10	MEAN S.D. N	237.7 14.2 32	246.7* 13.6 32	242.5 11.7 32	243.5 9.2 32
WEEK 11	MEAN S.D. N	250.5 10.7 6	260.2 9.1 11	252.0 14.7 17	254.0 10.6 25
WEEK 12	MEAN S.D. N	261.0 30.0 5	267.5 6.4 2	284.3 21.2 4	250.5 13.7 15
WEEK 13	MEAN S.D. N	352.0 33.0 3	362.5 17.7 2	261.3** 21.4 3	251.0** 22.4 7
WEEK 14	MEAN S.D. N		302.0 - 1	292.3 47.0 3	253.7 23.7 7
WEEK 15	MEAN S.D. N		363.0 - 1	271.5 30.4 2	263.4 25.1 7
WEEK 16	MEAN S.D. N		293.0 - 1	269.0 28.9 2	260.4 18.6 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

corrected maternal weight (terminal body weight minus gravid uterine weight) was significantly lower by 13% and 7%, respectively. Maternal weight gain throughout pregnancy (gestation days 0 through 20) was lower by 49% and 26% at HD and MD, respectively vs. control. For those females that were allowed to deliver spontaneously, the mean body weight after delivery (Lactation Day 0) was significantly lower at HD and MD vs. control by 11% and 7%, respectively; similar differences in maternal body weight vs. control were registered on Lactation Day 4 through 14, but by weaning (Lactation day 21) the mean maternal weight has normalized and the differences from control (-4% and -5% at MD and HD) were no longer statistically significant. At LD, there were no notable differences in mean maternal weight or weight gain in comparison to control during gestation or lactation.

F0 Mean maternal body weights and body weight gain during gestation

SEGMENT 1 STUDY IN RATS FG GENERATION MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- grams					
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/DAY
DAY 0	MEAN	246.2	256.8**	248.3	251.5
	S.D.	13.8	12.9	12.7	16.1
	N	28	30	26	22
DAY 7	MEAN	280.7	284.8	288.8**	284.0**
	S.D.	12.8	13.7	14.3	13.2
	N	28	30	26	22
DAY 14	MEAN	314.8	315.5	292.1**	277.7**
	S.D.	14.3	17.3	19.3	15.7
	N	28	30	26	22
DAY 20	MEAN	382.0	385.3	348.9**	321.3**
	S.D.	23.2	27.7	34.5	23.8
	N	28	30	26	22

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

SEGMENT 1 STUDY IN RATS FG GENERATION MEAN MATERNAL BODY WEIGHT CHANGES DURING GESTATION - grams					
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/DAY
DAYS 0 TO 7	MEAN	34.58	29.33**	19.82**	12.41**
	S.D.	7.48	7.19	5.22	5.24
	N	28	30	26	22
DAYS 7 TO 14	MEAN	33.93	30.79	23.85**	13.73**
	S.D.	8.58	12.31	8.31	9.33
	N	28	30	24	22
DAYS 14 TO 20	MEAN	67.32	69.73	56.81	43.58**
	S.D.	12.29	17.64	18.45	18.42
	N	28	30	26	22
DAYS 0 TO 20	MEAN	135.75	128.67	108.56**	69.73**
	S.D.	20.84	26.24	26.24	23.38
	N	28	30	26	22
DAYS 7 TO 20	MEAN	101.25	109.43	88.65**	57.32**
	S.D.	17.48	24.28	24.24	21.38
	N	28	30	26	22

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

F0 Mean maternal body weights and body weight gain during lactation

SEGMENT 1 STUDY IN RATS FG GENERATION MEAN MATERNAL BODY WEIGHTS DURING LACTATION -- SUMMARY					
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/DAY
DAY 0	MEAN	291.6	289.8	279.5*	268.0**
	S.D.	16.9	18.1	17.1	16.5
	N	13	12	12	9
DAY 4	MEAN	318.2	307.3	285.8*	288.3*
	S.D.	17.6	26.2	21.3	12.6
	N	13	12	11	4
DAY 7	MEAN	318.7	316.8	293.4**	288.0*
	S.D.	16.8	19.4	20.7	5.3
	N	13	12	11	3
DAY 14	MEAN	334.8	328.2	308.8**	301.7*
	S.D.	18.4	29.7	18.6	5.0
	N	13	12	11	3
DAY 21	MEAN	315.7	312.4	302.8	301.0
	S.D.	36.2	25.3	20.5	13.3
	N	15	12	11	3

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

MEAN MATERNAL BODY WEIGHT CHANGES DURING LACTATION -- grams					
DOSE LEVEL		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		0.0 MG/KG/DAY	4 MG/KG/DAY	12 MG/KG/DAY	36 MG/KG/DAY
DAYS 0 TO 4	MEAN	18.54	17.58	14.18	5.25
	S.D.	14.50	11.11	8.54	18.78
	N	13	12	11	9
DAYS 4 TO 7	MEAN	8.54	9.58	7.55	2.09
	S.D.	9.50	6.33	7.81	3.61
	N	13	12	11	5
DAYS 7 TO 14	MEAN	16.15	11.62	16.64	19.07
	S.D.	14.97	16.27	15.89	17.87
	N	13	12	11	3
DAYS 14 TO 21	MEAN	-19.15	-15.58	-5.36	-0.67
	S.D.	35.70	23.15	21.17	14.37
	N	13	12	11	3
DAYS 0 TO 7	MEAN	27.00	27.00	21.73	13.00
	S.D.	8.36	12.01	8.01	11.53
	N	13	12	11	3
DAYS 0 TO 14	MEAN	43.23	38.42	36.36	26.67
	S.D.	12.38	22.71	17.15	18.61
	N	13	12	11	3
DAYS 0 TO 21	MEAN	24.00	22.83	31.00	26.00
	S.D.	34.42	14.47	23.11	5.23
	N	13	12	11	3

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

Food consumption: In males, significantly decreased mean food consumption vs. control were noted at HD (weeks 3 through 9) and MD (weeks 7-10); at LD, the mean food consumption was significantly increased. In females during pre-mating and mating periods, food consumption was significantly increased at all dose levels at weeks 8-9, and at HD additionally at weeks 9-10. During lactation, mean maternal food consumption was significantly decreased vs. control at MD (during the first 2 weeks post partum) and HD (at all intervals).

F0 reproductive performance:

Disturbances in estrous cycle were induced at all dose levels in a dose-dependent manner. Prolonged periods of diestrous stage (≥ 5 days) were observed during the pre-mating (in 18, 22, and 28 females at LD, MD and HD, respectively), as well as during the mating period (in 7, 15 and 25 animals at LD, MD and HD, respectively, vs. 2 in control). This resulted in lower female fertility indices, i.e. 72%, 88% and 97% at HD, MD and LD, respectively, vs. 100% in control (a significant negative trend, as well as statistically significant at HD). The pregnancy rate was lower in MD and HD groups. A significant negative trend was noted for male fertility, without significant differences between control and any of the treated groups. The mean absolute and relative testis and epididymis weights and absolute weights of seminal vesicles were lower in the HD group vs. control; the mean absolute prostate weight was decreased in all dosed groups vs. control (see sponsor's table below). Mean body weight was significantly reduced in HDM and MDM.

FO GENERATION SUMMARY OF PARENTAL ORGAN WEIGHTS AVERAGE ORGAN WEIGHTS (g)					
DOSE LEVEL		MALES			
		GROUP 1 0.0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 12 MG/KG/DAY	GROUP 4 36 MG/KG/DAY
FINAL BODY WEIGHT g	MEAN	626.7	608.6	581.4b	457.6b
	S.D.	54.9	32.1	47.1	40.9
	N	31	32	32	31
TESTES	MEAN	3.9110	3.8256	3.7224	3.6926b
	S.D.	0.3181	0.2152	0.2571	0.3372
	N	31	32	32	31
EPIDIDYMIDES	MEAN	1.8582	1.7801	1.7123	1.6310a
	S.D.	0.3279	0.3194	0.3756	0.1832
	N	31	32	32	31
SEMINAL VESICLES	MEAN	2.4517	2.5197	2.2773	2.0706b
	S.D.	0.5672	0.4341	0.4576	0.5291
	N	31	32	32	31
PROSTATE	MEAN	1.0529	0.9278a	0.8535b	0.7974b
	S.D.	0.2139	0.1982	0.2288	0.1980
	N	31	32	32	31

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

The following sponsor's tables summarize the reproductive performance results.

Reproductive Performance Segment 1 Study in Rats F0 Generation						
	Group 1 0	Group 2 4	Group 3 12	Group 4 36	Naive ^a	Combined ^b
No. of males paired with at least one female	31	32	32	32	32	32
No. (%) males mated ^c	31 (100)	31 (97)	30 (94)	25 (78)**	32 (100)	32 (100)
No. (%) of males successfully mated with at least one female	31 (100)	31 (100)	29 (93)	23 (92)	29 (91)	31 (97)
No. of females paired with at least one male	32	32	32	32	32	64
No. (%) females mated	32 (100)	31 (97)	30 (94)	23 (78)	32 (100)	NA
No. (%) females pregnant (Fecundity)	32 (100)	31 (100)	29 (93)	23 (92)	29 (91)	NA
No. (%) females with abnormal gestation and delivery	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Female Fertility ^d	100	97	98	72**	91	NA
Male Fertility ^e	100	100	93	92	91	97

^a Data presented is for the Group 4 treated males and the naive females.
^b Data presented is for the Group 4 treated males with the naive and Group 4 treated females combined.
^c Significant negative trend (Groups 1-4).
 Significantly different from control: * = p ≤ 0.05; ** = p ≤ 0.01.

Male Fertility Index = $\frac{\text{number of males shown to be fertile}}{\text{number of males mated}} \times 100$

Female Fertility Index = $\frac{\text{number of females pregnant}}{\text{number of females paired}} \times 100$

Female fecundity Index = $\frac{\text{number of females pregnant}}{\text{number of females mated}} \times 100$

Mated = Evidence of sperm or vaginal plug, or a litter was produced
 Pregnancy = Females with evidence of implantation.

Maternal and embryofetal parameters at Caesarean section: Corrected maternal weight (terminal body weight minus gravid uterine weight) and net body weight gain were significantly lower at MD and HD in comparison to control; gravid uterine weight was decreased dose-dependently at MD and HD, statistically significant at the HD.

SEGMENT 1 STUDY IN RATS F0 GENERATION SUMMARY OF UTERINE AND NET BODY WEIGHTS (grams)					
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/DAY
GRAVID UTERUS	MEAN	72.53	77.76	57.55	46.11**
	S.D.	15.43	12.82	27.81	21.10
	N	18	18	16	14
CORRECTED WEIGHT	MEAN	310.47	309.52	289.14**	271.11**
	S.D.	14.92	14.87	22.79	18.37
	N	18	18	16	14
NET CHANGE FROM DAY 0	MEAN	82.14	53.41	41.89**	20.96**
	S.D.	12.95	10.59	13.30	13.39
	N	18	18	16	14

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P < 0.05; ** = P < 0.01
 CORRECTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
 NET WEIGHT CHANGE FROM DAY 0 = CORRECTED WEIGHT MINUS DAY 0 BODY WEIGHT

Mean number of corpora lutea and implantation sites were significantly lower at the 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 the mean per cent of preimplantation loss was not significantly different from control in any

of the treated groups (see sponsor's table on the next page). There were no significant differences in the rate of resorptions; however, two dams (one from MD and one from HD group) had no viable fetuses at term.

SEGMENT I STUDY IN RATS F0 GENERATION SUMMARY OF CESAREAN SECTION DATA					
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/DAY
Females Selected	N	19	18	18	17
Pregnant ^a	N	18	15	16	14
	X	95	100	89	82
Aborted	N	0	0	0	0
	X	0.0	0.0	0.0	0.0
Died	N	0	0	0	0
	X	0.0	0.0	0.0	0.0
Delivered Early	N	0	0	0	0
	X	0.0	0.0	0.0	0.0
Dams with Viable Fetuses	N	18	18	15	13
	X	100	100	94	95
Dams with no Viable Fetuses	N	0	0	1	1
	X	0.0	0.0	6.3	7.1
Corpora Lutea	MEAN	16.2	16.4	14.4	12.6**
	S.D.	2.8	1.8	3.7	2.4
	N	18	18	16	14
	TOTAL	291	295	230	176
Implantation Sites	MEAN	14.3	15.3	11.3	10.5**
	S.D.	3.0	2.3	5.4	3.7
	N	18	18	16	14
	TOTAL	257	275	180	147
Preimplantation Loss	MEANS	12.4	6.7	25.9	17.3
	S.D.	13.2	9.9	28.6	22.7
Resorptions: Total	MEAN	0.9	0.9	0.3	1.4
	S.D.	1.1	0.9	0.6	2.9
	N	18	18	16	14
	TOTAL	16	17	4	20
Early	MEANS	6.0	6.6	7.0	13.4
	S.D.	7.9	6.9	24.9	26.6
	MEAN	0.9	0.9	0.3	1.4
	S.D.	1.1	0.9	0.6	2.9
Late	N	18	18	16	14
	TOTAL	16	17	4	20
	MEANS	6.0	6.6	7.0	13.4
	S.D.	7.9	6.9	24.9	26.6
Dead Fetuses	MEAN	0.0	0.0	0.0	0.0
	S.D.	0.0	0.0	0.0	0.0
	N	18	18	16	14
	TOTAL	0	0	0	0
Postimplantation Loss	MEANS	6.0	6.6	7.0	13.4
	S.D.	7.9	6.9	24.9	26.6

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

Embryofetal growth was retarded in HD group, as indicated by a significantly lower fetal weight vs. control values.

No external or visceral malformations were observed in the treated groups, but visceral variation rate was increased in the HD group (see sponsor's table on the next page).

Significant positive trends and significantly higher fetal incidence values in HD group vs. control were found for the dilatation of lateral and third brain ventricles, dilatation of heart ventricles and total soft tissue variations.

SUMMARY OF FETAL SOFT TISSUE VARIATIONS					
DOSE LEVEL		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		0.0 MG/KG/DAY	4 MG/KG/DAY	12 MG/KG/DAY	36 MG/KG/DAY
Litters Evaluated	N	18	18	15	13
Fetuses Evaluated	N	118	130	88	83
Live	N	118	130	88	83
Dead	N	0	0	0	0
DILATATION OF LATERAL VENTRICLE(S)					
Fetal Incidence ^a	N	0	0	0	6**
	X	0.0	0.0	0.0	9.5**
Litter Incidence ^a	N	0	0	0	2
	X	0.0	0.0	0.0	15
DILATATION OF THIRD VENTRICLE					
Fetal Incidence ^a	N	0	0	0	5**
	X	0.0	0.0	0.0	7.9**
Litter Incidence ^a	N	0	0	0	2
	X	0.0	0.0	0.0	15
DILATATION OF VENTRICLE(S) OF THE HEART					
Fetal Incidence ^a	N	0	3	1	5**
	X	0.0	2.3	1.2	7.9**
Litter Incidence ^a	N	0	2	1	2
	X	0.0	11	6.7	15
INCREASED RENAL PELVIC CAVITATION					
Fetal Incidence ^a	N	1	1	0	3.2
	X	0.8	0.8	0.0	3.2
Litter Incidence ^a	N	1	1	0	7.7
	X	5.6	5.6	0.0	7.7
TOTAL FETAL SOFT TISSUE VARIATIONS					
Fetal Incidence ^a	N	1	4	1	12**
	X	0.8	3.1	1.2	15**
Litter Incidence ^a	N	1	3	1	4
	X	5.6	17	6.7	31

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P ≤ 0.05; ** = P ≤ 0.01.
 N = Number
^a SIGNIFICANT POSITIVE TREND

Maternal and pup parameters upon natural delivery (see sponsor's tables on the next page)

The following dose-dependent effects were registered: lower pregnancy rates (93%, 86%, and 60% at LD, MD, and HD vs. 100% in control group, statistically significant at HD), increased duration of pregnancy (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), increased pre-, perinatal and neonatal mortality, as demonstrated by decreased livebirth index (95%, 89% and 83% at LD, MD, and HD vs. 99% in control group, statistically significant at MD and HD), increase in stillborn pup number (8, 18 and 17 at LD, MD, and HD vs. 2 in control group, statistically significant at MD and HD) and increase in neonatal deaths (mean viability indices, i.e. N alive on postnatal Day 4/ N liveborn = 96%, 80% and 24% at LD, MD, and HD vs. 98% in control group, statistically significant at MD and HD). Total litter deaths occurred within the first 4 postnatal days in 1 and 6 litters from MD and HD groups, respectively. There was no pup lethality after the neonatal period (pups surviving to weaning/pups alive on day 4 post-cull) or after weaning up to assignment to the behavioral or maturation phase of F1 generation.

SEGMENT I STUDY IN RATS
 NATURAL DELIVERY DATA AND LITTER DATA -- SUMMARY

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/DAY
Females: Selected	N	13	14	14	15 ^a
Pregnant	N	13	13	12	9 ^a
Delivering	N	100	93	96	69
	N	13	12	12	9
	X	100	92	100	100
Duration of Gestation:	MEAN	21.7	22.0	22.5 ^a	22.6 ^a
	S.D.	0.7	0.4	0.5	0.5
	N	10	11	10	8
Females with Liveborn Pups	N	13	12	12	9
Gestation Index	N	100	92	100	100
With Stillborn Pups ^d	N	1	2	4	5 ^a
	X	7.7	17	33	56
Females with no liveborn Pups	N	0	0	0	0
	X	0.0	0.0	0.0	0.0
Females with no Pups Delivered	N	0	1	1	1
	X	0.0	0.3	0.3	1.1
Pups Delivered	TOTAL	177	160	144	97
	MEAN	13.62	15.00	12.00	10.78 ^a
	S.D.	1.85	1.64	2.43	3.11
	N	13	12	12	9
Liveborn ^d	TOTAL	175	172	176	80
Stillborn	TOTAL	2	8	18 ^a	17 ^a
Uncertain	TOTAL	0	0	0	0
Implantation Sites	TOTAL	189	192	155	104
	MEAN	14.54	16.00	12.92	11.56 ^a
	S.D.	1.91	1.91	2.23	3.57
	N	13	12	12	9

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

N = Number of Females or Litters.
 TOTAL = Number of Pups or Implants.

- ^a All nonconfirmed females selected for cesarean section were allowed to deliver.
- ^b One female B38543 that was not confirmed and did not deliver is not included in the calculations on this table.
- ^c SIGNIFICANT NEGATIVE TREND
- ^d SIGNIFICANT POSITIVE TREND
- ^e Ritized pregnancies excluded.

