4. **Hematology Changes**: A decrease of eosinophils counts were seen in treatment related manner in animals included in palonosetron treatment groups (eosinophil counts were 0.17 to $0.22X10^9/l$ in males and were 0.12, 0.14, 0.13, 0.14 and $0.06X10^9/l$ in females belonging 2 control and 3 treatment study groups. The differences were only of statistical importance.

5. **Toxicokinetic/Plasma concentration Estimation**: The peak plasma concentrations on day 1 were less than the concentrations seen on week 26, 52, 78 and 104. The steady state was not reached on day 1. The increase in peak plasma concentrations of the compound was linear but non-dose proportional. The plasma concentrations of the compound were more in females than males. On week 26, the plasma concentrations (AUC values) were 136.9 and 308.2 times the AUC value in man reported by sponsor in a study at the suggested clinical dose of 5 ug/kg. The pharmacokinetic data of the study animals are shown in the following tables. The half-lives of the palonosetron in males included in high dose treatment group were estimated to be 1.5, 2.2 and 2.1 hr on study weeks 26, 52 and 78 (not calculated for study day 1 and week 104). The half-life of the compound in females was more variable as it was 0.8 to 4.2 hr on study week 26, 0.8 to 2.4 hr on week 52 and 78. The plasma concentrations (Cmax and AUC values) of the compound in male and female rats are shown below (sponsor's table)

TABLE 21

Pharmacokinetic parameters of Palonosetron on Day 1 and during Weeks 26, 52, 78 and 104 of 104-Week Rat Carcinogenicity Study[1]

a. Cmax (ng/ml)

Sex	Doses		Cmax			
M	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
	15	19.48	253.2	99.8	119.6	120.3
	30	153.4	593.3	212.8	557.8	276.9
	60	427.3	1744.7	1293.7	1521.2	1117.5
F	15	25.90	119.7	392.7	350.6	181.4
	45	141.2	718.7	1224.6	1180.7	662.8
	90	702.8	1645.2	2349.7	1288.0	2014.0

b. **$AUC_{(0-24hr)}$ (ng.h/ml)**

Sex	Doses		$AUC_{(0-24hr)}$ (ng.h/ml)			
M	(mg/kg/day)	Day 1	Wk26	Wk 52	Wk 78	WK 104
	15	38.8	195.0	215.3	462.6	311.5[a]
	30	361.7	372.1	1088.5[a]	1606.6	1766.8
	60	1402.0	4078.4	6139.5	6294.8	4968.0[b]
F	15	39.3	211.3	662.4	624.8	275.0[a]
	45	479.6	2758.8	3308.4	3391.4	4162.3[a]
	90	2511.2	9185.3	14933.3	6441.7	9537.2[a,c]

Cmax values calculated from 3 animals; except [a]2 animals; $AUC_{(0\text{-}24hr)}$ values calculated from 18 samples, except [a]17 samples, [b]15 samples, c = samples taken during week 103; [1] = 65 of rats/group

At the peak levels, the metabolite RS-17825-007 levels were present in a linear but in a non-dose proportional manner within 0.25 to 1 hr post dosing of palonosetron in mid and high dose treatment groups. AUC values of the metabolite from study week 26 to 104 were similar indicating that the compound and metabolite were not accumulated after the repeat administration of the compound. The metabolite to compound ratio was higher after repeat dosing than the single dose of the compound and the half life of the compound at different intervals were not estimated from the data. The pharmacokinetic profile of the metabolite is tabulated below (tables taken from sponsor submission):

TABLE 22

Pharmacokinetic parameters of Rs-17825-007 on Day 1 and during Week 26, 52, 78 and 104 of 104-Week carcinogenicity Study in Rats[1]

Sex	Doses (mg/kg/day)	Cmax (ng/ml) Day 1	Wk26	Wk 52	Wk 78	WK 104
M	15	BLQ	BLQ	11.5	14.0	BLQ
	30	BLQ	43.1	43.9	55.4	18.7
	60	32.4	117.8	55.5	60.5	53.2
F	15	BLQ	BLQ	22.4	18.4	BLQ
	45	BLQ	53.1	77.3	91.2	38.4
	90	56.33	93.8	96.3	55.9	59.3

b. $AUC_{(0\text{-}24hr)}$ (ng.h/ml)