Pup Survival Indices					
Livebirth Index	MEANX	99	95	89 ^a	83 ^a
(Number born alive/number born)	MEANX				
Viability Index	MEANX	98	98	80 ^a	24 ^a
(Number alive Day 4 precull/ Number liveborn)	MEANX				
Weaning Index	MEANX	100	100	100	100
(Number alive at weaning/ number alive at Day 4 postcull)					
Pup Disposition					
Called day 4	TOTAL	68	69	22	4
Killed	TOTAL	0	9	9	0
Died	TOTAL	1	3	17	52
Cannibalized	TOTAL	0	0	1	1
Missing	TOTAL	2	4	6	1
Pups Surviving at 21 days	TOTAL	104	96	80	21
Pups Dying, Killed, Missing, and/or Cannibalized ^b					
days 0-4	TOTAL	3	7	24	55
days 5-21	TOTAL	0	0	0	0
Entire Litter Died, Killed, Missing, and/or Cannibalized					
days 0-4	N	0	0	1	6
days 5-21	N	0	0	0	0
Total Number and Mean Males Percent by Litter					
day 0	TOTAL	85	80	64	36
	MEANX	48	53	48	42
day 4 precull	TOTAL	84	82	55	11
	MEANX	49	52	55	44
day 21	TOTAL	55	49	40	19
	MEANX	53	51	49	47

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

N = Number of Litters.
 TOTAL = Number of Pups or Implants.

- ^a SIGNIFICANT NEGATIVE TREND
- ^b STATISTICAL ANALYSES WERE CONDUCTED ON VIABILITY INDICES

Mean pup weight was lower in MD and HD groups vs. control from postnatal day 4 onward, statistically significant at postnatal day 14 (see sponsor's table on the next page).

F1 pup weight

Pup Weight/Litter (grams)	MEAN	S.D.	n	MEAN	S.D.	n	MEAN	S.D.	n	MEAN	S.D.	n
day 0 MALES	6.00	0.67	13	6.10	0.64	12	6.24	0.74	9	6.00	0.65	9
Covariate Adjusted MEAN	6.16			6.31			6.18			5.63		
day 0 FEMALES	5.68	0.62	13	5.79	0.45	12	5.82	0.67	9	5.71	0.65	9
Covariate Adjusted MEAN	5.77			6.02			5.73			5.69		
day 4 MALES - Precull	9.01	1.02	13	9.00	1.03	12	9.09	1.71	9	7.49	1.32	9
Covariate Adjusted MEAN	9.28			9.21			9.38			7.14		
day 4 FEMALES - Precull	8.95	1.24	13	8.45	0.90	12	9.05	1.30	9	7.60	1.94	9
Covariate Adjusted MEAN	8.57			8.61			8.88			7.43		
day 4 MALES - Postcull	9.05	1.19	13	8.91	0.99	12	9.59	1.70	9	7.59	1.51	9
Covariate Adjusted MEAN	9.27			9.17			9.40			7.29		
day 4 FEMALES - Postcull	9.04	1.19	13	8.54	1.04	12	9.14	1.44	9	7.61	1.94	9
Covariate Adjusted MEAN	8.71			8.82			9.08			7.52		
day 7 MALES	14.82	2.12	13	14.99	1.99	12	14.73	2.59	9	12.09	2.31	9
Covariate Adjusted MEAN	14.82			14.59			14.73			12.01		
day 7 FEMALES	14.17	2.19	13	14.12	1.99	12	14.89	2.19	9	12.09	2.31	9
Covariate Adjusted MEAN	13.99			14.04			14.40			12.22		
day 14 MALES	32.87	3.27	13	31.58	2.58	12	29.48	3.81	9	24.85	2.13	9
Covariate Adjusted MEAN	32.89			31.91			29.28*			24.43**		
day 14 FEMALES	31.27	3.37	13	30.27	3.03	12	29.31	3.06	9	24.45	1.92	9
Covariate Adjusted MEAN	31.45			30.48			29.19			24.29**		
day 21 MALES	49.59	6.24	13	49.55	5.80	12	48.08	6.38	9	40.18	2.46	9
Covariate Adjusted MEAN	50.14			50.10			47.70			39.44		
day 21 FEMALES	47.09	6.91	13	47.18	4.99	12	46.83	5.79	9	39.95	4.09	9
Covariate Adjusted MEAN	48.23			47.51			46.10			39.52		

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
 n = Number of Litters.

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.

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 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. The higher doses employed in this study induced dose-dependent decreased parental F0 fertility (male and female), prolonged gestation, increased prenatal and neonatal lethality of F1 progeny, and reduced F1 pre- and postnatal growth (as indicated by lower body weight at term and postnatally).

Embryofetal development (Segment II)

Three Segment II studies were performed:

- Oral embryotoxicity study of iloperidone in rats
- Oral embryotoxicity study of iloperidone metabolite P95 12113 in rats
- Oral embryotoxicity study of iloperidone in rabbits

Study title: Oral Embryotoxicity Study of Iloperidone (HP 873) in Wistar Rats

Key study findings: Iloperidone administration to pregnant Wistar rats at doses of 0 (vehicle control), 4, 16, and 64 mg/kg/day by oral gavage on Gestation Days 7 through 18 induced at HD and MD a significant dose-dependent reduction in maternal weight (by 18% and 6%, respectively, vs. control at term) and in maternal weight gain (by up to 92% and 34% of control values, respectively). Maternal food consumption was decreased at HD by up to 11% vs. control. Placental weights were statistically significantly lower at HD (by 17% vs. control) and MD (by 7% vs. control). Clinical signs associated with pharmacological action of the test agent (sedation, ptosis) were present in all dosed groups, dose-dependently. The high dose induced a marked (over 5-fold) increase in post-implantation embryonic lethality. Early post-implantation death of all conceptuses occurred in two thirds of the treated HD dams. The surviving HD fetuses exhibited growth retardation (as expressed by significantly decreased fetal weight and crown/rump length at term by 12% and 7%, respectively as compared to control, and retarded skeletal ossification). An increased incidence of minor skeletal abnormalities (fragmented and/or displastic thoracic vertebral centra) and skeletal variations (supernumerary thoracic rib) was registered in the HD group. No increase in external or visceral abnormalities was registered in any of the dosed groups. Intrauterine development was not adversely affected at MD and LD. The embryo/fetal lethality and mean fetal body weight and length in these groups did not differ appreciably from control.

Based on the study findings, iloperidone induces developmental toxicity (expressed as embryofetal lethality, retarded intrauterine development and minor skeletal abnormalities) at oral doses above 16 mg/kg/day. Signs of maternal toxicity (reduced weight and weight gain, reduced placental weight) are induced at and above 16 mg/kg/day. The NOAEL for developmental toxicity in this study is 16 mg/kg/day (6 times the MRHD of 24 mg/day on an mg/m² basis).

Study no.: 92.0011; Report No. 94.0623

Volume # and page #: N.A.

Conducting laboratory and location: Pharma Development Corporate Toxicology, Hoechst Actiengesellschaft, Frankfurt/Main

Date of study initiation: 11 May 1993

GLP compliance: yes

QA reports: yes

Lot numbers and potency: RC 5634; purity 99.1% (HPLC)

Vehicle: Starch mucilage (20 g/l)

Methods

Doses: 4, 16, 64 mg/kg/day

Species/strain: Rat, Wistar

Number/sex/group: 22-24 mated females

Route, formulation, volume: Oral gavage, suspension in 2% aqueous starch, dosing volume 5 ml/kg (all groups)

Satellite groups used for toxicokinetics: None

Study design: Mated female Sprague-Dawley rats (22-24/group) were administered iloperidone at doses of 0 (vehicle control), 4, 16, and 64 mg/kg/day by oral gavage on Gestation Days 7 through 18 (day of sperm detection defined as Gestation Day 1). Cesarean section was performed on Gestation Day 21 for evaluation of maternal reproductive parameters, pre- and postimplantation embryofetal lethality, fetal viability, weight, gender, and morphology.

Parameters and endpoints evaluated:

Maternal: survival and clinical signs (daily), body weight and food consumption (weekly), reproductive parameters (number of corpora lutea in ovaries, number of implantations (uterine staining by ammonium sulfide), resorptions (number and diameter), placental weights, live and dead fetuses).

Fetal: viability, gender, individual weight, crown-rump length, external, visceral (Bouin's fixative) and skeletal (alizarin staining) anomalies.

The findings obtained at the autopsy and at fetal examination were statistically evaluated separately for the fetuses and for the litters.

Results

Mortality (dams): One HD dam was killed moribund after 9 treatments. There were no spontaneous deaths in any of the groups.

Clinical signs (dams): Sedation and ptosis occurred in all dosed groups in a dose-related manner.

Body weight (dams): Mean maternal body weights were dose-dependently decreased at HD and MD, by 18% and 6%, respectively, vs. control at term; the decrease was statistically significant from gestation day 14 onward. Mean body weight gains were markedly reduced during the treatment period by up to 92% and 34% of control values at HD and MD, respectively. There were no changes in mean body weight or weight gain at LD.

Segment II study in rats – Maternal body weight (mean)

BODY WEIGHT (G) OF DAMS DURING PREGNANCY		GROUP 1 0 ML/KB	GROUP 2 4 ML/KB	GROUP 3 16 ML/KB	GROUP 4 64 ML/KB
MULTIVARIATE COMPARISONS					
DAY					
0	MEAN	299.9	296.4	298.0	298.0
	S.D.	11.3	8.3	10.7	13.7
	(NO. OF DAMS)	20	20	20	0
7	MEAN	279.7	226.6	225.7	225.0
	S.D.	16.7	10.3	13.1	10.7
	(NO. OF DAMS)	20	20	20	0
14	MEAN	257.0	232.3	244.0 b	227.3 b
	S.D.	17.2	11.1	14.0	10.1
	(NO. OF DAMS)	20	20	20	0
19	MEAN	299.9	293.7	282.8 b	242.8 b
	S.D.	23.3	17.1	18.4	34.1
	(NO. OF DAMS)	20	20	20	0
21	MEAN	323.7	317.7	343.9 b	248.5 b
	S.D.	23.8	18.2	20.6	22.4
	(NO. OF DAMS)	20	20	20	0

0 : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LOWER THAN CONTROL * : SIGNIFICANTLY DIFFERENT FROM CONTROL
 0 : EVALUATION BY POSSIBLE 5 GROUP CONTAINING LESS THAN 5 ANIMALS
 N/A : WITHIN/OUTSIDE THE REPORT RANGE
 STATISTICAL ANALYSIS BASED ON GAUSS VERSUS PRELIMINARY VALUES

Segment II study in rats - Maternal body weight gain

BODY WEIGHT GAIN (G) OF DAMS DURING PREGNANCY		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 16 MG/KG	GROUP 4 64 MG/KG
DAY					
0 - 7	MEAN	28.3	30.2	27.7	26.2
	S.D.	4.4	5.8	8.2	11.4
	(NO. OF DAMS)	20	20	20	6
	MEAN	27.9	25.7	18.4	2.3
7 - 14	S.D.	4.2	6.4	7.8	13.7
	(NO. OF DAMS)	20	20	20	6
14 - 19	MEAN	42.9	41.4	38.8	15.3
	S.D.	8.6	8.9	7.7	20.1
	(NO. OF DAMS)	20	20	20	6
	MEAN	25.9	24.1	25.2	25.7
19 - 21	S.D.	3.9	3.5	3.1	12.1
	(NO. OF DAMS)	20	20	20	6

NO STATISTICAL EVALUATION

Food consumption: Decreased in the HD group (up to 11% vs. control values) during the dosing period; no different from control at MD and LD.

Maternal food consumption

DAILY FOOD CONSUMPTION (G) / 100 G BODY WEIGHT OF DAMS DURING PREGNANCY		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 16 MG/KG	GROUP 4 64 MG/KG
MULTIVARIATE COMPARISONS					
DAY					
1 - 7	MEAN	8.4	8.4	8.4	8.4
	S.D.	0.5	0.7	0.8	1.0
	(NO. OF DAMS)	20	20	20	6
	MEAN	7.9	8.1	8.0	7.9
7 - 14	S.D.	0.5	0.6	0.6	0.6
	(NO. OF DAMS)	20	20	20	6
14 - 19	MEAN	7.6	7.8	7.8	7.9
	S.D.	0.5	0.3	0.1	0.7
	(NO. OF DAMS)	20	20	20	6
	MEAN	6.7	6.4	6.9	7.1
19 - 21	S.D.	0.3	0.4	0.8	1.1
	(NO. OF DAMS)	20	20	20	6

C-section data: The high dose induced a marked (over 5-fold) increase in post-implantation embryonic lethality. Early post-implantation death of all conceptuses occurred in two thirds of the treated HD dams. The surviving HD fetuses exhibited growth retardation (as expressed by significantly decreased fetal weight and crown/rump length at term by 12% and 7%, respectively as compared to control, and retarded skeletal ossification). Placental weights were statistically significantly lower in HD and MD groups. The placental weight reduction was marked at HD (by 17% vs. control) and mild at MD (by 7% vs. control). An increased incidence of minor skeletal abnormalities (fragmented and/or displastic thoracic vertebral centra) and skeletal variations (supernumerary thoracic rib) was registered in the HD group. No increase in external or visceral abnormalities was registered in any of the dosed groups.

Intrauterine development was not adversely affected at MD and LD. The embryofetal lethality and mean fetal body weight and length in these groups did not differ appreciably from control. The somewhat lower body length of the fetuses in the MD group was only marginal and was within the normal range of the laboratory historical control values.

The results are presented in the sponsor's tables reproduced below and on the next page.

Segment II study in rats - Embryo/fetal lethality

SURVEY OF RESULTS DURING GESTATION AND AT CAESARIAN SECTION			GROUP 1	GROUP 2	GROUP 3	GROUP 4
			0	4	16	64
			MG/KG	MG/KG	MG/KG	MG/KG
NUMBER OF						
- PREGNANCIES	ME TOTAL		20	20	20	21
- INTERCURRENT DEATH	ME TOTAL		0	0	0	1
- FEMALES WITH ABORTION	ME TOTAL		0	0	0	11
- FEMALES WITH PREMATURE DELIVERY	ME TOTAL		0	0	0	0
- FEMALES AT TERM WITH INTRAUTER. DEATHS ONLY	ME TOTAL		0	0	0	3
- FEMALES AT TERM WITH LIVE FETUSES	ME TOTAL		20	20	20	6
- CORPORA LUTEA	TOTAL		287	281	296	81
	MEAN		14.4	14.1	14.8	13.5
	S.D.		1.7	1.7	2.3	2.4
- IMPLANTATIONS	TOTAL		266	272	275	79
	MEAN		14.0	13.6	13.7	13.2
	S.D.		1.5	2.1	1.9	2.1
PRE-IMPLANTATION LOSS %						
	ME MEAN		2.24	3.12	4.15	2.15
POST-IMPLANTATION LOSS %						
	ME MEAN		5.05	3.48	6.83	27.23
- EARLY INTRAUTERINE DEATHS	TOTAL		15	19	19	24
	MEAN		0.75	0.95	0.95	4.00
	S.D.		1.48	0.83	1.32	3.29
% OF IMPLANTATIONS	MEAN		5.05	3.48	6.83	27.23
	S.D.		9.39	5.62	8.88	34.90
- LATE INTRAUTERINE DEATHS	TOTAL		0	0	0	0
	MEAN		0.00	0.00	0.00	0.00
	S.D.		0.00	0.00	0.00	0.00
% OF IMPLANTATIONS	MEAN		0.00	0.00	0.00	0.00
	S.D.		0.00	0.00	0.00	0.00
- TOTAL INTRAUTERINE DEATHS	TOTAL		15	19	19	24
	MEAN		0.75	0.95	0.95	4.00
	S.D.		1.48	0.83	1.32	3.29
- LIVE FETUSES	TOTAL		265	262	254	55
	MEAN		13.3	13.1	12.7	9.2
	S.D.		1.6	2.0	2.1	4.2

Fetal and placental weight

SURVEY OF RESULTS IN LIVE FETUSES AT CAESARIAN SECTION			GROUP 1	GROUP 2	GROUP 3	GROUP 4
			0	4	16	64
			MG/KG	MG/KG	MG/KG	MG/KG
NUMBER OF FETUSES	TOTAL		265	262	254	55
	MEAN		13.3	13.1	12.7	9.2
	S.D.		1.6	2.0	2.1	4.2
% OF IMPLANTATIONS	MEAN		94.95	96.52	93.17	72.77
	S.D.		9.39	5.62	8.88	34.90
MALES (%)	ME		52.1	49.2	48.4	52.7
BODY WEIGHT (G)	MEAN		3.3	3.3	3.3	2.9
	S.D.		0.2	0.2	0.2	0.3
CROWN/RUMP LENGTH (MM)	MEAN		35.5	35.4	34.9	33.1
	S.D.		0.8	1.0	0.8	0.8
PLACENTAL WEIGHT (G)	MEAN		0.46	0.45	0.43	0.38
	S.D.		0.06	0.04	0.04	0.06

a : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LESS THAN CONTROL
 n : EVALUATION NOT POSSIBLE, GROUP CONTAINS LESS THAN 5 ANIMALS ME : NO STATISTICAL EVALUATION
 N/A : WITHIN/OUTSIDE THE NORMAL RANGE

Segment II Study in Rats - Skeletal defects

CLASS	GROUP 1 0 MG/KG		GROUP 2 4 MG/KG		GROUP 3 16 MG/KG		GROUP 4 64 MG/KG	
	INCIDENCE BY FOREPA/LYTER		INCIDENCE BY FOREPA/LYTER		INCIDENCE BY FOREPA/LYTER		INCIDENCE BY FOREPA/LYTER	
	NO.	%	NO.	%	NO.	%	NO.	%
SKELETAL DEFECTS								
NUMBER OF FETUSES EXAMINED	139		137		131		77	
NUMBER OF LITTERS EXAMINED	28		26		29		17	
SKELETON								
NO ABNORMALITIES DETECTED	49 (35.3)		42 (30.7)		33 (25.2)		8	
THORACIC VERT. CENTRA								
DISLOCATED, FRAGMENTED, DYSPLASIA	MIN	3 (15.0)	1 (5.0)	1 (5.0)	1 (5.0)	1 (10.7)	1 (16.7)	1 (16.7)
SACRAL AND/OR CAUDAL VERT. CENTRA								
OSIFICATION OF LESS THAN 2 VERTICAL CENTRES	NET	75 (53.9)	77 (56.2)	76 (57.3)	72 (92.3)	72 (92.3)	72 (92.3)	72 (92.3)
EXTRA VERTEBRAL/EXTRA RIB								
ANALOGUE OF A 14TH THORACIC VERTebra AND AN ANALOGUE	VAR	0	0	0	4* (16.0)	4* (16.0)	10** (31.5)	4** (44.7)
POSSIBLE VERT. ARCHES								
9TH AND 10TH OR 13TH AND 14TH THORACIC ARCH	MIN	0	0	0	0	0	2 (26.3)	2 (26.3)
STERNUM								
LONGITUDINALLY DISPLACED, FRAGMENTED	MIN	1 (9.7)	1 (8.0)	2 (15.2)	2 (16.0)	2 (26.3)	2 (26.3)	2 (26.3)
NON-OSIFIED OR MEANLY OSIFIED	NET	18 (12.9)	19** (13.9)	21 (16.0)	21 (27.1)	21 (27.1)	19** (24.7)	19** (24.7)
RIB								
WAVY AND/OR THICKENED - BILATERAL	MIN	1 (7.1)	1 (7.3)	4 (30.9)	4 (30.9)	4 (50.6)	2 (25.0)	2 (25.0)
FOREPA								
NON-OSIFIED METACARPALS - BILATERAL	NET	42 (30.2)	41 (29.9)	47* (36.6)	47* (61.0)	47* (61.0)	23** (29.7)	23** (29.7)
PHALANX III OF 1ST TO 5TH TOES - BILATERAL	NET	3 (2.2)	3 (2.2)	3 (2.3)	3 (3.7)	3 (3.7)	4* (5.1)	4* (5.1)

FISHER'S EXACT:- GROUP 1 COMPARED WITH ALL OTHER GROUPS (* P < 0.05 ** P < 0.01, ONE TAIL)

Conclusion: Based on the study findings, iloperidone induces developmental toxicity (expressed as embryofetal lethality, retarded intrauterine development and minor skeletal abnormalities) at oral doses above 16 mg/kg/day. Signs of maternal toxicity (reduced weight and weight gain, reduced placental weight) are induced at and above 16 mg/kg/day. The NOAEL for developmental toxicity in this study is 16 mg/kg/day.

Study title: ILO522 metabolite P95 12113: An oral embryotoxicity study in rats

Key study findings: P95 12113 (P95), the predominant circulating metabolite of iloperidone in humans, was administered to timed-pregnant Wistar Hanover rats via oral gavage as a suspension in 0.5% (w/v) sodium carboxymethylcellulose at doses of 0 (vehicle control), 20, 80 and 200 mg/kg/day on Gestation Days 7 through 17. The doses were selected on the basis of a preceding 13-week oral toxicity study of P95 in rats that showed decreased body weight and food consumption in males (but not in females) at doses of 200 mg/kg/day and higher. In the present study, no signs of maternal toxicity (mortality, body weight, weight gain, food consumption, necropsy findings and reproductive parameters) were noted; maternal pharmacological clinical signs were observed at all tested doses (relaxation and ptosis at LD, MD and HD; reduced locomotor activity at MD and HD). There was no effect on embryo/fetal intrauterine lethality, number of live fetuses, and fetal weight at term. Gross external malformations (gastroschisis) were registered in 2 fetuses from one litter in HD group; it is uncertain if this was a treatment-related effect since on a litter basis the incidence of this finding was reported to be within the historical control values for similar abdominal closure defects in this species and strain. A dose-dependent, increased incidence of incomplete ossification of skull bones was found in all dose groups, i.e., incomplete parietal ossification in 8%, 11% and 12% of fetuses from 4%, 5% and 7% of the litters at LD, MD, and HD, respectively, vs. 0% in control (statistically significant at all dose levels) and incomplete interparietal ossification in 8%, 10% and 14% of fetuses from 26%, 27% and 27% of the litters at LD, MD, and HD, respectively, vs. 5% and 19% in control fetuses and litters, respectively (statistically significant at HD). The incidence of incomplete sternal ossification was dose-dependently increased in all treated groups, although the difference vs. control did not reach statistical significance (i.e., in 7%, 11% and 12% of fetuses at LD, MD, and HD, respectively, vs. 5% in control fetuses). According to the sponsor, all observed incidences of incomplete skeletal ossification in the treated groups were within the historical control range, and therefore "not attributable to the test article". However, the dose-related increase of these incidences argues in favor of a treatment-related effect. Maternal P95 plasma exposure (AUC) values were 210, 254 and 2355 h.ng/ml for the LD, MD and HD, respectively; the corresponding C_{max} values were 12, 111 and 1221 ng/ml. The high dose (200 mg/kg/day) produced plasma exposure (AUC =2355 ng.h/ml) in pregnant rats approximately 4 times the human P95 plasma AUC value (569 ng.h/ml) when the parent compound (iloperidone) was administered to schizophrenic patients at a dose of 24 mg/day (12 mg b.i.d.).

In conclusion, iloperidone metabolite P95 administered to pregnant rats at oral doses of 20, 80 and 200 mg/kg/day during the period of major organogenesis (Gestation Days 7 through 17), produced dose-dependent maternal pharmacological effect (signs of sedation) at all dose levels, but no maternal toxicity. Maternal plasma exposure (AUC) at HD was approximately 4 times the mean human plasma AUC of metabolite P95 when the parent compound (iloperidone) was administered at the dose of 12 mg/kg/day. The treatment did not induce embryo/fetal mortality or congenital malformations but produced a dose-dependent increase in the incidence of retarded skeletal ossification vs. the concurrent control (predominantly manifested as incomplete ossification of skull

bones) at all tested dose levels, ranging from 8% (LD) to 14% (HD). These values, however, were within the historical control range for the tested species and strain.

Study no.: 007138

Volume # and page #: N.A.

Conducting laboratory and location: Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

Date of study initiation: 22 August 2000

GLP compliance: yes

QA reports: yes

Test article: Iloperidone metabolite P95 12113

Lot numbers and potency: batch no. 0038001; Content of active ingredient: 100.6%

Vehicle: 0.5% (w/v) sodium carboxymethylcellulose (CMC), type 7HF, aqueous solution

Methods

Doses: 20, 80 and 200 mg/kg/day

Species/strain: Rat, Wistar Hanover — WI(Glx/BRL/Han)IGS BR

Number/sex/group: 25 timed-pregnant females

Route, formulation, volume: Oral gavage, P95 12113 suspension in 0.5% (w/v) CMC, dosing volume 10 ml/kg (all groups)

Satellite groups used for toxicokinetics: No. animals: 3 per control and 5 per each

dose group

Group	Number/group		Animal numbers ^{a,b}		Dose (mg/kg/day)	Concentration (mg/mL)
	main study	satellites	main study	satellites		
1 Control	25	3	1-49	5901-5905	0	0
2 Low	25	5	55-103	5911-5919	20	2
3 Mid	25	5	109-157	5925-5933	80	8
4 High	25	5	163-211	5939-5947	200	20

Study design: Timed-pregnant female Wistar Hanover rats (25/group) were administered iloperidone metabolite P95 12113 (P 95) via oral gavage as a suspension in 0.5% sodium CMC at doses of 0 (vehicle control), 20, 80, and 200 mg/kg on Gestation Days 6 through 17. The doses were selected on the basis of a preceding subchronic (13-week) oral toxicity study of P95 12113 conducted in rats at doses of 50, 200 and 500 mg/kg that produced pharmacological clinical signs (relaxation and ptosis) at all dose levels and a decreased body weight and food consumption in males (but not in females) at doses of 200 mg/kg/day and higher. Preliminary TK results from week 1 of that study indicated that the dose of 200 mg/kg/day produced plasma exposure (AUC) value in female rats approximately 65 times the human plasma exposure of metabolite P95 12113 when the parent compound (iloperidone) was administered at the dose of 12 mg/kg/day (6 mg b.i.d.).

Ref:

Longo LM. ILO522 metabolite P95 12113: 13-week oral (gavage) toxicity study in rats with a 4-week recovery period (Study no. 007008). Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, US. 20-Oct-2000.

Body weight and food consumption were measured at specific time points throughout gestation, and clinical signs were recorded daily. All main study females were sacrificed on gestation Day 21, and a gross necropsy was performed. Gravid uterine weights and

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reproductive parameters were recorded. Fetuses were examined for external abnormalities and fetal sex and weight were recorded. Fetal visceral and skeletal examinations were subsequently performed. Satellite timed-pregnant animals (3 for controls and 5/dose for P95-treated animals) were treated during the same time period for toxicokinetic analyses. Plasma samples were taken on gestation Days 17 and 18 for determination of P95 concentration.

Parameters and endpoints evaluated:

Maternal: survival and clinical signs (daily), body weight and food consumption (G. days 0, 3, 6, 9, 12, 15, 18 and 21), gross evaluation of dams (major viscera and placenta), reproductive parameters (gravid uterine weight, number of corpora lutea in ovaries, number of implantations, resorptions (number and diameter), placental weights, live and dead fetuses).

Fetal: viability, gender, individual weight, external, visceral (fresh visceral examination), and skeletal (alizarin staining) examination.

The findings obtained at the autopsy and at fetal examination were statistically evaluated separately for the fetuses and for the litters.

TK: Maternal blood samples (approx. 0.5 ml each) for TK were collected from the orbital sinus of each satellite animal on G day 17 at 1, 2, 4, 6 and 24 h. after the last dose.

Results

Mortality (dams): There were no spontaneous deaths in any of the groups.

Clinical signs (dams): Relaxed vaginal and anal openings and ptosis occurred in all dosed groups. Decreased locomotor activity and hypersensitivity to touch occurred at MD and HD.

Body weight (dams): Body weight parameters were not affected by treatment in any of the dosed groups.

Food consumption: not affected by treatment in any of the dosed groups.

C-section data:

Maternal gross necropsy observations, reproductive parameters, fetal weight and sex ratio showed no changes in the dosed groups vs. control (see sponsor's table on the next page).

Fetal external abnormalities: Gross external malformations: hindlimb malrotation was found in 1 LD fetus (0.6% incidence); and gastroschisis was found in 1.2% of the HD fetuses (2 fetuses of one and the same litter from the HD group) (see sponsor's table on the next page). It is uncertain if the latter finding is treatment-related, as the incidence of this malformation on a litter basis (4.5%) was within the laboratory historical control values for similar abdominal closure defects in this species and strain.

Fetal visceral abnormalities: There were no treatment-related visceral malformations. Occasional findings of visceral variations (i.e., small renal papilla and/or dilated ureters, common visceral finding in this species) were registered in the control and MD groups (see sponsor's table on the next page).

IL0522 METABOLITE 985 12113: AN ORAL EMBRYO-FETAL DEVELOPMENT
 STUDY IN RATS
 STUDY IDENTIFICATION NO.: 087138
 Summary of Cesarean Data (PCN90)

DOSAGE		0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Females Mated	N	25	25	25	25
Pregnant	N	21	19	22	23
Aborted	N	84.0	76.0	88.0	82.0
Premature Births	N	0	0	0	0
Female Mortality	N	0	0	0	0
Pregnant at C-section	N	21	19	22	23
Dams with Viable Fetuses	N	21	19	22	22
Dams with All Resorptions	N	0	0	0	1
Corpora Lutea	N	230	217	240	266
	MEAN	11.0	11.4	10.3	11.6
	S.D.	1.9	2.1	2.9	2.6
Implantation Sites	N	201	168	199	192
	MEAN	9.6	8.8	9.0	8.3
	S.D.	2.9	3.3	3.2	2.9
Preimplantation Loss	%	12.6	22.6	17.1	27.0
Postimplantation Loss	%	10.0	6.5	5.5	10.4
Dead Fetuses	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Resorptions, total	N	20	11	11	20
	MEAN	10.0	6.5	5.5	10.4
	S.D.	1.1	0.8	1.1	0.9
Early Resorptions	N	18	9	11	19
	MEAN	9.5	5.4	5.3	9.9
	S.D.	0.9	0.8	0.9	0.8
Late Resorptions	N	1	2	0	1
	MEAN	0.5	1.2	0.0	0.5
	S.D.	0.2	0.3	0.0	0.2
Viable Fetuses	N	181	157	188	172
	%	30.0	31.5	34.8	39.6
	MEAN	8.6	8.3	8.5	7.9
	S.D.	2.8	3.2	2.9	3.1
Viable Male Fetuses	N	93	83	104	81
	%	45.9	52.9	55.3	47.1
Live Fetal Body Weight (g)	MEAN	5.1	5.2	5.0	5.2
	S.D.	0.2	0.4	0.4	0.3
Male Fetuses	MEAN	5.3	5.4	5.3	5.3
	S.D.	0.3	0.4	0.4	0.3
Female Fetuses	MEAN	5.0	4.9	4.8	5.1
	S.D.	0.3	0.3	0.4	0.4

SUMMARY OF FETAL EXTERNAL MALFORMATIONS					
DOSAGE		0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Litters Evaluated	N	21	19	22	22
Fetuses Evaluated	N	181	157	188	172
Live	N	181	157	188	172
Dead	N	0	0	0	0
GASTROSCISSIS	N	0	0	0	2
Fetal Incidence	%	0.0	0.0	0.0	1.2
Litter Incidence	%	0.0	0.0	0.0	1.0
MALROTATED LIMBS	N	0	1	0	0
Fetal Incidence	%	0.0	0.6	0.0	0.0
Litter Incidence	%	0.0	5.3	0.0	0.0
TOTAL FETAL EXTERNAL MALFORMATIONS	N	0	1	0	2
Fetal Incidence	%	0.0	0.6	0.0	1.2
Litter Incidence	%	0.0	5.3	0.0	4.5

SUMMARY OF FETAL VISCERAL VARIATIONS					
DOSAGE		0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Litters Evaluated	N	20	18	21	20
Fetuses Evaluated	N	84	74	90	79
Live	N	84	74	90	79
Dead	N	0	0	0	0
RENAL PAPILLA-SMALL	N	0	0	1	0
Fetal Incidence	%	0.0	0.0	1.1	0.0
Litter Incidence	%	0.0	0.0	4.8	0.0
URTER-DILATED	N	2	0	2	0
Fetal Incidence	%	2.4	0.0	2.2	0.0
Litter Incidence	%	10.0	0.0	9.5	0.0
TOTAL FETAL VISCERAL VARIATIONS	N	2	0	2	0
Fetal Incidence	%	2.4	0.0	2.2	0.0
Litter Incidence	%	10.0	0.0	9.5	0.0

Fetal skeletal abnormalities:

The total incidence of fetal skeletal malformations in the treated groups was similar to the control group, as shown in the sponsor's table below.

SUMMARY OF FETAL SKELETAL MALFORMATIONS					
	DOSAGE	0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Litters Evaluated	N	21	19	22	22
Fetuses Evaluated	N	97	83	98	93
Live	N	97	83	98	93
Dead	N	0	0	0	0
MAXILLA-FUSED					
Fetal Incidence	N	5	2	0*	0
	t	5.2	2.4	0.0	0.0
Litter Incidence	N	2	2	0	0
	t	9.5	10.5	0.0	0.0
STERNUM-FUSED					
Fetal Incidence	N	5	2	0*	0
	t	5.2	2.4	0.0	0.0
Litter Incidence	N	2	2	0	0
	t	9.5	10.5	0.0	0.0
REN-NAVY					
Fetal Incidence	N	5	7	5	9
	t	5.2	8.4	5.1	9.7
Litter Incidence	N	3	6	4	4
	t	14.3	31.6	18.2	18.2
TOTAL FETAL SKELETAL MALFORMATIONS					
Fetal Incidence	N	10	9	5	9
	t	10.3	10.8	5.1	9.7
Litter Incidence	N	4	7	4	4
	t	19.0	36.8	18.2	18.2

Statistical key: * = p<0.05

Skeletal ossification: A dose-dependent, increased incidence of incomplete ossification of skull bones was found in all dose groups, as shown in sponsor's table below and on the next page, i.e., incomplete parietal ossification in 8%, 11% and 12% of fetuses from 4%, 5% and 7% of the litters at LD, MD, and HD, respectively, vs. 0% in control (statistically significant at all dose levels) and incomplete interparietal ossification in 8%, 10% and 14% of fetuses from 26%, 27% and 27% of the litters at LD, MD, and HD, respectively, vs. 5% and 19% in control fetuses and litters, respectively (statistically significant at HD). The incidence of incomplete sternal ossification was dose-dependently increased in all treated groups, although the difference vs. control did not reach statistical significance (i.e., in 7%, 11% and 12% of fetuses at LD, MD, and HD, respectively, vs. 5% in control fetuses). According to the sponsor, all observed incidences of incomplete skeletal ossification in the treated groups were within the historical control range, and therefore "not attributable to the test article". However, the dose-related increase of these incidences argues in favor of a treatment-related effect.

SUMMARY OF FETAL SKELETAL VARIATIONS					
	DOSAGE	0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Litters Evaluated	N	21	19	22	22
Fetuses Evaluated	N	97	83	98	93
Live	N	97	83	98	93
Dead	N	0	0	0	0
INTERPARIETAL-INCOMPLETE OSSIFICATION					
Fetal Incidence	N	5	8	10	14*
	t	5.2	9.6	10.2	15.1
Litter Incidence	N	4	5	6	6
	t	19.0	26.3	27.3	27.3
PARIETAL-INCOMPLETE OSSIFICATION					
Fetal Incidence	N	0	8**	11**	12**
	t	0.0	9.6	11.2	12.9
Litter Incidence	N	0	4*	5*	7**
	t	0.0	21.1	22.7	31.8

*p<0.05; **p<0.01

(Continued)

SUMMARY OF FETAL SKELETAL VARIATIONS					
DOSE		0 MG/ KG/DAY	20 MG/ KG/DAY	80 MG/ KG/DAY	200 MG/ KG/DAY
Litters Evaluated	N	21	19	22	22
Fetuses Evaluated	N	97	83	98	93
Live	N	97	83	98	93
Dead	N	0	6	0	0
SUPRAOCCIPITAL-INCOMPLETE OSSIFICATION					
Fetal Incidence	N	1	4	5	3
%	%	1.0	4.8	5.1	3.2
Litter Incidence	N	1	2	3	3
%	%	4.8	10.5	13.6	13.6
HYDROCEPHALIC-INCOMPLETE OSSIFICATION					
Fetal Incidence	N	1	3	2	4
%	%	1.0	3.6	2.0	4.3
Litter Incidence	N	1	2	2	3
%	%	4.8	10.5	9.1	13.6
STERNUM-INCOMPLETE OSSIFICATION					
Fetal Incidence	N	5	6	11	11
%	%	5.2	7.2	11.2	11.8
Litter Incidence	N	4	5	4	4
%	%	19.0	26.3	18.2	18.2

Toxicokinetics

The following sponsor's tables summarize the plasma concentration of metabolite P95 in pregnant rats on day 17/18 of the study.

Toxicokinetic parameters for P95 in plasma of pregnant rats

20 mg/kg/day			80 mg/kg/day			200 mg/kg/day		
Rat #	AUC (h*ng/mL)	Cmax (ng/mL)	Rat #	AUC (h*ng/mL)	Cmax (ng/mL)	Rat #	AUC (h*ng/mL)	Cmax (ng/mL)
5913	NC	5.78	5927	228	114	5939	2153	1170
5915	NC	11.8	5931	225	106	5941	2617	1240
5917	210	19.5	5933	310	112	5943	598	373
						5945	3641	2580
						5947	2765	741
Mean	210	12.4		254	111		2355	1221
SD		6.9		48.2	4.2		1120	837
CV		55.6		18.9	3.8		47.6	68.5

NC=not calculated, insufficient data

For two of the three animals in the 20 mg/kg/day group there was only one time point that showed measurable concentrations of the test article (1 hour). AUC values were not calculated for those animals. For the third animal, the AUC was calculated.