Sex	Doses (mg/kg/day)	$AUC_{(0\text{-}24hr)}$ (ng.h/ml) Day 1	Wk26	Wk 52	Wk 78	WK 104
M	15	a	a	a	a[a]	a
	30	19.4	234.6	208.8	80.5	50.7
	60	90.2	669.3	353.4	360.4	258.3
F	15	a	a	a	a	a
	45	15.5[b]	200.7	157.4	292.9	160.2[b]
	90	298.6	630.9	671.7	305.4	337.4[bc]

Cmax values calculated from 3 animals; except [a]2 animals; [b]sample taken during week 103, [a] $AUC_{(0\text{-}24hr)}$ values not calculated, $AUC_{(0\text{-}24hr)}$ values calculated from 18 samples, except [b]17 samples, c = samples taken during week 103; [1] = 65 of rats/group

Orally administered palonosetron produced a dose related but non-proportional plasma peak concentration from low to high doses of the study. The estimated half lives was short, i.e., from 1.5 to 2.2 hr in males and 0.8 to 4.2 hr in females during the study as shown in the table above. There was no evidence of accumulation of the compound during the study. The study indicated that the exposure of the compound in female was higher than male animals during the study.

6. **Organ Weights Changes**: The absolute weight of liver was increased by 24.0 and 23.0% in males and females and, adrenal weight was increased by 37.5% and 30.9% in males and females included in high dose treatment group. The mean absolute weight of lung/bronchi and spleen were increased by 8.4 and 46.0% among males of high dose treatment group. The absolute weight of spleen of the animals of high dose treatment group was increased by 33.1 and 21.3% in males and females, respectively. The absolute weights of salivary glands and testes in males of high dose treatment group testes were lower than control animals by 12.2 and 56.3%, respectively. The absolute weight of ovaries was decreased in a treatment related manner, i.e., 70.5, 72.5 and 71.6% among females of low, mid and high dose treatment groups, respectively. The mean relative weight (in relation to body weight) of liver was increased by 36.8 and 56.1% in male and female of high dose treatment group and, uterus + cervix relative weight was reduced by 1.7, 2.32 and 2.5 times than the weight of the tissues of the control group animals.

7. **Physical Examination/Ophthalmoscopic Changes**: These changes were not observed during the study.

8. **Gross Pathology Changes**: At sacrifice, an increase in the incidences of dark areas in adrenals was seen in 2, 0, 1, 4 and 8 males and, 9, 11,15, 19 and 15 females included in 0, 0, low, mid and high dose treatment groups, respectively. Enlarged adrenal was seen in 2 males of high dose treatment group. Small epididymides was seen in 0, 0, 2, 1 and 11 males of control 1, control 2, low, mid and high dose treatment groups, respectively. The enlarged kidneys were reported in only 2, 0, 0, 1 and 5 males of control 1, control 2, low, mid and high dose treatment groups, respectively. The flaccid testes were seen in 7, 10, 6, 5 and 42 males, testicular fluid in subscapsular region in 2, 0, 0, 1 and 11 males, small testes in 0, 0, 3, 0 and 18 in males and, blue colored testes in 0, 0, 2, 3 and 9 males were reported in of control 1, control 2, low, mid and high dose treatment groups, respectively. Enlarged and swollen liver was seen 15 males and 16 females of high dose treatment group. Only a trend of an increase of mammary masses wee seen in both sees of animals. These and the other pathological findings noted in the animals are shown in the following table.

TABLE: Pathological Changes in Organs/Tissues of Rats*

Abnormality		Treatment Groups (male/female;mg/kg/day)				
		0/0	0/0	15/15	30/45	60/90
Dark Adrenal	M	2	0	1	4	8
	F	9	11	15	19	15
Enlarged Adrenal	M	0	0	0	0	6
	F	1	0	2	1	1
Epididymides small	M	0	0	2	1	11
Epididymides swollen	M	0	0	0	0	3
Enlar. Kidneys	M	2	1	2	1	7
	F	0	0	0	0	2
Liver Swollen	M	6	4	5	4	15
	F	11	7	13	11	16
Mammary Gland Mass	M	4	2	6	6	9
	F	25	21	24	31	33