Rats in all treated groups had measurable plasma concentrations of P95. Over the dose range, plasma exposure increased more than dose-proportionally for both Cmax and AUC, as shown in the sponsor's table on the next page. (For AUC, this applied for the difference between MD and HD groups; LD group was not included in the analysis since only an AUC for a single animal in that group could be obtained).

Dose normalized toxicokinetic parameters for P95 in plasma from pregnant rats

20 mg/kg/day			80 mg/kg/day			200 mg/kg/day		
Rat #	AUC (h*ng/mL)	Cmax (ng/mL)	Rat #	AUC (h*ng/mL)	Cmax (ng/mL)	Rat #	AUC (h*ng/mL)	Cmax (ng/mL)
5913	NC	0.289	5927	2.85	1.43	5939	10.8	5.85
5915	NC	0.590	5931	2.81	1.33	5941	13.1	6.20
5917	10.5	0.975	5933	3.87	1.40	5943	2.99	1.87
						5945	18.2	12.9
						5947	13.8	3.71
Mean	10.6	0.618		3.18	1.38		11.8	6.10
SD		0.344		0.602	0.052		5.60	4.18
CV		55.6		18.9	3.76		47.6	68.5

NC=not calculated. Insufficient data

Thus, the TK study showed that all dosed groups were exposed to P95, and plasma exposure (AUC and Cmax) increased over proportionally with the dose. The high dose (200 mg/kg/day) produced plasma exposure (AUC=2355 ng.h/ml) in pregnant rats approximately 4 times the human P95 plasma AUC value (569 ng.h/ml) when the parent compound (iloperidone) was administered to schizophrenic patients at a dose of 24 mg /day (12 mg b.i.d.), as shown in the sponsor's table below.

Mean (CV%) P95-12113 pharmacokinetic parameters in schizophrenic patients following iloperidone administration in multiple escalating oral doses (b.i.d.)**

Parameters	Mean (CV%)			
	2.0 mg	4.0 mg	8.0 mg	12.0 mg
t_{max}^{55} (h)*	2.8 (67)	2.5 (69)	2.5 (70)	2.8 (33)
C_{max}^{55} (ng/mL)	9.02 (41)	19.06 (39)	37.74 (37)	58.48 (38)
C_{min}^{55} (ng/mL)	5.80 (43)	12.00 (32)	24.72 (29)	36.65 (32)
AUC_t (ng·h/ml)	88.99 (37)	187.1 (34)	379.7 (32)	568.9 (35)
C_{avg}^{55} (ng/mL)	7.42 (37)	15.59 (34)	31.64 (32)	47.41 (35)
N	28	24	20	16

*Median (Range)

**Each patient's dose was increased from 2 mg twice a day up to 12 mg twice a day over a 31-day period; patients were maintained on each dose for 7 days.

Conclusion: Iloperidone metabolite P95 administered to pregnant rats at oral doses of 20, 80 and 200 mg/kg/day during the period of major organogenesis (Gestation Days 7 through 17), produced dose-dependent maternal pharmacological effect (signs of sedation) at all dose levels, but no maternal toxicity. Maternal plasma exposure (AUC) at HD was approximately 4 times the mean human plasma AUC of metabolite P95 when the parent compound (iloperidone) was administered at the dose of 12 mg/kg/day (6 mg b.i.d.). The treatment did not induce embryo/fetal mortality or congenital malformations but produced a dose-dependent increase in the incidence of retarded skeletal ossification vs. the concurrent control (predominantly manifested as incomplete ossification of skull bones) at all tested dose levels, ranging from 8% (LD) to 14% (HD). These values, however, were within the laboratory historical control range for the tested species and strain.

Study title: Oral Embryotoxicity Study of Iloperidone (HP 873) in Himalayan Rabbits (Effect on Morphological Development) (Segment II)

Key study findings: Iloperidone administration at oral (gavage) doses of 0, 4, 10 and 25 mg/kg/day to pregnant rabbits from gestation day 6 through 18 caused maternal mortality at the HD (1/15) and induced dose-dependent drug-related clinical signs (sedation at all dose levels and ptosis at MD and HD). Maternal water intake was reduced at all dose levels in a dose-dependent manner; food intake was reduced at MD and HD. Maternal body weight gain was markedly reduced at HD during the 1st week of treatment due to reduced food consumption, resulting in about 5% decrease in mean body weight vs. control on gestation days 13 and 19 (statistically significant). No signs of embryo/fetal toxicity or teratogenicity were observed in LD and MD groups. The high dose induced increase in embryo/fetal intrauterine lethality and a decrease in fetal viability at term. Based on these results, the NOAEL for embryo/fetal toxicity is 10 mg/kg/day.

Study no.: 92.0012; Report no. 94.0660

Volume # and page #: N.A.

Conducting laboratory and location:

Pharma Development Corporate Toxicology, Hoechst Actiengesellschaft, Frankfurt/Main

Date of study initiation: May 7, 1992

GLP compliance: Yes

QA reports: yes

Drug, lot #, and % purity: Batch No. RC 4840; 99.8%

Vehicle: Starch mucilage (20 g/l)

Methods

Doses: 0, 4, 10, 25 mg/kg/day

Species/strain: Rabbit, Himalayan

Number animals/group: 15-16 pregnant females

Route, formulation, volume: oral gavage, suspension in 2% starch aqueous solution; dose volume 5 ml/kg body weight in all groups.

Satellite groups used for toxicokinetics: none

Study design: Mated female Himalayan rabbits (15-16/group) were administered iloperidone at doses of 0 (vehicle control), 4, 10, and 25 mg/kg/day by oral gavage on Gestation Days 6 through 18 (day of sperm detection defined as Gestation Day 0). Cesarean section was performed on Gestation Day 29 for evaluation of maternal reproductive parameters, pre- and postimplantation embryofetal lethality, neonatal viability, weight, gender, and morphology.

Parameters and endpoints evaluated:

Maternal: survival and clinical signs (daily), body weight and food consumption (weekly), reproductive parameters (number of corpora lutea in ovaries, number of implantations, resorptions (number and diameter), placental weights, live and dead fetuses), organ weight (heart, liver, kidneys and spleen), gross necropsy.

Fetal: Viability at Cesarean section, 24 h survival rate in incubator, gender, individual weight, crown-rump length, external, visceral (Bouin's fixative) and skeletal (alizarin staining) anomalies.

The findings obtained at the autopsy and at fetal examination were statistically evaluated separately for the fetuses and for the litters.

Results

Mortality (dams): There was one maternal death in HD group after 4 days of dosing (on gestation day 9/10); the sponsor assessed the death as drug-related although the cause of death was not determined because, due to autolysis, pathomorphological examination could not be performed. Another case of maternal death occurred in the control group (on gestation day 13) as a result of gavage error (confirmed pathomorphologically).

Clinical signs (dams): Compound-related sedation was observed in all animals at all dose levels. Ptosis occurred at MD and HD, in 11 and 13 animals, respectively. These clinical signs appeared about 1.5 h after dosing and persisted for several hours; in most cases, the signs disappeared on the following day, except for 5 HD females in which the signs persisted for "some days" after the discontinuation of dosing.

Reduced water consumption and defecation was observed at all dose levels, dose-dependently (in 3, 4 and 9 animals at LD, MD and HD, respectively), as shown in the sponsor's table below.

STUDY NO: RK0649		TITLE: EMBRYOTOXICITY IN RABBITS ON NP 573 (P 88 8736)			
		START DAY NO: 0	FINISH DAY NO: 29		
		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		0	4	18	25
		MG/KG	MG/KG	MG/KG	MG/KG
URINE COLOURED REDDISH					
NO. OF OBS.	2				
NO. OF ANIMALS	1				
DAYS FROM - TO	26	29			
REDUCED DEFECACTION					
NO. OF OBS.			20	21	89
NO. OF ANIMALS			3	4	9
DAYS FROM - TO			11	22	8
				15	8
PALPEBR. FISSURE NARROW					
NO. OF OBS.				82	114
NO. OF ANIMALS				7	10
DAYS FROM - TO				6	6
				18	19
PALPEBR. FISS. VERY NARROW					
NO. OF OBS.				39	26
NO. OF ANIMALS				4	3
DAYS FROM - TO				7	6
				18	18
SLEEPINESS					
NO. OF OBS.			158	178	179
NO. OF ANIMALS			15	15	15
DAYS FROM - TO			6	6	6
			18	18	19
REDUCED WATER CONSUMPTION					
NO. OF OBS.			22	28	88
NO. OF ANIMALS			3	4	9
DAYS FROM - TO			10	22	8
				15	8
					21

Body weight (dams): No significant effect on maternal body weight was observed at the LD and MD. At HD, the dams lost weight due to reduced food consumption, resulting in about 5% decrease in mean body weight vs. control on gestation days 13 and 19 (statistically significant), but subsequently, upon treatment discontinuation they gained more weight than control, resulting in a similar body weight at term (see sponsor's tables on the next page).

Food consumption (dams): Maternal food consumption was unchanged at LD. At MD and HD, it was decreased significantly and dose-dependently during the treatment period (i.e., 25% and 2x lower than control at MD and HD, respectively, during the 1st week of

treatment). Food consumption at MD and HD increased significantly and dose-dependently after discontinuation of treatment.

BODY WEIGHT (G) OF DAMS DURING PREGNANCY		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 10 MG/KG	GROUP 4 25 MG/KG
MULTIVARIATE COMPARISONS					
DAY					
0	MEAN S.D. (NO. OF DAMS)	2527.5 116.1 13	2557.0 152.7 15	2625.4 130.9 14	2543.4 135.2 14
6	MEAN S.D. (NO. OF DAMS)	2577.4 110.1 13	2607.1 153.3 15	2665.5 125.7 14	2599.1 128.7 14
13	MEAN S.D. (NO. OF DAMS)	2594.8 124.4 13	2581.7 108.8 15	2631.2 114.5 14	2675.9 151.8 14
19	MEAN S.D. (NO. OF DAMS)	2670.2 148.9 13	2606.0 124.2 15	2716.7 137.7 14	2553.5 179.2 14
29	MEAN S.D. (NO. OF DAMS)	2798.1 156.1 13	2839.9 102.8 15	2855.7 155.7 14	2749.6 151.6 14

a : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LESS THAN CONTROL * : SIGNIFICANTLY DIFFERENT FROM CONTROL
 N : EVALUATION NOT POSSIBLE, GROUP CONTAINS LESS THAN 5 ANIMALS
 N/A : WITHIN/OUTSIDE THE NORMAL RANGE
 STATISTICAL ANALYSIS BASED ON GAINS VERSUS PRELIMINARY VALUES

BODY WEIGHT GAINS (G) OF DAMS DURING PREGNANCY		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 10 MG/KG	GROUP 4 25 MG/KG
DAY					
0 - 6	MEAN S.D. (NO. OF DAMS)	49.9 49.3 13	50.1 40.1 15	40.1 59.5 14	55.6 40.3 14
6 - 13	MEAN S.D. (NO. OF DAMS)	17.4 36.1 13	-25.3 71.2 15	-34.3 52.6 14	-123.2 69.1 14
13 - 19	MEAN S.D. (NO. OF DAMS)	75.4 47.9 13	104.3 57.4 15	83.5 49.0 14	77.6 76.4 14
19 - 29	MEAN S.D. (NO. OF DAMS)	127.9 54.0 13	153.9 84.9 15	141.0 52.9 14	196.1 65.0 14

NO STATISTICAL EVALUATION

DAILY FOOD CONSUMPTION (G) / 100 G BODY WEIGHT OF DAMS DURING PREGNANCY		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 10 MG/KG	GROUP 4 25 MG/KG
MULTIVARIATE COMPARISONS					
DAY					
0 - 6	MEAN S.D. (NO. OF DAMS)	4.2 0.6 13	4.3 0.7 15	4.4 0.5 14	4.4 0.9 14
6 - 13	MEAN S.D. (NO. OF DAMS)	4.0 0.7 13	3.5 0.8 15	3.1 0.5 14	2.1 1.0 14
13 - 19	MEAN S.D. (NO. OF DAMS)	3.9 0.7 13	3.8 0.9 15	3.5 0.6 14	3.3 1.1 14
19 - 29	MEAN S.D. (NO. OF DAMS)	3.2 0.5 12	3.6 0.5 15	3.9 0.5 14	4.6 0.6 12

a : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LESS THAN CONTROL * : SIGNIFICANTLY DIFFERENT FROM CONTROL
 N : EVALUATION NOT POSSIBLE, GROUP CONTAINS LESS THAN 5 ANIMALS
 N/A : WITHIN/OUTSIDE THE NORMAL RANGE

Terminal and necroscopic evaluations: Maternal necropsy findings: Gross necropsy findings were unremarkable. Histopathology examination was not performed in this study. Organ weights of kidney at HD and of liver at MD and HD and were dose-dependently higher (by 6%, 9% and 19%, respectively) vs. the concurrent control values.

C-section data (implantation sites, pre- and post-implantation loss, etc.):

Mean number of corpora lutea per dam (indicative of the ovulation prior to the start of treatment) was similar across groups. The mean number of implantations per dam was significantly lower in HD group in comparison to control, but this change was not drug-related since the treatment commenced post implantation. The post-implantation embryo/fetal lethality was significantly higher, and the number of live fetuses/litter was significantly lower in HD group vs. control group (see sponsor's table below). The smaller litter size in HD group can be attributed to the treatment-related increase in post-implantation embryo/fetal lethality as well as to the lower number of implantations in HD group.

		SURVEY OF RESULTS DURING GESTATION AND AT CAESARIAN SECTION			
		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		0	4	10	25
		MG/KG	MG/KG	MG/KG	MG/KG
NUMBER OF					
- PREGNANCIES	ME TOTAL	15	15	15	15
- INTERCURRENT DEATH	ME TOTAL	0	0	0	1
- FEMALES WITH ABORTION	ME TOTAL	1	0	1	0
- FEMALES WITH PREMATURE DELIVERY	ME TOTAL	0	0	0	0
- FEMALES AT TERM WITH INTRAUTER. DEATHS ONLY	ME TOTAL	1	0	0	0
- FEMALES AT TERM WITH LIVE FOETUSES	ME TOTAL	13	15	14	14
- CORPORA LUTEA	TOTAL	108	112	121	113
	MEAN	8.3	7.5	8.8	8.1
	S.D.	1.8	1.4	1.7	1.9
- IMPLANTATIONS	TOTAL	95	99	90	82
	MEAN	7.3	6.6	6.4	5.9
	S.D.	1.4	2.2	2.6	2.3
PRE-IMPLANTATION LOSS %					
	ME MEAN	11.28	13.72	26.46	28.46
POST-IMPLANTATION LOSS %					
	ME MEAN	9.70	10.28	15.35	20.48
- EARLY INTRAUTERINE DEATHS	TOTAL	6	9	9	19
	ME MEAN	0.46	0.60	0.64	1.36
	S.D.	0.78	1.30	0.93	1.60
% OF IMPLANTATIONS	MEAN	6.54	9.32	12.67	19.77
	S.D.	10.64	21.53	19.72	18.59
- LATE INTRAUTERINE DEATHS	TOTAL	3	1	3	1
	ME MEAN	0.23	0.07	0.21	0.07
	S.D.	0.60	0.26	0.43	0.27
% OF IMPLANTATIONS	MEAN	3.16	0.95	2.87	0.71
	S.D.	8.38	3.69	6.14	2.67
- TOTAL INTRAUTERINE DEATHS	TOTAL	9	10	12	20
	ME MEAN	0.69	0.67	0.86	1.43
	S.D.	1.18	1.29	1.17	1.83
- LIVE FOETUSES	TOTAL	86	89	78	62
	MEAN	6.6	5.9	5.6	4.4
	S.D.	1.8	2.5	2.7	1.9
% OF IMPLANTATIONS					
	MEAN	90.30	89.72	84.65	79.52
	S.D.	16.57	21.41	23.38	20.36

a : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LESS THAN CONTROL
 N : EVALUATION NOT POSSIBLE, GROUP CONTAINS LESS THAN 5 ANIMALS ME : NO STATISTICAL EVALUATION
 N/A : WITHIN/OUTSIDE THE NORMAL RANGE

Fetal viability and weight:

Viability of fetuses delivered by Caesarean section was similar to control at LD and MD, but reduced at HD, as shown by the lower survival rate of HD fetuses 24 h after delivery in comparison to the concurrent and previous control data for the conducting laboratory (statistical analysis not performed).

The mean fetal body weight and length were comparable across groups. Placental weight and macroscopic appearance in the dose groups were similar to control.

SURVEY OF RESULTS IN LIVE FOETUSES AT CAESARIAN SECTION		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 10 MG/KG	GROUP 4 25 MG/KG
NUMBER OF FOETUSES	TOTAL	86	89	78	62 b
	MEAN	6.6	5.9	5.6	4.4
	S.D.	1.8	2.5	2.7	1.9
MALES (%)	NE	58.8	57.3	40.3	46.8
BODY WEIGHT (G)	MEAN	39.0	41.7	39.9	41.0
	S.D.	2.9	2.6	4.0	3.7
CROWN/RUMP LENGTH (MM)	MEAN	94.7	96.9	94.0	95.7
	S.D.	3.9	3.5	4.5	3.9
PLACENTAL WEIGHT (G)	MEAN	4.89	5.61	5.32	5.36
	S.D.	0.70	0.69	0.81	0.70
SURVIVAL RATE 24 (X) HOURS	MEAN	89.1	96.1	95.1	80.6
	S.D.	19.3	8.3	8.7	18.3

a : SIGNIFICANTLY HIGHER THAN CONTROL b : SIGNIFICANTLY LESS THAN CONTROL
 N : EVALUATION NOT POSSIBLE, GROUP CONTAINS LESS THAN 5 ANIMALS NE : NO STATISTICAL EVALUATION
 N/A : WITHIN/OUTSIDE THE NORMAL RANGE

Fetal morphology

The results of external, visceral and skeletal examination are summarized in the sponsor's tables reproduced on the next 2 pages.

External abnormalities: The incidence of external malformations tended to be slightly and insignificantly higher at MD [n=2 (1 case of micropthalmia and 1 case of forepaw deformity)] and HD [n=3 (1 case of cleft palate and omphalocele; 2 cases of forelimb deformity)] in comparison to control (1 case of "blister on the back of the lumbar vertebral column") and LD (1 case of "blister on the parietal cranial region").

Visceral abnormalities: There were no remarkable findings or inter-group differences, except for a dose-related increase in the incidence of distended and/or displaced stomach.

Skeletal abnormalities: There were no differences in the incidence of skeletal abnormalities or the degree of skeletal ossification between dosed and control groups.