Testes Flaccid		7	10	6	5	42
Testes Subscap. Fluid		2	0	0	1	11
Axill.Lymph Node Mass	M	5	3	8	6	15
	F	1	3	1	2	1
Mandibulr Lymph Node	M	1	1	0	1	4
	F	1	0	1	1	6
Pancreat. Lymph Node Masses	M	0	1	2	3	8
	F	0	0	1	1	0
Skin Masses Present	M	8	5	13	12	17
	F	4	5	1	10	12

*= 65/sex/group

9. **Histopathological Changes**:

a. **Non-Neoplastic Changes**: a. Males: Epididymal hypospermia, the absence of colloid from seminal vesicle and testicular tubular germinal epithelial degeneration were seen in higher incidences ($p<0.05 - 0.005$) than in control group animals. A significant increase in the incidences of progressive senile renal nephropathy ($p<0.05$) were seen in males of high dose treatment group (see table). Sinus erythrocytes and erythrophagocytosis in mesenteric lymph node were present in slightly higher incidences in males of the high dose group than control group. A dose related increase in the incidents of accumulation of alveolar macrophages of lung was seen in treatment groups males. The degeneration of testicular tubular germinal epithelium was noted in high dose treatment group (60 Vs 14-16 in control group). The incidences of epithelial hyperplasia of thymus and thymus cysts were high among males of high dose group animals. The epidermal hyperplasia of slight to moderate nature was present in mid and high dose treatment groups (see table below).

b. Females: Increased incidences of adrenal cortical vacuolation were seen in females of mid and high dose treatment groups animals, i.e., 6 males in each of mid and high dose treatment group, respectively (Vs 2 in control group). The incidences of adrenal medullary hyperplasia, chronic renal nephropathy (senile) were higher than control in females of high dose treatment group. The focal medullary hyperplasia was noted in 8 and 11 males and females of high dose treatment group. In mesenteric lymph nodes, sinus erythrocytes and erythrophagocytosis were reported in higher incidences in high dose treated animals than control females. The accumulation of alveolar macrophages in lung was noted in higher incidences, i.e., 26 females in high dose treatment group animals. The islet cell hyperplasia of pancreas was noted in 0, 1, 1, 1 and 3 females of study groups. The diffuse hyperplasia of pituitary was found in 0, 1, 0, 1 and 5 females. The incidences of scabs on tail were 7, 6, 10, 23, and 30 females and the observed epidermal hyperplasia was of slight to moderate nature in animals (see table below). Clear cell foci in liver were seen in 9, 13, 21, 20 and 25 females. Follicular abscess was in a dose-related manner.

TABLE: Incidences of Non-Neoplastic Lesions in Control and Treatment groups Rats[1]

Histopathological Lesion		Treatment Groups (N = 65/sex/group)				
		Control 1	Control 2	Low Dose	Mid Dose	High Dose
Adrenal						
Cortical Vacuolation	M	9	16	15	12	11
	F	2	2	0	6	6
Medullary Hyperplasia Focal	M	7	4	6	12	8
	F	2	3	5	3	11
Male Reproductive Organs:						
Epididymal Hypospermia		9	11	6	5	58
Absence of Colloid Seminal Vesicle		1	5	3	1	8
Test. Tubular Germ Epithel. Degen.		14	16	14	10	60
Progressive Senile	M	15	19	19	15	34
Nephropathy	F	8	9	7	10	18
Liver						
Focal Congestion	M	4	12	19	13	16
	F	11	8	15	15	6
Lungs						
Accumul. Alveolar Macroph.	M	14	10	23	25	30
	F	13	13	8	13	26
Perivasc. Lymphoid Aggreg.	M	2	4	3	5	6
Lungs	F	0	1	4	4	3
Mammary Gland						
Caudal Secretory Activity	M	6	2	8	11	10
	F	31	31	29	35	16
Acinar Hyperplasia	F	11	15	12	18	22
S. Muscle Thigh						
Myofibre Degeneration	M	4	5	10	8	8
	F	0	0	0	0	1
Spleen						
Extramedullary Haematopiesis	M	2	1	1	2	6
	F	6	4	8	10	11
Hemosiderosis	M	4	8	8	6	9
	F	31	29	36	29	50
Thymus						
Epithelial Hyperplasia	M	0	0	0	0	4
	F	6	5	4	5	19
Thymus Cysts	M	2	0	3	4	7
	F	15	20	27	27	24
Tail						
Epidermal Hyperplasia	M	5	9	10	17	21
	F	5	3	13	14	11
Follicular Abscess	M	4	5	10	9	19
	F	1	4	8	10	13
Scabs	M	7	10	10	17	23
	F	7	6	10	23	30