Conclusion: Iloperidone administration at oral (gavage) doses of 0, 4, 10 and 25 mg/kg/day to pregnant rabbits from gestation day 6 through 18 caused maternal mortality at the HD (1/15) and induced dose-dependent drug-related clinical signs (sedation at all dose levels and ptosis at MD and HD). Maternal water intake was reduced at all dose levels in a dose-dependent manner; food intake was reduced at MD and HD. Maternal body weight gain was markedly reduced at HD during the 1st week of treatment due to reduced food consumption, resulting in about 5% decrease in mean body weight vs. control on gestation days 13 and 19 (statistically significant). No signs of embryo/fetal toxicity or teratogenicity were observed in LD and MD groups. The high dose induced increase in embryo/fetal intrauterine lethality and a decrease in fetal viability at term. Based on these results, the NOAEL for embryo/fetal toxicity is 10 mg/kg/day (8x the MRHD of 24 mg/day on an mg/m2 basis).

Segment II Study in Rabbits: Fetal morphology (External and visceral examination)

CLASS	GROUP 1 0 MG/KG		GROUP 2 4 MG/KG		GROUP 3 10 MG/KG		GROUP 4 25 MG/KG	
	INCIDENCE BY FORTUS/LITTER		INCIDENCE BY FORTUS/LITTER		INCIDENCE BY FORTUS/LITTER		INCIDENCE BY FORTUS/LITTER	
	NO.	%	NO.	%	NO.	%	NO.	%
EXTERNAL/VISCERAL DEFECTS OBTAINED AT AUTOPSY								
LUNG								
LOBUS MEDIALIS DEXTER OR LOBUS INFERIOR MEDIALIS - APLASIA, LOBUS SUPERIOR DEXTER AND LOBUS MEDIALIS DEXTER OR LOBUS MEDIALIS DEXTER AND LOBUS DEXTER INFERIOR LATERALIS - COMPLETELY FUSED	MIN	3 (15.4)	1 (6.7)	0	0	0	0	0
ABDOMINAL CAVITY								
BLOOD IN ABDOMINAL CAVITY	MIN	0	0	1 (7.1)	0	1 (7.1)	0	0
STOMACH								
ENLARGED AND TAUT WITH FLUID	MIN	1 (7.7)	0	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)
KIDNEY								
DISPLACED - CAUDAD OR CRANIAL AND/OR TRANSVERSE POSITION - LEFT	VAR	0	1 (6.7)	3 (21.4)	1 (7.1)	3 (21.4)	1 (7.1)	1 (7.1)
PELVIS DISTENDED - RIGHT	MIN	0	2 (13.3)	0	0	0	0	0
FOREPAW								
BENT IN CARPAL REGION - LATERAD - UNI- OR BILATERAL	MAJ	0	0	1 (7.1)	2 (14.3)	1 (7.1)	2 (14.3)	2 (14.3)
LUNG								
LOBUS MEDIALIS DEXTER OR LOBUS INFERIOR MEDIALIS - APLASIA, LOBUS SUPERIOR DEXTER AND LOBUS MEDIALIS DEXTER OR LOBUS MEDIALIS DEXTER AND LOBUS DEXTER INFERIOR LATERALIS - COMPLETELY FUSED	MIN	3 (15.4)	1 (6.7)	0	0	0	0	0
ABDOMINAL CAVITY								
BLOOD IN ABDOMINAL CAVITY	MIN	0	0	1 (7.1)	0	1 (7.1)	0	0
STOMACH								
ENLARGED AND TAUT WITH FLUID	MIN	1 (7.7)	0	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)	1 (7.1)
KIDNEY								
DISPLACED - CAUDAD OR CRANIAL AND/OR TRANSVERSE POSITION - LEFT	VAR	0	1 (6.7)	3 (21.4)	1 (7.1)	3 (21.4)	1 (7.1)	1 (7.1)
PELVIS DISTENDED - RIGHT	MIN	0	2 (13.3)	0	0	0	0	0
FOREPAW								
BENT IN CARPAL REGION - LATERAD - UNI- OR BILATERAL	MAJ	0	0	1 (7.1)	2 (14.3)	1 (7.1)	2 (14.3)	2 (14.3)
EXTERNAL/VISCERAL DEFECTS OBTAINED AT BODY CROSS-SECTION EXAMINATION								
NUMBER OF FETUSES EXAMINED		39	41	33		29		
NUMBER OF LITTERS EXAMINED		13	14	12		14		
EXTERNAL/VISCERAL								
NO ABNORMALITIES DETECTED		34 (87.2) 12 (92.3)	36 (87.8) 14 (100)	27 (81.8) 12 (100)		18 (62.1) 13 (92.9)		
ORAL CAVITY/ABDOMINAL CAVITY								
CLEFT PALATE, OMPHALOCELE WITH PROTRUSION OF LIVER TISSUE	MAJ	0	0	0		1 (7.1)		
HEART								
BLOOD IN PERICARDIUM	MIN	2 (5.1) 1 (7.7)	0	0		0		
ABDOMINAL CAVITY								
BLOOD IN ABDOMINAL CAVITY	MIN	0	0	1 (3.0) (8.3)		0		
STOMACH								
ENLARGED, TAUT WITH FLUID OR SOFT MASS, DISPLACED - DEXTRAD, TRANSVERSE POSITION	MIN	2 (5.1) 2 (15.4)	1 (2.4) 1 (7.1)	4 (12.1) 3 (23.1)		7* (25.9) 5 (35.7)		
KIDNEY								
DISPLACED - CAUDAD - LEFT, TRANSVERSE POSITION - LEFT	VAR	1 (2.6) 1 (7.7)	3 (9.8) 3 (21.4)	1 (3.0) 1 (8.3)		3 (10.7) 2 (14.3)		

Segment II Study in Rabbits: Fetal morphology (Skeletal examination)

CLASS	GROUP 1 0 MG/KG		GROUP 2 4 MG/KG		GROUP 3 10 MG/KG		GROUP 4 25 MG/KG	
	INCIDENCE BY FETUS/LITTER		INCIDENCE BY FETUS/LITTER		INCIDENCE BY FETUS/LITTER		INCIDENCE BY FETUS/LITTER	
	NO.	%	NO.	%	NO.	%	NO.	%
SKELETAL DEFECTS								

NUMBER OF FETUSES EXAMINED	47 *		48		45		34	
NUMBER OF LITTERS EXAMINED	13		15		14		14	
SKELETON								

NO ABNORMALITIES DETECTED	15 (32.4) 7 (53.8)		13 (27.1) 7 (46.7)		14 (31.1) 10 (71.4)		10 (29.4) 8 (57.1)	
SKULL								

OPENING IN PARIETALS - OVAL- SHAPE OR CIRCULAR AND SMALL - RIGHT	MIN	0	0	0	2 (4.4) 2 (14.3)	0	0	0
THORACIC VERTEBRA/RIBS								

8TH THORACIC VERTEBRAL ARCH REDUCED IN SIZE - RIGHT	MIN	0	0	0	0	0	1 (2.9) 1 (7.1)	0
8TH THORACIC VERTEBRAL CENTRA PARTIAL APLASIA, 7TH AND 8TH RIB FUSED - PROXIMAL PART - RIGHT	MIN	0	0	0	0	0	0	0
CAUDAL VERT. CENTRA								

LONGITUDINALLY DISPLACED OR DISLOCATED T11H	MIN	0	2 (4.2) 1 (6.7)	0	0	0	0	0
OSSEIFICATION OF LESS THAN 13 VERTEBRAL CENTRES	RET	1 (2.2) 1 (7.7)	1 (2.1) 1 (6.7)	0	0	0	0	0
STERNEBRA								

NON-OSSIFIED OR WEAKLY OSSIFIED	RET	31 (67.4) 10 (76.9)	34 (70.8) 12 (80.0)	30 (66.7) 12 (85.7)	21 (61.8) 11 (78.6)	0	0	0
LONGITUDINALLY DISPLACED OR FUSED	MIN	0	0	0	2 (4.4) 2 (14.3)	1 (2.9) 1 (7.1)	0	0
RIB								

SHORTENED 12TH - RIGHT	MIN	1 (2.2) 1 (7.7)	0	0	0	0	0	0
EXTRA RIB								

AT 7TH CERVICAL VERTEBRA - SHORT - UNILATERAL	VAR	1 (2.2) 1 (7.7)	2 (4.2) 2 (13.3)	0	0	2 (5.9) 2 (14.3)	0	0
AT 13TH THORACIC VERTEBRA - SHORT OR NORMALLY LONG - UNILATERAL	VAR	0	0	1 (2.2) 1 (7.1)	2 (5.9) 1 (7.1)	0	0	0
HINDLIMB								

TALUS NON-OSSIFIED - BILATERAL	RET	0	0	1 (2.2) 1 (7.1)	0	0	0	0

FISHER'S EXACT:- GROUP 1

COMPARED WITH ALL OTHER GROUPS

(* P < 0.05 ** P < 0.01, ONE SIDED)

Prenatal and postnatal development

Study title: Segment III Study in Rats

Key study findings: loperidone was administered at oral doses of 0, 4, 16 and 36/48 mg/kg/day, by gavage, to pregnant CD rats (25/group) from gestation day 17 through post-partum (lactation) day 21. The HD dose level was reduced from 48 to 36 mg/kg/day 1 week after initiation of dosing. The HD was maternally toxic (even after the dose reduction from 48 to 36 mg/kg/day), as demonstrated by maternal mortality (moribund sacrifices) and a marked significant reduction of body weight (by 12% vs. control) during gestation and lactation; signs of maternal toxicity were also present at MD, as demonstrated by significant reductions in mean body weight during lactation (by 7% vs. control) and in weight gain during gestation and lactation. No signs of maternal toxicity were seen at LD. Dose-related, apparently pharmacological clinical signs (sedation, hypoactivity, ptosis) were seen in all of the HD and in most of the MD animals, while in LD group only few animals exhibited clinical signs. The treatment caused a dose-related prolongation of the duration of gestation (the mean duration of gestation in control, LD, MD and HD groups was 21.9, 22.1, 22.3 and 22.8 days, respectively, statistically significant at MD and HD), as well as a prolonged delivery at HD, lasting up to 24 hours (in 30% of the HD females). A dose-dependent decrease in the proportion of liveborn pups was registered (mean livebirth indices = 96%, 91% and 58% at LD, MD and HD, respectively vs. 100% in control), along with increased number of stillbirths (15, 33 and 131 at LD, MD and HD, respectively vs. 1 in control). There was also a significant and marked increase in the postnatal offspring mortality at MD and HD, particularly during early postnatal life. The mean viability indices of F1 generation (N pups alive on Day 4 pre-cull/N liveborn) were 91%, 75% and 19% at LD, MD and HD, respectively vs. 98% in control. Total litter deaths occurred in 14 HD litters and in 1 litter each from MD and LD within the first 5 days of life. The mean viability indices at weaning (N pups surviving to weaning/N pups alive Day 4 post-cull) were decreased at the HD group (74% vs. 100% in control). The observed high perinatal- and postnatal mortality (stillbirths and neonatal deaths) in F1 generation at HD and MD can be a consequence, at least in part, to the extended gestation and prolonged parturition through increased time from placental detachment to parturition and a delay or lack of maternal stimulation and nursing. Signs consistent with lack of maternal care were documented in MD and HD. At gross pathology examination of pups that died during lactation or culled on day 4, "empty stomachs" were found in 2 (1/1%), 2 (1.4%), 15 (8.6%) and 32 (13%) pups in 1 (4.3%), 2 (9.5%), 7 (30%) and 13 (59%) litters in Control, LD, MD, and HD groups, respectively, indicative of poor maternal care at MD and HD.

Mean body weight values of F1 offspring were significantly and dose-dependently lower in comparison to control at HD (by 15% at birth and by 32% on postnatal day 4, pre-cull) and at MD (by 6% at birth and by 13% on postnatal day 4, pre-cull), indicative of retardation in prenatal, and particularly in early postnatal growth at MD and HD. The attainment of developmental landmarks (eye opening, generalized hair growth, incisor eruption, pinna unfolding, gripping reflex, surface righting reflex, pupil and auditory reflexes, and sexual maturation), as well as postnatal neurobehavioral development were apparently unaffected at any dose level (however, it should be noted that in the high dose group the number of F1 offspring tested for general activity in open field was much

smaller than in any other group: 6 vs. 24-25 in the other dose groups). No effects were noted in F₁ reproductive performance and in prenatal development and viability of the next F₂ generation. The mean number of F₂ pups born, live litter size, live born index (%), mean body weight and postnatal survival from birth to PND 1 in the treated groups were not significantly different from the control group.

In conclusion, iloperidone oral administration to pregnant rats from gestation day 17 through parturition and lactation up to postnatal day 21 at doses of 4, 16 and 48/36 mg/kg/day, caused maternal general toxicity at HD and MD, expressed in maternal mortality (moribund sacrifices) at HD and significant decrease in maternal body weight and body weight gain at HD and MD during the treatment period, as well as in adverse maternal reproductive effects demonstrated by a significantly prolonged gestation (at MD and HD) and excessive prolongation of parturition (at HD), resulting in impaired viability of F₁ generation. The high perinatal- and postnatal mortality (stillbirths and neonatal deaths) in F₁ generation at HD and MD can be a consequence, at least in part, to the extended gestation and prolonged parturition through increased time from placental detachment to parturition and a delay or lack of maternal stimulation and nursing. Signs consistent with lack of maternal care were documented in MD and HD. The growth of the surviving F₁ offspring was impaired at MD and HD, as demonstrated by the reduced pup weight at birth and weight gain through weaning. However, there was no apparent adverse effect on F₁ development, including behavior, sexual maturation and reproductive capacity, at any of the administered dose levels. At the low dose, there were signs of maternal sedation induced by iloperidone exposure, but there was no evidence of adverse effect on parturition, maternal care, pup survival, growth and development. Under the conditions of this study, the NOAEL is 4 mg/kg/day (1.6 times the maximal recommended dose in humans on mg/m² basis).

Study no.: _____

Volume # and page #: N.A.

b(4)

Conducting laboratory and location: Hoechst-Roussel Pharmaceuticals Inc.,
Somerville, N.J. 08876, USA

Date of study initiation: April 23, 1993

GLP compliance: Yes

QA reports: yes

Drug, lot #, and % purity: Iloperidone (HP 873), Lot # RC 5634;
Assumed purity 100% (not provided in the report)
Vehicle: 2% aqueous starch

Methods

Doses: 0, 4, 16 and 36/48 mg/kg/day

Species/strain: Rat, —CD®(BR)

Number/sex/group: F₀ dams: 25/group; F₁ generation: 2 pups/sex/litter

Route, formulation, volume, and infusion rate: oral gavage, suspension in 2%
starch aqueous solution; dose volume 5 ml/kg body weight in all groups

Satellite groups used for toxicokinetics: None

b(4)

Study design and methods: Virgin female rats and untreated resident male rats of the same strain and source were cohabited 1:1 in a cage for mating. After confirmation of mating (by an intravaginal copulatory plug or by the presence of sperm in a vaginal lavage), the female was placed in an individual maternity cage and the day was designated as GD 0. The bred females (F₀ maternal animals) were randomly assigned to groups based on stratification of the GD 0 body weights. Iloperidone at oral doses of 0, 16 and 36/48 mg/kg/day was administered from gestation day 17 through post-partum (lactation) day 21. The progeny was not directly administered the test article during the study; the F₁ pups were potentially exposed to the test article *in utero* and during lactation, through maternal milk. F₀ females were allowed to deliver naturally and rear their pups to weaning (PND 21); females with total litter deaths and that did not deliver (up to post-mating day 25) were sacrificed. All surviving F₀ females with viable pups were sacrificed on postnatal day 21. A gross necropsy was performed for each of these females. F₁ litters were examined daily for survival and growth. Standardization of litter size to 8 pups per litter (4/ sex where possible) was performed on PN day 4 by a random selection. Following weaning, selected F₁ animals were assigned to either behavioral or reproductive capacity testing (following a 70-day maturation phase prior to breeding). Upon mating within the respective dose groups, pregnant F₁ females were allowed to deliver naturally and F₂ offspring were examined and sacrificed on postnatal day 1.

Parameters and endpoints evaluated: F₀ maternal animals: clinical signs and mortality (twice daily); weight (on gestation days 0, 7, 14, 17 and 20, and on lactation days 0, 4, 7, 10, 14, 17 and 21), food consumption (weekly throughout pregnancy and lactation) as well as pregnancy maintenance, parturition and lactation. F₀ females with viable pups on postnatal day 21, females with total litter loss and that did not deliver (up to post-mating day 25) were euthanized. A gross necropsy was performed for each of these females. For females that delivered, the numbers of former implantation sites were recorded. Uteri, ovaries and abnormal tissues were preserved in 10% neutral-buffered formalin for possible future histopathologic examination as deemed necessary by the gross findings. F₁ generation was examined for growth, viability and development, including reproductive and behavioral performance. F₁ litters were examined daily for survival and pups were individually weighed on PN days 1, 4, 7, 10, 14, 17, and 21. Standardization of litter size to 8 pups per litter (4/ sex where possible) was performed on PN day 4 by a random selection. During lactation and growth of F₁ pups, the following physical and neurobehavioral developmental evaluations were performed, beginning on the days listed and continuing until the entire litter attained a positive result, or until weaning (as listed in the sponsor's table below).

F1 pre-weaning development tests

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 10 seconds

At weaning (PN Day 21), 2 F1 pups per sex per litter were randomly selected for evaluation of sexual maturation (i.e., vaginal opening beginning on day 28 or testes descend beginning on day 22) and behavioral testing (i.e., open field activity on days 22 and 60, and learning capacity in water maze at the age of 42 days). Following a growth period of 70 days after weaning, F1 males and females (1 animal/sex/litter) were cohoused for up to 21 days within respective dose groups for mating. Body weight of pregnant F1 females was registered weekly; animals were observed daily for clinical signs, maintenance of gestation and parturition. Upon delivery, the F2 offspring were examined for viability and external abnormalities; F2 pups were sacrificed on postnatal day 1 and preserved in 10% neutral-buffered formalin. F1 parental males and females were sacrificed; gross necropsy was performed and abnormal viscera and reproductive organs were preserved in 10% neutral-buffered formalin.

Results

F₀ maternal:

Mortality: There was no spontaneous maternal mortality. There were 3 moribund sacrifices of pregnant HD females: one on gestation day 22 (clinical signs of labored respiration, "cold to touch", pale appearance) and 2 sacrifices *in extremis* following a prolonged delivery. Gross pathology findings of "mottled livers" were recorded in 2 of these cases, and "pale kidneys, pale placenta and distended stomach" – in 1 case. Additionally, 14 HD females and 1 female each in MD and LD groups were sacrificed following total litter deaths.