[1] = 65 of rats/group

b. **Neoplastic Changes:**

Increased incidences of the benign pheochromocytoma were seen in a treatment related manner in 9, 13, 16, 18 and 27 males of 0, 0, 15, 30 and 60 mg/kg/day treatment groups. Among females, the incidences of benign pheochromocytoma were 1, 0, 2, 4 and 7 in 0, 0, 15, 45 and 90 mg/kg/day treatment groups. The incidences were 28.7 and 41.5% in mid and high dose treatment groups males. The background control data range provided by sponsor for males was 10.9 to 25%. The incidence of the tumor was 10.8% in females, which was more than the background range of 2 to 10%. The pairwise p values were 0.0004 for 60 mg/kg/day treatment group male 0.0004 for females of 90 mg/kg/day treatment group (pairwise comparison with pooled control). The p values with control 1 and 2 were 0.0007 and 0.0132 for high dose males. These were not significant for control 2. The combined incidences of benign and malignant pheochromocytoma were significantly increased for males of 60 mg/kg/day treatment group (trend test $p < 0.001$). The pairwise p test with pooled controls for the combined benign and malignant pheochromocytoma was not significant in these animals. The increase in the incidences of islet cell adenoma ($p<0.05$ and pairwise $p<0.029$) and combined incidences of islet cell adenoma and carcinoma (trend $p<0.005$) was significant in study males. The pairwise comparison showed that the combined incidences were significantly higher in all the treatment groups study animals ($p<0.01$). The incidences of rare benign hepatocellular adenoma were increased in males and females of high dose treatment group. The increase in incidences was significant (trend test $p<0.0002$) in high dose treatment group females and incidences were significant by pairwise testing ($p<0.0012$) and the incidences were more than the historical control range of 0 to 5.3. The thyroid C-cell adenoma incidences (common) were increased in high dose females (exact $p>0.0001$; pairwise p with pooled control $p<0.0053$). The mammary adeno-carcinoma incidences in females of 45 and 90 mg/kg/day treatment groups were more than control 1 but not when compared with control 2 or pooled control animals. The combined incidences of mammary adeno-carcinoma and benign fibroadenoma were within sponsor background range of 1.4 to 6.0%. The significant increase in the incidences of benign adenoma pars distalis (common) were seen in male rats included in low, mid and high dose treatment groups (pair wise p values were 0.0001, 0.0005 and 0.0005 in animals of 3 treatment groups). The incidences were greater than the historical control data of sponsor laboratory.

TABLE

Incidences of Neoplastic Lesions in Control and Treatment groups Rats

Histopathological Lesion		Treatment Groups						
		Cont. 1	Cont. 2	Low Dose	Mid Dose	High Dose	Trend Test (p value)	Pairwise p (pooled control)
Adrenals:								
Benign Pheochromocytoma	M	9	13	16	18	27	<0.0001*	0.004**
	F	1	0	2	4	7	<0.0001*	0.002**
Malignant Pheochromocytoma	M	1	1	1	4	2	0.158	
	F	2	1	1	0	1	0.658	
Combined Incidences	M	10	14	17	22	29	<0.001*	
	F							

		3	1	3	4	8	>0.1	
Liver								
Malignant Hepatocellular Carcinoma (MHC)	M	2	1	1	0	0	0.9797	
	F	0	0	0	1	0	0.4524	
Hepatocellular Adenoma (BHA)	M	10	3	3	4	5	0.093	
	F	0	0	3	3	6	0.0002*	0.0012**
Combined Incidences of MHC +BHA	M	12	4	4	4	5	--	
	F	0	0	3	4	6	<0.001	
Pancreas								
Acinar Cell Adenoma	M	0	2	2	2	6	0.007	0.018**
	F	0	0	0	0	0	0.194	--
Acinar Cell Adenocarcinoma	M	0	0	1	0	1	--	
	F	0	0	1	0	0	--	
Combined Incidences of Acinar cell Adenoma +Carcinoma	M	0	2	3	2	7	-	
	F	0	0	1	0	0	-	
Islet Cell Adenoma	M	3	4	8	9	10	0.0125*	0.029**
	F	2	5	3	6	1	0.625	
Islet cell Carcinoma	M	3	2	8	5	7	0.0475	
	F	0	1	1	1	1	0.2784	
Combined incidences of Islet cell Adenoma +Carcinoma	M	6	6	16	14	17	0.001*	0.006**
	F	2	6	4	7	2	--	
Thyroid								
Thyroid Follicular Cell Adenoma	M	0	3	1	2	6	0.00127	0.062
	F	1	0	0	0	3	0.0257	0.109
Thyroid C-Cell Adenoma	M	5	11	13	10	16	0.0136	
	F	5	5	10	10	15	0.0001*	0.0053
C-Cell Carcinoma	M	1	0	1	4	0	--	
	F	0	0	1	3	0	--	
Combined C-Cell Adenoma +C-Cell carcinoma	M	6	11	14	14	16	--	
	F	5	5	10	13	15	0.01	
Pituitary								
Benign Adenoma-Par Distalis	M	22	29	45	43	43	<0.0001	0.005
	F	45	48	53	56	34	<0.69	
Mammary Gland								
Adenocarcinoma	M	0	0	0	0	2	0.0366	
	F	9	16	12	20	21	0.0026	
Adenoma	M	0	0	0	0	0	--	
	F	0	1	0	0	0	--	
Benign fibroadenoma	M	0		4	1	1	--	
	F	45	31	34	41	28	--	
Combined Benign and Malignant	M	0	1	4	1	3	0.0042*	0.002**
	F	49	34	37	49	42	--	

* = Trend test $p < 0.025$; ** = Pairwise $p < 0.005$

In summary, the study was conducted in adequate number of animals (male/female) at the oral gavage doses of 0, 0, 15, 30 and 60 mg/kg/day in males and, 0, 0, 15, 45 and 90 mg/kg/day in females. The administered compound attained a non-dose proportional plasma concentrations of the parent compound and the metabolite RS-17825 (major human metabolite). The plasma concentrations in females were more than males of the treatment groups during the study. On study week 26, the exposure of the compound in male and female animals was 136.9 and 308.2 times the plasma concentration (AUC values) achieved after the suggested clinical dose of 5 ug/kg in man. Increased incidences of benign pheochromocytoma in male and females were seen. Increased incidences of combined benign and malignant pheochromocytoma and, pancreatic islet cell adenoma and combined incidences of islet cell adenoma and carcinoma were seen in all treatment group animals. The adenoma of par-distalis incidences were significantly high in males of treatment groups. The incidences of hepatocellular adenoma and thyroid C-cell adenoma were increased in females of high dose treatment group. The increased incidences of tail squamus cell papilloma in high dose males were reported.

REPRODUCTIVE TOXICITY STUDIES:

1. Intravenous male fertility study with RS-25259-197 in rats: (Report. No. 6267)

Testing Laboratories: Syntex Discovery Research, Palo Alto, CA

Study Started: April 6, 1992

Study Completed: December 16, 1992

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: Crl: CD^R (SD)BR VAF/Plus strain Rats; Males approximately 15 weeks old, weighing 427-577 g; females approx. 4-5 months old, weighing 262-404 g (post mating day 1 weights for females).

Drug Batch No.: PA15303-51/11902, 11903, and 11904

Methods: RS-25259-197 was intravenously administered (via the tail vein) to 4 groups of 10 male rats were at doses of 0 (vehicle), 1, 3, or 10 mg/kg/day for a period of 2 weeks prior to mating with untreated females and continuously for 4 weeks thereafter. The vehicle used in the present study was a sodium phosphate buffer solution which consisted of 0.087 g% sodium chloride, USP; 0.020 g% monobasic sodium phosphate monohydrate, USP; and 0.058 g% dibasic sodium phosphate anhydrous, USP in purified water, USP. RS-25259-197 and vehicle were each administered in total volumes of 1 ml/kg. Dose selection was based on the results of a 1 month i.v. toxicity study (Syntex 89-R-91, AT 5962), wherein rats given a 10 mg/kg daily dose exhibited transient clinical signs, but no clinical or anatomic pathological changes. Male

rats were observed daily for general condition and weighed weekly and terminally. Female body weights were determined on day 1 of pregnancy or at the end of the cohabitation period (nonpregnant females) weekly thereafter and terminally. During the 4 day cohabitation period females were examined daily for the presence of a copulatory plug or sperm in the vaginal lavage. Females with evidence of mating were euthanized on gestation day 14, whereas nonpregnant females were euthanized at 13 days after the end of the mating period. All females were subjected to partial necropsies in which the whole reproductive tract was examined. The number of corpora lutea, live fetuses (viable implants) resorptions (non-viable implants) and abnormal conditions were also determined in pregnant females. Following review of the gestational data, males were euthanized and discarded, with no gross examinations conducted.