Clinical signs: Dose-related, apparently pharmacological signs of sedation, hypoactivity, ptosis were seen in all of the HD and in most of the MD animals, while in LD group only few animals exhibited clinical signs. At HD (before the dose reduction), the clinical signs persisted in all animals through the next day after dosing; after HD reduction from 46 to 38 mg/kg/day, all animals appeared free of clinical signs on the following day. The distribution of the HD pregnant females according to gestation day at the time of the HD reduction from 46 to 38 mg/kg/day is shown in the following sponsor's table. As shown in the table, the duration of dosing at the level of 46 mg/kg/day was not uniform for all HD animals.

Distribution of HD maternal females according to gestation day at the time of HD reduction from 46 to 38 mg/kg/day

Day Dose Level Changed:	Gestation Day						Lactation Day	
	18	19	20	21	22	24	0	1
No. of Animals	2	2	1	7	5	2	1	4
No. of litters surviving to Day 21	1	1	0	2	2	2	0	0

In parallel to sedation, a marked decrease in food consumption was noted in the HD group (by 50% vs. control on g. days 17-20). The mean maternal body weight on g. day 20 was approximately 12% lower in HD group in comparison to control. Mean body weight gain was decreased in all dose groups for the same time period, and was 15%,

22%, and 121% less than control at LD, MD, and HD, respectively (statistically significant at MD and HD). Since the start of dosing was on g. day 17, all these maternal effects occurred during the latter stages of gestation

Mean maternal (F0) body weight during gestation (g)

MEAN MATERNAL BODY WEIGHTS DURING GESTATION -- grams					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
DAY 0	MEAN	254.3	260.5	260.2	257.3
	S.D.	13.3	14.5	11.5	11.3
	N	25	23	24	23
DAY 7	MEAN	295.9	301.6	303.0	297.7
	S.D.	15.4	16.0	15.4	14.1
	N	25	23	24	23
DAY 14	MEAN	333.0	336.1	330.3	336.6
	S.D.	16.7	17.2	16.9	16.8
	N	25	23	24	23
DAY 17	MEAN	370.4	373.9	377.9	374.4
	S.D.	21.5	21.6	18.3	20.1
	N	25	23	24	23
DAY 20	MEAN	413.3	410.6	411.3	365.4**
	S.D.	26.9	26.2	23.9	25.9
	N	25	23	24	23

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

Mean maternal (F0) body weight gain during gestation (g/day)

MEAN MATERNAL BODY WEIGHT CHANGES DURING GESTATION - grams					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
DAYS 0 TO 7	MEAN	39.64	41.13	42.75	40.43
	S.D.	5.15	6.27	7.62	5.89
	N	25	23	24	23
DAYS 7 TO 14	MEAN	37.60	34.52	35.29	38.91
	S.D.	9.46	9.09	8.78	9.00
	N	25	23	24	23
DAYS 14 TO 17	MEAN	36.00	37.78	39.63	37.83
	S.D.	7.77	10.55	5.76	6.93
	N	25	23	24	23
DAYS 17 TO 20	MEAN	42.80	36.85	33.46*	-9.04**
	S.D.	9.84	10.89	10.84	15.43
	N	25	23	24	23
DAYS 7 TO 17	MEAN	74.46	72.30	74.92	76.74
	S.D.	13.48	14.66	9.64	10.72
	N	25	23	24	23
DAYS 0 TO 20	MEAN	157.00	150.09	151.13	108.13**
	S.D.	21.73	25.69	17.49	20.89
	N	25	23	24	23
DAYS 7 TO 20	MEAN	117.36	106.96	106.38	67.70**
	S.D.	20.12	23.48	16.91	19.56
	N	25	23	24	23

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

During lactation, the mean maternal body weight was significantly lower than control values at HD (postnatal days 0 through 17) and MD (postnatal days 10 through 17) by up to 12% and 7%, respectively; body weight gain was significantly lower than control values at HD during the 2nd postnatal week (by 94%) and at MD during the 3rd postnatal week (by 72%).

Mean maternal (F0) body weight during lactation (g)

MEAN MATERNAL BODY WEIGHTS DURING LACTATION -- SUMMARY					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
DAY 0	MEAN	315.2	317.0	309.3	296.1**
	S.D.	19.1	21.7	19.7	19.4
	N	25	23	24	22
DAY 4	MEAN	325.7	336.1	319.4	297.9*
	S.D.	38.1	21.1	19.6	12.8
	N	25	22	23	7
DAY 7	MEAN	338.8	339.0	328.7	307.2**
	S.D.	22.5	21.0	20.9	12.9
	N	25	22	23	8
DAY 10	MEAN	353.7	357.7	339.6*	308.0**
	S.D.	20.3	17.5	22.3	14.1
	N	25	22	23	6
DAY 14	MEAN	336.6	329.5	329.0	313.5
	S.D.	24.7	23.7	30.9	16.9
	N	25	22	23	6
DAY 17	MEAN	361.0	362.1	335.9*	319.8**
	S.D.	17.8	15.6	37.2	16.0
	N	25	22	23	6
DAY 21	MEAN	330.8	318.9	316.7	298.7
	S.D.	26.3	31.0	22.4	38.2
	N	25	22	23	6

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

Mean maternal (F0) body weight gain during lactation (g/day)

MEAN MATERNAL BODY WEIGHT CHANGES DURING LACTATION -- grams					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
DAYS 0 TO 4	MEAN	10.56	19.09	10.22	11.86
	S.D.	26.09	11.05	11.63	7.54
	N	25	22	23	7
DAYS 4 TO 7	MEAN	13.12	2.91	9.30	10.09
	S.D.	22.76	14.93	7.16	4.38
	N	25	22	23	8
DAYS 7 TO 10	MEAN	14.84	16.14	10.83	6.63*
	S.D.	12.58	13.13	6.75	3.25
	N	25	22	23	8
DAYS 10 TO 14	MEAN	-17.04	-27.79	-10.57	5.59
	S.D.	24.72	27.19	28.25	10.25
	N	25	22	23	8
DAYS 14 TO 17	MEAN	24.32	32.68	6.91*	6.33
	S.D.	22.53	24.43	29.69	7.17
	N	25	22	23	6
DAYS 17 TO 21	MEAN	-30.16	-43.27	-19.22	-21.17
	S.D.	20.86	26.60	36.03	34.38
	N	25	22	23	6
DAYS 0 TO 7	MEAN	23.68	22.00	19.52	23.83
	S.D.	13.88	19.57	12.04	8.18
	N	25	22	23	8
DAYS 0 TO 14	MEAN	21.48	12.41	19.78	30.17
	S.D.	20.39	26.99	31.93	15.20
	N	25	22	23	6
DAYS 0 TO 21	MEAN	15.64	1.82	7.48	15.33
	S.D.	25.45	27.97	25.56	29.71
	N	25	22	23	8

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

Mean food consumption was significantly decreased at HD compared to control on gestation days 17-20 (upon initiation of treatment) (by 50%) and on lactation days 14-17 (by 18%).

Therefore, the HD employed in this study was maternally toxic (even after the dose reduction from 48 to 36 mg/kg/day), based on maternal mortality (moribund sacrifices) and a marked significant reduction of body weight (by 12% vs. control) during gestation and lactation; signs of maternal toxicity were also present at MD, as demonstrated by

significant reductions in body weight gain during gestation and lactation and in mean body weight during lactation (by 7% vs. control). No signs of maternal toxicity were seen at LD.

F₀ reproductive performance and litter data

The treatment resulted in a dose-related prolongation of the duration of gestation (the mean duration of gestation in control, LD, MD and HD groups was 21.9, 22.1, 22.3 and 22.8 days, respectively), statistically significant at MD and HD. A prolonged delivery, lasting up to 24 hours, was observed in 30% of pregnant animals (n=7) at HD only. A parallel decrease in the proportion of liveborn pups was registered (the mean livebirth indices were 96, 91 and 58% at LD, MD and HD, respectively vs. 100% in control), along with increased number of stillbirths, excessive at HD (n= 15, 33 and 131 at LD, MD and HD, respectively vs. 1 in control). There was also a significant and marked increase in the postnatal offspring mortality at MD and HD, particularly during early postnatal life. The mean viability indices (N pups alive on Day 4 pre-cull/N liveborn) were 91%, 75% and 19% at LD, MD and HD, respectively vs. 98% in control). Total litter deaths occurred in 14 HD litters and in 1 litter each from MD and LD within the first 5 days of life. The mean viability indices at weaning (N pups surviving to weaning/N pups alive Day 4 post-cull) were decreased at the HD group (74% vs. 100% in control). Thus, the decrease in F1 viability at birth and postnatal survival was excessive at HD, and less pronounced but significant at MD, with a clear dose-dependence.

SEGMENT III STUDY IN RATS F ₀ GENERATION NATURAL DELIVERY DATA AND LITTER DATA -- SUMMARY					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
Females: Mated	N	25	25	25	25
	N	25	23	24	23
Pregnant	%	100	92	96	92
	N	25	23	24	22
Delivering	%	100	92	96	88
	N				
Duration of Gestation:	MEAN	21.9	22.1	22.3**	22.8**
	S.D.	0.4	0.5	0.5	0.7
	N	25	23	24	22
Females with Liveborn Pups	N	25	23	24	20
	%	100	100	100	87
	Gestation Index				
	Vith Stillborn Pups	N	1	6	11
	%	4.0	26	46	95
Females with no Liveborn Pups	N	0	0	0	2
Females with no Pups Delivered	%	0.0	0.0	0.0	9.1
	N	0	0	0	0
	%	0.0	0.0	0.0	0.0
Pups Delivered	TOTAL	372	323	360	310
	MEAN	14.88	14.04	15.33	14.45
	S.D.	3.73	4.62	2.28	3.11
	N	25	23	24	22
Liveborn	TOTAL	371	308	335	187
	TOTAL	1	15	30	117
	Uncertain	TOTAL	0	0	3
Implantation Sites	TOTAL	390	349	408	336
	MEAN	15.60	15.17	16.79	15.27
	S.D.	3.65	4.42	2.70	5.28
	N	25	23	24	22

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

N = Number of Females or litters

Reproduction Equations

Percent Pregnant = $\frac{\text{number of females pregnant}}{\text{number of females mated}} \times 100$

Gestation Index (Parturition Index) = $\frac{\text{number of females delivering live pups}}{\text{number of pregnancies}} \times 100$

Mated = Evidence of sperm or vaginal plug, or a litter was produced.

F1 GENERATION NATURAL DELIVERY DATA AND LITTER DATA -- SUMMARY					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 40/35 MG/KG/DAY
Pup Survival Indices					
Livebirth Index (Number born alive/number born)	MEANS	100	96	91	58
Viability Index (Number alive Day 4 precull/ number liveborn)	MEANS	98	91	75	19
Weaning Index (Number alive at weaning/ number alive at Day 4 postcull)	MEANS	100	100	98	74
Pup Disposition					
Culled day 4	TOTAL	167	122	71	4
Killed	TOTAL	0	0	0	7
Died	TOTAL	2	11	73	123
Cannibalized	TOTAL	0	1	2	8
Missing	TOTAL	3	3	14	13
Pups Surviving at 21 days	TOTAL	194	171	175	33
Pups Dying, Killed, Missing, and/or Cannibalized					
days 0-4	TOTAL	10	15	86	144
days 5-21	TOTAL	0	0	3	6
Entire Litter Died, Killed, Missing, and/or Cannibalized					
days 0-4	#	0	1	1	15
days 5-21	#	0	0	0	1
Total Number and Mean Males Percent by Litter					
day 0	TOTAL	173	150	171	101
	MEANS	45	51	50	58
day 4 precull	TOTAL	167	144	127	21
	MEANS	44	49	50	48
day 21	TOTAL	95	85	86	18
	MEANS	48	50	51	58

SIGNIFICANTLY DIFFERENT FROM CONTROL: * = P<0.05; ** = P<0.01.
 # = Number of Litters.
 TOTAL = Number of Pups or Implants.
 a Due to prolonged deliveries, the dams for litter Nos. 838621 and 838624 were sacrificed in extremis; all pups were killed on Day 6.

The high perinatal- and postnatal mortality (stillbirths and neonatal deaths) in F1 generation at HD and MD can be a consequence, at least in part, to the extended gestation and prolonged parturition through increased time from placental detachment to parturition and a delay or lack of maternal stimulation and nursing, as suggested by the sponsor. Signs consistent with lack of maternal care were documented in MD and HD (i.e., pups "apparently weak" in 2 MD litters and in 7 HD litters in first 2 weeks of life, "cold to touch" in 1 MD litter and in 4 HD litters in first 4 days of life, "pale pups" in 3 HD litters). Gross pathology examination of pups that died during lactation and pups culled on day 4 noted "empty stomachs" in 2 (1/1%), 2 (1.4%), 15 (8.6%) and 32 (13%) pups in 1 (4.3%), 2 (9.5%), 7 (30%) and 13 (59%) litters in Control, LD, MD, and HD groups, respectively, indicative of poor maternal care at MD and HD.

F₁ physical development:

Mean body weight values of F1 pups were significantly and dose-dependently lower in comparison to control at HD (by 15% at birth and by 32% on postnatal day 4, pre-cull) and at MD (by 6% at birth and by 13% on postnatal day 4, pre-cull), showing a retardation in prenatal, and particularly in early postnatal growth ant MD and HD. Postnatal body weight gains of F1 offspring from birth through weaning were markedly lower at HD relative to control values (see sponsor's tables on the next page).

F1 generation mean body weight

DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 40/36 MG/KG/DAY
Pup Weight/Litter (grams)					
day 0 MALES	MEAN	6.36	6.57	6.10	5.55
	S.D.	0.45	0.62	0.45	0.45
	N	24	23	23	18
	Covariate Adjusted MEAN	6.39	6.51	6.13	5.55**
day 0 FEMALES	MEAN	6.12	6.12	5.72	5.22
	S.D.	0.67	0.62	0.46	0.46
	N	25	22	24	17
	Covariate Adjusted MEAN	6.11	6.09	5.76*	5.23**
day 4 MALES - Precull	MEAN	9.67	10.84	9.25	7.78
	S.D.	1.58	1.64	1.34	1.83
	N	24	22	22	6
	Covariate Adjusted MEAN	10.31	11.17	9.14*	6.91**

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

N = Number of litters

F1 generation mean body weight gain from birth through weaning

Mean Pup Body Weight Gains Based on Covariate-Adjusted Means								
Interval	Males				Females			
	1	2	3	4	1	2	3	4
Days 0-4 (precull)	3.92	4.66	3.01	1.36	3.90	4.51	3.09	0.65
Days 0-4 (postcull)	4.08	4.71	3.08	1.35	3.92	4.55	3.15	0.76
Days 4 (postcull) - 7	5.47	6.18	5.66	4.99	5.34	6.04	5.61	5.37
Days 7-14	16.45	16.12	14.41	11.91	16.07	16.15	14.27	9.80
Days 14-21	20.44	18.84	17.26	15.19	18.70	17.64	16.18	14.04
Days 0-21	46.44	45.85	40.41	33.44	44.04	44.38	39.21	29.97

F1 Developmental landmarks: The attainment of developmental landmarks (eye opening, generalized hair growth, incisor eruption, pinna unfolding, gripping reflex, surface righting reflex, pupil and auditory reflexes, and sexual maturation) was apparently unaffected by treatment of the dams, although the pups were smaller in the MD and HD groups. The data are summarized in the following sponsor's table:

F1 generation: Developmental Landmarks

MEAN AGE IN DAYS OF PUPS REACHING CRITERION -- SUMMARY					
DOSE LEVEL		GROUP 1 0 MG/KG	GROUP 2 4 MG/KG	GROUP 3 16 MG/KG	GROUP 4 40/36 MG
TESTES DESCENDING	MEAN	27.65	27.09	27.48	29.32
	S.D.	0.38	0.75	0.88	0.92
	N	24	22	22	16
pups reaching criterion		100	100	100	100
VAGINAL OPENING	MEAN	33.54	33.55	33.61	33.57
	S.D.	1.20	1.20	1.45	0.91
	N	23	22	23	16
pups reaching criterion		100	100	100	100
EYE OPENING	MEAN	14.30	14.22	14.42	13.90
	S.D.	0.62	0.62	0.65	0.69
	N	23	22	23	16
pups reaching criterion		100	100	100	100
HAIR GROWTH	MEAN	9.80	9.41	9.73	9.22
	S.D.	0.76	0.67	0.76	0.64
	N	25	22	23	16
pups reaching criterion		100	100	100	100
INCISOR ERUPTION	MEAN	10.03	10.34	10.12	9.92
	S.D.	0.98	0.84	0.91	0.66
	N	23	22	23	16
pups reaching criterion		100	100	100	100
PINNA UNFOLDING	MEAN	2.84	2.59	2.99	2.69
	S.D.	0.62	0.64	0.87	0.77
	N	23	22	23	16
pups reaching criterion		100	100	100	100
GRIPPING REFLEX	MEAN	17.04	17.04	17.02	17.18
	S.D.	0.08	0.06	0.09	0.26
	N	23	22	23	16
pups reaching criterion		100	100	100	100

N = Number of litters

X pups reaching criterion = total number of pups with measure present/total number tested on first day of test.

F1 Behavioral evaluation (Open field activity, learning and memory)

Increased motor activity in open field test at weaning and maturity was observed at MD and HD relative to control. The significance of this finding in activity levels is unclear; it should be noted that the sample size in HD group was much smaller than control or other dose groups (6 vs. 24-25). There were no apparent differences between the treated groups and control in F1 generation learning and memory as tested in water maze at the age of 42 days.

F1 Open field testing – Mean activity counts

		Day 22			
		Activity Counts (5 Minute Blocks)			
Group		1-5	6-10	11-15	16-20
Males					
1 (Control)	Mean	257.83	137.28	84.33	41.86
	S.D.	55.28	57.38	70.90	50.47
	N	24	24	24	24
2 (Low)	Mean	288.23	180.59	113.95	71.86
	S.D.	55.96	62.19	69.15	61.52
	N	22	22	22	22
3 (Mid)	Mean	284.18	167.50	130.82*	75.88
	S.D.	89.82	64.78	83.88	66.01
	N	22	22	22	22
4 (High)	Mean	269.63	173.50	175.17*	120.33*
	S.D.	21.35	81.58	33.80	70.26
	N	6	6	6	6
Females					
1 (Control)	Mean	251.44	144.56	77.80	58.36
	S.D.	79.90	82.97	74.18	94.20
	N	25	25	25	25
2 (Low)	Mean	284.41	177.59	120.50	76.23
	S.D.	45.52	64.56	69.00	73.96
	N	22	22	22	22
3 (Mid)	Mean	287.27	195.77*	133.14*	89.73
	S.D.	73.45	82.85	64.37	72.77
	N	22	22	22	22
4 (High)	Mean	294.17	200.67*	142.33	127.50
	S.D.	24.62	19.50	62.21	68.79
	N	6	6	6	6

		Day 60			
		Activity Counts (5 Minute Blocks)			
Group		1-5	6-10	11-15	16-20
Males					
1 (Control)	Mean	485.25	375.13	282.04	214.33
	S.D.	90.40	79.91	76.29	85.97
	N	24	24	24	24
2 (Low)	Mean	518.91	409.27	295.73	249.95
	S.D.	113.88	97.29	91.42	103.16
	N	22	22	22	22
3 (Mid)	Mean	585.77	411.05	305.18	242.77
	S.D.	73.48	81.60	103.43	73.52
	N	22	22	22	22
4 (High)	Mean	520.50	393.67	313.17	288.83
	S.D.	90.03	76.04	89.59	90.80
	N	6	6	6	6
Females					
1 (Control)	Mean	551.68	400.92	359.20	262.28
	S.D.	84.52	83.55	86.39	86.55
	N	25	25	25	25
2 (Low)	Mean	566.82	453.05	358.64	282.95
	S.D.	63.49	83.50	66.44	79.39
	N	22	22	22	22
3 (Mid)	Mean	571.05	467.14*	393.14	329.05
	S.D.	100.35	91.30	115.19	106.26
	N	22	22	22	22
4 (High)	Mean	527.00	449.17	344.83	349.33
	S.D.	62.51	73.22	80.91	73.42
	N	6	6	6	6

*Significantly different from control p<0.05

F1 Reproductive Performance and F2 litter data

No effects were noted in F1 reproductive performance. The male and female fertility indices were 88%, 95%, 100% and 100%, and the livebirth indices were 99%, 99%, 98% and 100%, in Control, LD, MD, and HD group, respectively. The duration of pregnancy and parturition were similar between the treated groups and control. There were no neonatal deaths prior to the scheduled sacrifice of F2 litters on lactation day 1. The data are summarized in sponsor's tables reproduced below.