Results: Male rats which received the 10 mg/kg dose exhibited vocalization immediately after dosing for up to 45 sec on various days. Males in all other groups appeared normal with no mortality observed in any group. Males in all treated groups had non dose-dependent suppression of body weight gains (-23 to -34%) compared to gains in control groups. All dams survived to the scheduled sacrifice, with no gross pathologic changes observed. No treatment-related effects on mating performance: [proportion (%) of males mating with at least 1 female; proportion (%) of males with at least 1 female pregnant and the proportion (%) of males with at least 1 female pregnant among those with evidence of mating] were observed. Table 6, on the following page presents a summary of the gestational indices of female rats examined at mid gestation (Reproduced from Sponsor's Summary Table 4, vol 1, pgs. 82-83).

Table 6. Summary of Reproductive Indices in Female Rats Examined at Mid Gestation (Reproduced from Sponsor's Summary Table 4, vol 1., pgs. 82-83)

Group	Vehicle	RS-25259-197 Dose (mg/kg) 1	3	10
Variable				
# Animals	20	20	20	20
# Preg. (%)	15 (75%)	16 (80%)	14 (70%)	13 (65%)
# w/ Resorp. (%)	6 (40%)	4 (25%)	9 (64%)	7 (53%)
# Corpora lutea	18.1 ± 2.1	17.8 ± 2.6	17.6 ± 2.8	16.7 ± 3.7
# Implantations	15.8 ± 1.9	14.2 ± 3.2	15.9 ± 0.9	13.1 ± 4.2
Live litter size	15.2 ± 1.7	13.9 ± 3.4	14.8 ± 1.1	12.1 ± 4.1*
# Total resorptions	0.7 ± 0.8	0.3 ± 0.6	1.1 ± 0.7	0.9 ± 0.9
Implantation index	88.2 ± 10.7	79.6 ± 16.4	91.8 ± 8.4	77.6 ± 17.6
Resorption index	3.9 ± 4.3	3.4 ± 7.4	6.6 ± 4.3	8.3 ± 10.5

* Significantly different from control values $P < 0.05$
IMPLANTATION INDEX = (IMPLANTATIONS/CORPORA LUTEA) X 100; RESORPTION INDEX = (TOTAL RESORPTION/IMPLANTATIONS) X 100

Briefly, the data in Table 6 (above) show that treatment of male rats with RS-25259-197 at doses up to 10 mg/kg for 2 weeks prior to and during mating had no effect on the No. of corpora lutea,

implantations, and resorptions. A significant reduction in the live litter size was observed, however it's relation to treatment is not apparent as no other gestational parameters showed treatment-related changes.

In conclusion, intravenous administration of RS-25259 to male rats at doses of 1, 3, or 10 mg/kg/day for 2 weeks prior to mating, produced transient vocalizations at the high doses and suppressed body weight gain at all doses, but had no effects on mating performance or fertility. However, the 2-week dosing schedule used currently is not in accordance with the recommended duration for a normal Segment I Fertility and Reproductive Toxicity Study in male rats. Thus, the aforementioned study cannot be used in lieu of a normal Segment I study in male rats.

2. Segment I. Fertility and Reproductive Performance Toxicity of Orally Administered RS-25259-007 in Male Rats: (Study # 41-R-94/ AT 6700)

Testing Laboratory: Syntex Discovery Research, Palo Alto, CA

Dates of Start and Completion of Study: August 19, 1993 and June 27, 1994

GLP and QAU Requirements: Statement was included.

Animals: Sprague Dawley female and male rats (Crl: CD^R (SD)BR VAF/Plus strain) with an average weight of 260 g (females) and of non-specified weights (males) were used in the study.

Lot No. of RS-25259-007: Lot # 2422, 24 and 25.