F1 Reproductive Performance Segment III Study in Rats F1 Generation				
	Group 1 0 mg/kg/day	Group 2 4 mg/kg/day	Group 3 16 mg/kg/day	Group 4 48/36 mg/kg/day
No. of males paired with at least one female	25	22	23	6
No. (%) of males successfully mated with at least one female	21 (84)	21 (95)	23 (100)	6 (100)
No. of females paired with at least one male	25	22	23	6
No. (%) females mated	24 (96)	22 (100)	23 (100)	6 (100)
No. aborted	0	0	0	0
No. delivered early	0	0	0	0
No. (%) females with abnormal gestation and delivery	0	0	0	0
Female Fertility	88	95	100	100
Male Fertility	88	95	100	100

Percent of Males Successfully Mated = $\frac{\text{number of males shown to be fertile}}{\text{number of males paired}}$

Percent of Females Mated = $\frac{\text{number of females mated}}{\text{number of females paired}}$

Percent Pregnant = $\frac{\text{number of females pregnant}}{\text{number of females paired}} \times 100$

Female Fertility Index = $\frac{\text{number of females pregnant}}{\text{number of females mated}} \times 100$

Male Fertility Index = $\frac{\text{number of males impregnating females}}{\text{number of males mated}} \times 100$

Gestation Index (Parturition Index) = $\frac{\text{number of females delivering live pups}}{\text{number of pregnancies}} \times 100$

Mated = Evidence of sperm or vaginal plug, or a litter was produced.

F1 MATURATION PHASE NATURAL DELIVERY DATA AND LITTER DATA -- SUMMARY						
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/D	
Females:	Mated	N	24	22	23	6
	Pregnant	N	21	21	23	6
	Delivering	N	88	95	100	100
		X	21	29	23	5
		88	91	100	83	
Duration of Gestation:	MEAN	21.8	22.0	21.8	22.0	
	S.D.	0.4	0.6	0.7	0.6	
	N	21	20	23	5	
Females with Liveborn Pups		N	21	20	23	5
	Gestation Index	X	100	95	100	83
	With Stillborn Pups	N	2	4	4	0
		X	9.5	20	17	0.6
Females with no Liveborn Pups	N	0	0	0	0	
	X	0.0	0.0	0.0	0.0	
Females with no Pups Delivered	N	0	0	0	1	
	X	0.0	0.0	0.0	20	
Pups Delivered	TOTAL	306	309	336	75	
	MEAN	14.67	15.45	14.61	15.00	
	S.D.	2.65	2.26	3.37	1.58	
	N	21	20	23	5	
Liveborn	TOTAL	306	305	329	75	
	Stillborn	TOTAL	2	4	7	0
	Uncertain	TOTAL	0	0	0	0
Implantation Sites	TOTAL	330	327	358	78	
	MEAN	15.71	16.35	15.57	15.60	
	S.D.	1.99	2.06	3.58	1.14	
	N	21	20	23	5	

The mean number of F2 pups born, live litter size, live born index (%), mean body weight and postnatal survival from birth to PND 1 in the treated groups were not significantly different from the control group.

SEGMENT III STUDY IN RATS F1 MATURATION PHASE NATURAL DELIVERY DATA AND LITTER DATA -- SUMMARY					
DOSE LEVEL		GROUP 1 0 MG/KG/DAY	GROUP 2 4 MG/KG/DAY	GROUP 3 16 MG/KG/DAY	GROUP 4 48/36 MG/KG/DAY
Females: Mated	N	24	22	23	8
	X	21	21	23	6
	Pregnant	83	95	100	100
	X	21	20	23	5
Delivering	N	88	91	100	83
	X				
Duration of Gestation:	MEAN	21.8	22.0	21.8	22.0
	S.D.	0.4	0.9	0.7	0.8
	N	21	20	23	5
Females with Liveborn Pups	N	21	20	23	5
	X	100	95	100	83
	Gestation Index	2	4	4	0
	X	9.5	20	17	0.0
Females with no Liveborn Pups	N	0	0	0	0
	X	0.0	0.0	0.0	0.0
Females with no Pups Delivered	N	0	0	0	1
	X	0.0	0.0	0.0	20
Pups Delivered	TOTAL	308	302	336	75
	MEAN	14.67	15.45	14.61	15.00
	S.D.	2.65	2.26	3.37	1.58
	N	21	20	23	5
Liveborn	TOTAL	306	305	329	75
	TOTAL	2	4	7	0
	TOTAL	0	0	0	0
Stillborn	TOTAL	2	4	7	0
	TOTAL	0	0	0	0
	TOTAL	0	0	0	0
	TOTAL	0	0	0	0
Uncertain	TOTAL	0	0	0	0
	TOTAL	0	0	0	0
	TOTAL	0	0	0	0
	TOTAL	0	0	0	0
Implantation Sites	TOTAL	330	327	358	78
	MEAN	15.71	16.35	15.57	15.60
	S.D.	1.90	2.06	3.58	1.14
	N	21	20	23	5

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

In conclusion, iloperidone oral administration to pregnant rats from gestation day 17 through parturition and up to lactation day 21 at doses of 4, 16 and 48/36 mg/kg/day, caused maternal general toxicity at HD and MD, expressed in maternal mortality (moribund sacrifices) at HD and decrease in maternal body weight and body weight gain at HD and MD during the treatment period, as well as in adverse maternal reproductive effects demonstrated by a significantly prolonged gestation (at MD and HD) and excessive prolongation of parturition (at HD), resulting in high pre- and postnatal mortality in F1 generation. The high perinatal- and postnatal mortality (stillbirths and neonatal deaths) in F1 generation at HD and MD can be a consequence, at least in part, to the extended gestation and prolonged parturition through increased time from placental detachment to parturition and a delay or lack of maternal stimulation and nursing. Signs consistent with lack of maternal care were documented in MD and HD. The growth of the surviving F1 offspring was impaired, as demonstrated by reduced pup weight at birth and weight gain through weaning. However, there was no apparent adverse effect on F1 development, including behavior, sexual maturation attainment and reproductive capacity at any of the administered dose levels. At the low dose, there were signs of maternal sedatory effect and decreased body weight induced by iloperidone exposure, but except for a slight increase in the stillbirth rate (mean 0.6/litter vs. 0.04 in control) there was no evidence of adverse effect on parturition, maternal care, pup survival, growth and development. Under the conditions of this study, the NOAEL is 4 mg/kg/day.

Reproductive and Developmental Toxicity: Summary and conclusions

The following studies were performed to assess the reproductive and developmental toxicity of iloperidone:

- Fertility (Segment I) study in rats;
- Embryofetal development (Segment II) study in rats and rabbits;
- Pre- and postnatal development (Segment III) study in rats.

The Segment I rat fertility study evaluated the effect of iloperidone on male and female gonadal function, mating behavior and fertility, as well as on the development of 2 generations 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. The pregnancy rate was lower in MD and HD groups (86%, and 60%, respectively, vs. 100% in control), statistically significant at 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. The duration of pregnancy was increased (statistically significant at MD and HD). 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). Embryofetal growth was retarded at HD, as indicated by a significantly lower mean fetal weight at term vs. control. 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 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 (this dose is 1.6 times the human exposure at MRHD (24 mg/day) on an mg/m² basis). The higher doses employed in this study induced dose-dependent decreased parental F0 fertility (male and female), prolonged gestation, increased prenatal and neonatal lethality of F1 progeny, and reduced F1 pre- and postnatal growth (as indicated by lower body weight at term and postnatally).

Segment II Prenatal developmental toxicity study in rats:

Iloperidone administration to pregnant Wistar rats at doses of 0 (control), 4, 16, and 64 mg/kg/day by oral gavage on Gestation Days 7 through 18 induced at HD and MD a significant dose-dependent reduction in maternal weight (by 18% and 6%, respectively, vs. control at term) and in maternal weight gain (by up to 92% and 34% of control values, respectively). Maternal food consumption was decreased at HD by up to 11% vs. control. Placental weights were statistically significantly lower at HD (by 17% vs. control) and MD (by 7% vs. control). Clinical signs associated with pharmacological action of the test agent (sedation, ptosis) were present in all dosed groups, dose-dependently. The high dose induced a marked (over 5-fold) increase in post-implantation embryonic lethality. Early post-implantation death of all conceptuses occurred in two thirds of the treated HD dams. The surviving HD fetuses exhibited growth retardation (as expressed by significantly decreased fetal weight and crown/rump length at term by 12% and 7%, respectively as compared to control, and retarded skeletal ossification). An increased incidence of minor skeletal abnormalities (fragmented and/or displastic thoracic vertebral centra) and skeletal variations (supernumerary thoracic rib) was registered in the HD group. No increase in external or visceral abnormalities was registered in any of the dosed groups. Intrauterine development was not adversely affected at MD and LD. The embryo/fetal lethality and mean fetal body weight and length in these groups did not differ appreciably from control.

In conclusion, based on the study findings, iloperidone induces developmental toxicity (expressed as embryofetal lethality, retarded intrauterine development and minor skeletal abnormalities) at oral doses above 16 mg/kg/day. Signs of maternal toxicity (reduced weight and weight gain, reduced placental weight) are induced at and above 16 mg/kg/day. The NOAEL for developmental toxicity in this study is 16 mg/kg/day (6 times the MRHD of 24 mg/day on an mg/m² basis).

The predominant circulating iloperidone metabolite in humans (P95) administered to pregnant rats at oral doses of 20, 80 and 200 mg/kg/day during the period of major organogenesis (Gestation Days 7 through 17), produced dose-dependent maternal pharmacological effect (signs of sedation) at all dose levels, but no maternal toxicity. Maternal plasma exposure (AUC) at the high dose was approximately 4 times the mean human plasma AUC of metabolite P95 when the parent compound (iloperidone) was administered at the dose of 24 mg/day (12 mg b.i.d.). The treatment did not induce

embryo/fetal mortality or congenital malformations but produced a dose-dependent increase in the incidence of retarded skeletal ossification vs. the concurrent control (predominantly manifested as incomplete ossification of skull bones) at all tested dose levels, ranging from 8% (LD) to 14% (HD). These values, however, were within the historical control range for the tested species and strain.

Segment II Prenatal developmental toxicity study in rabbits:

Iloperidone administration at oral (gavage) doses of 0, 4, 10 and 25 mg/kg/day to pregnant Himalayan rabbits from gestation day 6 through 18 caused maternal mortality at the HD (1/15) and induced dose-dependent drug-related clinical signs (sedation at all dose levels and ptosis at MD and HD). Maternal food intake was reduced at MD and HD. Maternal body weight gain was reduced at HD during the 1st week of treatment due to reduced food consumption, resulting in about 5% decrease in mean body weight vs. control on gestation days 13 and 19 (statistically significant). The high dose induced increase in embryo/fetal intrauterine lethality and a decrease in fetal viability at term. No signs of embryo/fetal toxicity or teratogenicity were observed in LD and MD groups. Based on these results, the NOAEL for embryo/fetal toxicity is 10 mg/kg/day (8x the MRHD of 24 mg/day on an mg/m² basis).

Segment III Prenatal and postnatal developmental toxicity study in rats

Iloperidone oral administration to pregnant CD rats from gestation day 17 through weaning (postnatal day 21) at doses of 4, 16 and 48/36 mg/kg/day, caused maternal toxicity statistically significant at HD and MD (maternal mortality at HD and dose-dependent decrease in maternal body weight at HD, MD and LD), significantly prolonged gestation and parturition, high perinatal- and postnatal mortality (stillbirths and neonatal deaths) in F1 generation at HD and MD, and some increase in stillbirth rate at LD (mean stillbirth rate per litter 0.6 vs. 0.04 in control). The high perinatal- and postnatal mortality in F1 generation at HD and MD can be a consequence, at least in part, to the extended gestation and prolonged parturition through increased time from placental detachment to parturition and a delay or lack of maternal stimulation and nursing. Signs consistent with lack of maternal care were documented in MD and HD. The growth of the surviving F1 offspring was impaired at MD and HD, as demonstrated by the reduced pup weight at birth and weight gain through weaning. However, there was no apparent adverse effect on F1 development, including behavior, sexual maturation and reproductive capacity, at any of the administered dose levels. At the low dose, there were signs of maternal sedation and decreased maternal weight induced by iloperidone exposure, but there was no evidence of adverse effect on parturition, maternal care, pup survival, growth and development. Under the conditions of this study, the NOAEL was 4 mg/kg/day (1.6 times the human dose at the MRHD on an mg/m² basis).

2.6.6.7 Local tolerance

Local tolerance studies were conducted with iloperidone and its manufacturing intermediates as summarized in the following sponsor's table.

Iloperidone

			Test Article: Iloperidone		
Species/ Strain	Method of Administration	Doses	Gender and No. per Group	Noteworthy Findings	Study No.
Rabbit/ New Zealand White	Ocular	100 mg	M, F 3	Iloperidone was determined not to be a primary eye irritant.	0793-220
Rabbit/ New Zealand White	Topical	0.5 g	M, F, 3	Iloperidone was determined not to be a primary dermal irritant.	0693-220

Iloperidone manufacturing intermediates

Test article	Species/Strain	Method of Administration	Duration of Dosing	Doses	Test Article: Iloperidone metabolites		Study No.
					Gender and No. per Group	Approximate Median Lethal Dose or Noteworthy Findings	
	Rabbit/New Zealand White	Ocular	Acute (single dose)	100 mg	M, F 3	was determined to be moderately irritating to the eye	2294
	Rabbit/New Zealand White	Topical	Acute (single dose)	0.5 g	M, F 3	was determined to be a dermal non-irritant	2394
	Guinea Pig/ Hartley	Topical	Acute (induction/ challenge dose)	0.4 mL of 10%, 25%, and 50% solution (induction phase) and 100 mg of 100% solution (challenge phase)	M, F 10 for water/ 5 for water/ water 3 for positive control/ positive control	was not considered to be a dermal sensitizer in guinea pigs	1095
	Rabbit/New Zealand White	Ocular	Acute (single dose)	100 mg	M, F 3	was determined to be minimally irritating to the eye	1494
	Rabbit/New Zealand White	Topical	Acute (single dose)	0.5 g	M, F 3	was determined to be a dermal non-irritant	1594
	Guinea Pig/ Hartley	Topical	Acute (induction/ challenge dose)	100 mg	M, F 10 for water/ 5 for water/ water 3 for positive control/ positive control	was not considered to be a dermal sensitizer in guinea pigs	1195
	Rabbit/New Zealand White	Ocular	Acute (single dose)	50 mg	M, F 3	was determined to be moderately irritating to the eye	1894
	Rabbit/New Zealand White	Topical	Acute (single dose)	0.5 g	M, F 3	was determined to be a dermal non-irritant	1994
	Guinea Pig/ Hartley	Topical	Acute (induction/ challenge dose)	100 mg	M, F 10 for water/ 5 for water/ water 3 for positive control/ positive control	was not considered to be a dermal sensitizer in guinea pigs	1295

b(4)

b(4)

b(4)

Local tolerance studies, Iloperidone manufacturing intermediates (Continued)

					Test Article: Iloperidone metabolites		
Test article	Species/Strain	Method of Administration	Duration of Dosing	Doses	Gender and No. per Group	Approximate Median Lethal Dose or Noteworthy Findings	Study No.
	Rabbit/New Zealand White	Ocular	Acute (single dose)	100 mg	M, F 3	_____ was determined to be minimally irritating to the eye	2694
	Rabbit/New Zealand White	Topical	Acute (single dose)	0.5 g	M, F 3	I _____ was determined to be a dermal non-irritant	2794
	Guinea Pig/Hartley	Topical	Acute (induction/challenge dose)	100 mg	M, F 5 for water/ 5 for water/ water 3 for positive control/ positive control	_____ was not considered to be a dermal sensitizer in guinea pigs	1395

b(4)

Iloperidone

Primary eye irritation studies of iloperidone in rabbits (Study 0793-220)

The potential to produce eye irritation in New Zealand White rabbits (3/sex) was evaluated following a single topical application of iloperidone (100 mg). Treated eyes were examined for gross signs of eye irritation at 24, 48, and 72 h post-instillation and graded for iloperidone or for each metabolite. Based on clinical findings and eye irritation grading, iloperidone was not considered to be a primary eye irritant.

Primary dermal irritation study of iloperidone in rabbits (Study 0693-220)

The potential to produce skin irritation in New Zealand White rabbits (3/sex) was evaluated following a single topical application of iloperidone (0.5 g), applied at 2 sites per animal. Treatment sites were treated with powder aliquots of the test material, and covered with bandages for 24 hours post-application. Application sites were examined for gross signs of skin irritation at 24, 48, and 72 hours post-application and graded based on the Draize system. The results of these studies indicated that iloperidone is not a primary dermal irritant.

Iloperidone-manufacturing intermediate _____

Primary eye irritation studies of _____ in rabbits (Study 2294)

The potential for iloperidone production intermediate _____ to produce eye irritation in New Zealand White rabbits (3/sex/group) was evaluated following a single topical application of _____ (100 mg). Treated eyes were examined for gross signs of eye irritation at 24, 48, and 72 h post-instillation. Based on clinical findings and eye irritation grading, _____ was determined to be moderately irritating to the eye.

b(4)

Primary dermal irritation studies of _____ in rabbits (Study 2394)

The potential of _____ to produce skin irritation in New Zealand White rabbits (3/sex) was evaluated following a single topical application of _____ (0.5 g), applied at 2 sites per animal. Treatment sites were treated with powder aliquots of the test material, and covered with bandages for 24 hours post-application. Application sites were examined for gross signs of skin irritation at 24, 48, and 72 hours post-application and graded based on the Draize system. The results of these studies indicated that _____ is not a primary dermal irritant.

Dermal sensitization studies of _____ a guinea pigs (Study 1095)

The dermal sensitization of _____ was assessed in Hartley guinea pigs (23/sex). During the induction phase of the study, test material (100 mg of active test product or negative [distilled water] and positive [1-chloro-2,4-dinitrobenzene] control materials) was applied to the _____ patch, and the area was bandaged. Approximately 6 hours after dosing, patches were removed and the treated sites were moistened with distilled water. This procedure was repeated 3 times a week for 3 weeks, totaling 9 induction exposures. For the challenge phase, test material (100 mg of active test product, positive control material, or distilled water) was applied once, 18 days after the last induction application. The animals were examined for signs of irritation at 24 and 48 h. following each induction and challenge patch application, and responses were scored using a Primary Dermal Reaction scale. No dermal reactions to _____ were noted at 24 or 48 hours post-application during either the induction or challenge phase of the studies. Dermal reactions were noted at 24 and 48 hours in all animals treated with the positive control during both the induction and challenge phase. Therefore, _____ is not considered to be a dermal sensitizer in guinea pigs.

b(4)

Iloperidone manufacturing intermediate _____

Primary eye irritation study of _____ rabbits (Study 1494)

The potential to produce eye irritation in rabbits following a single topical application was evaluated for _____ (100 mg) using the same design described above _____ was determined to be minimally irritating to the eye.

Primary dermal irritation studies of _____ in rabbits (Study 1594)

The potential to produce skin irritation in rabbits following a single topical application was evaluated for iloperidone manufacturing intermediate _____ (0.5 g) in New Zealand White rabbits using the same design used for _____ as described above. The results indicated that _____ not a primary dermal irritant.

b(4)

Dermal sensitization studies of _____ guinea pigs (Study 1195)

The dermal sensitization capability of iloperidone manufacturing intermediate _____ was evaluated in Hartley guinea pigs using the same design used for _____ as described above. No dermal reactions to _____ were noted at 24 or 48 hours post-application during either the induction or challenge phase of the studies.

Iloperidone manufacturing intermediate _____

Primary eye irritation studies of _____ rabbits (Study 1894)

The potential to produce eye irritation in rabbits following a single topical application was evaluated for _____ (50 mg) in New Zealand White rabbits. Based on clinical findings and eye irritation grading, _____ was determined to be moderately irritating to the eye.

b(4)

Primary dermal irritation studies of _____ n rabbits (Study 1994)

The potential to produce skin irritation in rabbits following a single topical application was evaluated for iloperidone production intermediate _____ (0.5 g) in New Zealand White rabbits. The results indicated that iloperidone _____ is not a primary dermal irritant.

Dermal sensitization studies of _____ in guinea pigs (Study 1295)

The dermal sensitization of iloperidone production intermediate _____ was assessed in Hartley guinea pigs. No dermal reactions to _____ were noted at 24 or 48 hours post-application during either the induction or challenge phase of the studies.

Iloperidone manufacturing intermediate _____

Primary eye irritation studies of _____ n rabbits (Study 2694)

The potential to produce eye irritation in rabbits following a single topical application was evaluated for _____ (100 mg) in New Zealand White rabbits. Based on clinical findings and eye irritation grading _____ was determined to be minimally irritating to the eye.

Primary dermal irritation studies of _____ n rabbits (Study 2794)

The potential to produce skin irritation in rabbits following a single topical application was evaluated for _____ (0.5 g) in New Zealand White rabbits. The results indicated that _____ is not a primary dermal irritant.

Dermal sensitization studies of _____ n guinea pigs (Study 1395)

The dermal sensitization of _____ was assessed in Hartley guinea pigs. No dermal reactions to _____ were noted at 24 or 48 hours post-application during either the induction or challenge phase of the study.

In summary, the local tolerance studies showed that iloperidone was no primary eye or dermal irritant in rabbits. Iloperidone production intermediates _____ were minimally to moderately irritating to the eye, but none of these agents were determined to be a primary dermal irritant or dermal sensitizer.

2.6.6.8 Special toxicology studies

Special toxicology studies included immunotoxicity and ototoxicity studies in rats and guinea pigs, respectively, upon 1-week oral administration of iloperidone (ototoxicity study) or 4-week oral administration of iloperidone and its metabolite P95 (immunotoxicity study). No immunotoxicity or ototoxicity were noted in these studies. The design and findings of these studies are summarized in the following sponsor's table.

Other Toxicity Studies

Test Article	Species/Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study No.
Immunotoxicity							
Iloperidone and P95-12113	Rat/ Sprague-Dawley CD [®] (SD)BR)	p.o.	4 weeks	0, 4, 24, 50, 500	M, F 10	NOEL: Iloperidone: 24 mg/kg P95: 500 mg/kg No immunotoxicity observed with either test article.	89941
Ototoxicity							
Iloperidone	Guinea pig/ Not stated	p.o.	Acute (Single dose and multiple doses for 1 week)	Single: 200 and 400 Multiple: M: 200 F: 100	M, F 4	All females died at ≥200 mg/kg dose No evidence of auditory effects at any dose in either sex	95-1

b(4)

b(4)

Four-week oral (gavage) immunotoxicity study of ILO522 and ILO522 P95 metabolite in rats (Study 89941)

The potential immunotoxicity of iloperidone and its metabolite P95 12113 was studied upon a 4-week oral (gavage) administration to Sprague-Dawley CD-1:CD® (SD)BR rats (10/sex/dose) at iloperidone doses of 4 and 24 mg/kg/day, and P95 doses of 50 and 500 mg/kg/day. At study termination, hematological investigation and phenotype and natural killer cell assays were performed. Organ weights and macroscopic and microscopic examinations revealed no test article-related findings. There were no significant changes in lymphocyte subsets or natural killer cell activity associated with iloperidone or P95 12113 administration. It was concluded that administration of iloperidone or its metabolite P95 12113 resulted in no significant changes in the immune system. The NOEL for immunotoxicity was 24 mg/kg/d for iloperidone and 500 mg/kg/d for P95.

b(4)

Ototoxicity study in guinea pig (Study 95-1)

The effects of single and multiple (7 days) oral doses of iloperidone on auditory function were evaluated in male and female guinea pigs. The single-dose experiment was conducted at doses of 200 and 400 mg/kg for both males and females; the multiple-dose experiment used doses of 200 mg/kg for males and 100 mg/kg for females, based on the MTD determined in a preliminary dose-ranging study (200 and 100 mg/kg/d for males and females, respectively). Neither the single- nor multiple-dose experiment revealed No change in auditory function vs. control (saline) was found in either males or females treated with iloperidone. It was concluded that iloperidone is not ototoxic in guinea pigs.

2.6.6.9 Discussion and Conclusions
(As provided under specific chapters)

2.6.6.10 Tables and Figures
(Provided in the text)

2.6.7 TOXICOLOGY TABULATED SUMMARY

Sponsor's tables of pivotal studies pertinent to the primary indication and core pharmacology studies relevant to the primary pharmacodynamic effect are provided in the text

mg/day). However, mammary tumor incidences were not increased in the mid- and high-dose groups, although the duration of treatment was the same in the mid-dose and low dose groups. It is not clear why similar increases in mammary tumor incidences were not seen at higher doses.

- Iloperidone administration to rats for 2 years was not carcinogenic in males; in females, it produced an increased incidence of combined pancreatic benign and malignant islet cell tumors (islet cell adenomas and carcinomas) at HD that approached but did not reach the level of statistical significance required for common tumors ($\alpha=0.005$). Having in mind that the incidences of pancreatic islet cell tumors in this study were within the reported historical control range for this species and strain and that there was no other evidence indicating a treatment-related effect (such as multiplicity of tumors, increased incidence of pre-neoplastic findings), it is concluded there was no carcinogenic effect in either male or female rats attributable to the test article.
- In view of the proliferative effects seen with iloperidone metabolite P95 in the 6-month rat study, the Division required a 2-year carcinogenicity study with P95 in the rat which is ongoing (CAC meeting of March 25, 2008).
- Iloperidone induces decreased fertility, prolonged gestation, increased prenatal and neonatal mortality, and retarded growth of the progeny upon oral administration to male and female rats for a period starting 10 weeks prior to mating (males) or 2 weeks prior to mating (females) and continuing through gestation, parturition and lactation. The NOAEL is 4 mg/kg/day (1.6 times the human dose at MRHD (24 mg/day) on an mg/m² basis).
- Iloperidone oral administration to pregnant rats and rabbits during the period of major organogenesis induces developmental toxicity (embryofetal lethality in both species, retarded intrauterine development and minor skeletal abnormalities in the rat) at doses that are maternally toxic. The NOAEL for developmental toxicity is 16 mg/kg/day in rats and 10 mg/kg/day in rabbits (6- and 8 times, respectively, the human dose at MRHD of 24 mg/day on an mg/m² basis).
- Iloperidone perinatal and postnatal administration to rats (Gestation day 17 through postnatal day 21) produced, at maternally toxic doses, prolonged gestation and parturition, increased incidence of stillbirths, neonatal mortality, and retarded growth of progeny up to weaning, but did not affect neurobehavioral and reproductive development of the surviving pups. The NOAEL is 4 mg/kg/day (1.6 times the human dose at MRHD (24 mg/day) on an mg/m² basis).

Unresolved toxicology issues (if any):

Metabolite P95 2-year carcinogenicity study in rats is ongoing.

Recommendations: Approvable

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 Trade Secret / Confidential (b4)

~~X~~ Draft Labeling (b4)

~~X~~ Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Sonia Tabacova
6/30/2008 04:12:16 PM
PHARMACOLOGIST

Barry Rosloff
6/30/2008 04:55:08 PM
PHARMACOLOGIST

Tertiary Pharmacology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology
OND IO

NDA: 22-192

Submission date: September 27, 2007

Drug: iloperidone

Sponsor: Vanda Pharmaceuticals

Indication: Adults with schizophrenia

Reviewing Division: Division of Psychiatry Drug Products

Introductory Comments:

The pharm/tox reviewer and supervisor found the nonclinical information submitted for iloperidone to be sufficient to support its use for the proposed indication.

Reproductive and developmental toxicity:

The reviewer agreed with the sponsor's proposed pregnancy category of C. Studies in rats and rabbits showed that iloperidone induced embryotoxicity and growth/developmental delays. The metabolite P95 when tested alone in rats produced delayed skeletal ossification. Although some of these effects were observed at doses that induced some maternal toxicity, the toxicity was not excessive and so the effects may be due to direct effects of the drug and may not be only secondary to maternal toxicity. It is appropriate to include these findings in labeling and assign pregnancy category C.

Carcinogenicity:

No increase in tumors attributable to iloperidone was noted in male or female rats. Female mice had an increased incidence of mammary tumors although only in the low dose group (2.5 mg/kg/day). The increase was statistically significant, was notably above the historical range, and appeared to be drug related. The Executive Carcinogenicity Assessment Committee concluded that this finding could be included in the labeling. It was not clear why similar increases were not seen at higher doses.

The predominant human metabolite, P95, is a relatively minor metabolite in rodents. Consequently, the applicant conducted a 6 month study in rats of P95. P95 induced proliferative changes in multiple organs/tissues. The division, in consultation with the Executive Carcinogenicity Assessment Committee, recommended that the applicant conduct a carcinogenicity study of P95. The applicant submitted a protocol for a 2 year study in rats and recommended doses were provided to the applicant from the Executive Carcinogenicity Assessment Committee on June 14, 2007. This study is ongoing. The division agreed that this study could be submitted post approval provided that the labeling described the proliferative response observed with P95 in the 6 month study.

Conclusions:

I concur with the Division pharm/tox conclusion that the nonclinical data support approval of this NDA for adults. I concur with the labeling recommended by the reviewer.

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Paul Brown
7/22/2008 03:22:35 PM
PHARMACOLOGIST

Executive CAC

Date of Meeting: March 25, 2008

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
William Taylor, Ph.D., DSPTP, Alternate Member
Barry Rosloff, Ph.D., OND DPP, Team Leader
Sonia Tabacova, Ph.D., OND DPP, Presenting Reviewer

Author of Draft: Sonia Tabacova, Ph.D.

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

NDA # 22-192

Drug Name: Iloperidone

Sponsor: Vanda Pharmaceuticals

Background: Iloperidone, a new drug proposed for the treatment of schizophrenia, belongs to the chemical class of piperidiny-benzisoxazole derivatives and acts as an antagonist at selected dopaminergic, serotonergic, and adrenergic receptors. It has high (nM) affinity for 5HT_{2A}/NE_{α1}/NE_{α2c}/D₂/D₃/5HT_{1A} receptors in humans.

The protocols of the 2-year carcinogenicity studies of iloperidone in rats and mice were previously approved by the Executive CAC and the doses were selected in accordance with the Executive CAC recommendations (IND 36827, Interoffice Memorandum by Dr. J. De George of 7/20/1993 re. rat study protocol and IND 36827, Pharm/Tox Memorandum by Dr. L. Freed of 9/14/1994 re. mouse study protocol).

Rat Carcinogenicity Study: A 24-month oral oncogenicity study of ILO 522 in rats (Study No. 988054)

In the rat CD (SD) carcinogenicity study conducted at doses of 4, 8, and 16 mg/kg/d for 24 months, the treatment did not affect survival, but induced a dose-related, significant decrease in mean body weights in the dosed groups vs. control, by 13%, 22% and 28% in males and by 10%, 17% and 21% in females at the low dose, medium dose and high dose, respectively, as well as a decrease in food consumption and pharmacological clinical signs at all doses that subsided during the course of the study. Body weight gains in the treated groups normalized after the first 3-4 months of study and there were no signs of systemic toxicity in either clinical pathology or histopathology parameters. Signs of pharmacological effect were present at all dose levels, manifested in clinical signs and dose- and time-dependent pronounced increase in serum prolactin in both genders. Effects were much more pronounced in females, which exhibited non-neoplastic proliferative mammary changes (glandular hyperplasia and galactoceles, all dose levels). In males, there was no significant increase in neoplastic incidence or dose-dependence for any of the observed tumor types or combinations. In females, the combined incidences for pancreatic islet cell adenomas and islet cell carcinomas were increased (2, 2, 0, 3, and 7 for the two controls, LD, MD and HD, respectively). The incidence value at the high dose was within the historical control range for this species

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and strain and was not statistically significant ($p > 0.05$) in the pair-wise comparison of high dose vs. control incidence values; the dose-response trend analysis showed a p-value of 0.0051 that approached but did not reach the level of statistical significance required for common tumors ($\alpha = 0.005$). There was no increase in the incidence of other tumors or tumor combinations of any type, including mammary tumors.

An MTD was achieved or exceeded in this study, based on decreases in mean body weight of over 10% in all treated groups.

In conclusion, based on the lack of a dose-response relationship or statistically significant increase in tumor incidence in any of the observed tumor types in a valid carcinogenicity study, there was no carcinogenic effect in male and female rats attributable to the test article.

Mouse Carcinogenicity Study: A 24-month oral oncogenicity study of ILO 522 in mice (Study No. _____)

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Iloperidone administration to CD-1 (ICR) BR mice at doses of 2.5, 5, and 10 mg/kg/d in 2% aqueous starch by gavage caused a dose-dependent decrease in survival in females from all treated groups and in males at the high dose. For this reason, the high dose groups (both male and female) were terminated at study week 82 when the survival was approximately 33% for both genders and the number of survivors was 21 per sex. All the remaining females from the low dose, mid dose and control groups were discontinued at study week 90 when the survival was 33% and 32% in the low dose- and mid dose female groups, respectively, vs. 63% and 65% in the control female groups. For the remaining males, the duration of dosing was 104 weeks, and the survival rate at study week 103 was 42% and 38% in the low dose- and mid dose male groups, respectively, vs. 50% and 48% in the control male groups. Mean body weight was slightly decreased in all dosed male groups (the average difference vs. control was -4% and the maximal difference was -7.4%) and increased in all dosed female groups (the largest difference vs. control was +13%). Mean food consumption was increased in all treated groups of both genders throughout the study.

An increased incidence of malignant mammary tumors was seen in females at the lowest dose only (23% vs. 0%, 2% in Control 1 and 2; 3% in MD and 2% in HD groups); the incidence seen at the low dose group was higher than the historical control range for this species and strain. On an mg/m² basis, there is no safety margin between the lowest dose employed in the mouse carcinogenicity study (2.5 mg/kg/day) and the maximal recommended dose in humans (24 mg/day). However, iloperidone administration showed no dose relationship to mammary tumorigenesis. Mammary tumor incidences were not increased in the mid- and high-dose groups, although the duration of treatment was the same in the mid-dose and low dose groups. Increased incidence of proliferative mammary changes (duct ectasia/ galactocele and glandular hyperplasia) was seen in females from all dose groups without dose dependence.

The sponsor attributed the mammary gland changes, including the increased incidence of tumors at the low dose, to endogenous hormonal imbalances triggered by increased prolactin secondary to pharmacological inhibition of the dopamine receptor. Prolactin determination was performed once, at study week 4, in 10 animals/sex/group. Prolactin levels were increased in both genders; a dose-response was apparent for males but not for females.

Drug-related non-neoplastic lesions were observed in all treated groups and were noted in female mammary gland (proliferative mammary changes, i.e., glandular hyperplasia and duct ectasia/galactocele), uterus (uterine adenomyosis), in the heart (cardiomyopathy and/or atrial thrombosis) and in the lung (chronic interstitial inflammation/fibrosis and alveolar macrophages). Generally, the incidences of these findings did not increase dose-dependently.

The MTD in the mouse study was exceeded in the females based on the decreased survival in all iloperidone-treated female groups as compared to the control group. For the males, the MTD was 5 mg/kg/day based on a significant mortality increase at the next tested dose level of 10 mg/kg/day.

Executive CAC Recommendations and Conclusions:

Mouse:

- The Committee agreed that the study would be accepted, noting prior agreement on doses by the Exec CAC. The Committee noted that termination of some groups may have been conducted prematurely in this case, reducing the power of the test to detect neoplasms.
- The incidence of mammary tumors in the low dose females was significantly increased, was notably above the historical range, and appeared to be drug related. The Exec CAC believes this should be included in the labeling. It was not clear why similar increases were not seen at higher doses.

Rat:

- The Committee agreed that the study was adequate, noting prior agreement by the Exec CAC
- The Committee found that there were no statistically significant tumors attributable to the test article.

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

cc:\n
/Division File, DPP
Barry Rosloff /Team leader, DPP
Sonia Tabacova/Reviewer, DPP
Kimberly Updegraf/CSO/PM, DPP
/ASeifried, OND IO

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David Jacobson-Kram
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