Methods: One hundred and twenty female and 60 male rats were divided in 4 groups (15 males and 30 females/group). Male rats were administered a single oral dose of either 0, 18, 60 or 120 mg of RS-25259-007/kg/day (in a volume of 5 ml/kg/day adjusted daily according to daily body weight for at least 61 to 63 days prior to cohabitation and were mated with untreated females. The treatment of male rats continued during mating period and these animals were weighed and observed for physical changes weekly. The dose selection of the study was based on the results of 1-month oral toxicity study in rats (Study # 16-R-92, AT 6329). In this study, a dose of 60 mg/kg/day was a 'no effect dose' and a dose of 180 mg/kg/day produced a reduction in the body weight gain and abnormal histopathological changes in liver, testes and thymus. In the present study, 1/2 of the female rats included in each of the control and treatment groups were necropsied at midgestation and the other half were allowed a natural delivery (day 25/26 of gestation). The female rats were observed daily for clinical observations, weighed on day 1 of pregnancy, weekly and at termination of the study. Those rats who did not litter were necropsied 3 to 9 days after the expected day of parturition. These were not examined histopathologically. The numbers of pups born (live/dead) were recorded. On postpartum day 4, litter sizes were standardized to 8 pups/litter (1:1/M:F). The general condition of the pups, body weight, sex and number of live pups were recorded on postpartum day 4, 7, 14 and 21 of the study. At

midgestation, females were killed and mammary chain and reproductive tract were separated. The number of implantations, corpora lutea, distribution of live and dead fetuses/uterine horn determined and number of empty implantation and resorbed sites were noted. Pups died within 4 days of parturition were preserved in 70 % ethanol for examining external abnormalities.

Results:

1. **General Observational Effects on Dams**: RS25259 up to a dose of 120 mg/kg/day did not produce any effect in male rats. Two of the pregnant females developed an external encrustation. One female was killed during the study as it delivered all dead pups. A treatment related retardation in the body weight gain of 10.3 and 9.06 % were seen in groups of animals necropsied at midgestation and belonging to 18 and 60 mg/kg/day treatment groups. Since none of the mated female rat included in 120 mg/kg/day treatment group was pregnant, sponsor did not include the data of body weight change of females belonging to this group.

2. **General Reproductive and Fertility Data of Dams**: A treatment related reduction in the number of matings among males included in 120 mg/kg/day treatment group was seen. The percent of matings were 90, 96.7, 93.3, 73.3 % in control, 18, 60 and 120 mg/kg/day treatment groups, respectively. Sponsor reported incorrect mating of 87 % among animals treated with 120 mg/kg/day treatment group in Summary table # 4 of mating performance and fertility. None of the females those mated with a male belonging to 120 mg/kg/day treatment group was pregnant, thus RS-25259 at this dose was toxic to rats.

Implantation sites, live litter size, total resorptions and resorption index were not affected among 18 and 60 mg/kg/day treatment groups (Table). But implantation index was dose dependently reduced, this was 91.4, 87.9 and 77.4 % among animals included in control, 18 and 60 mg/kg/day treatment groups respectively.

3. **Effect on Litter Data**: The mean number of live fetuses/litter among animals included in 18 and 60 mg/kg/day of RS-25259 treatment groups was not statistically different from those of control group (14.4, 15.0 and 11.7 in control, 18 and 60 mg/kg/day treatment groups respectively). The percent survival index of F_1 rats included in 18 and 60 mg/kg/day treatment groups was not statistically different from the control group animals and these were 100 % in all of these treatment groups (Table). The body weight of the pups born to dams included in 18 and 60 mg/kg/day treatment group was also comparable with the control group.

Table 1
Segment I. Reproductive Performance Study of RS 25259 in Male Rats

Parameter Measured	Control 0	Low dose 18	Mid Dose 60	High Dose 120
Dams Data (F_o)				

Total # Dams used	30	30	30	30
Copulation Rate	90	96.7	93.3	73.3
Pregnancy Rate	100	100	93	0
Observations (C-Section)				
Mean number of Corpora lutea	18.2	7.8	18.1	-
Mean Implantation	16.4	15.8	13.8	-
Mean Litter Size	15.1	15.1	13.3	-
Mean Total Resorptions	1.3	0.7	0.4	-
% Resorption Index	8.2	4.3	3.1	-
Neonatal Obsrvations:				
Mean Gestation Period	21.5	21.3	21.8	-
# Born Alive	14.4	15.0	11.7	-
Live Pup Body Weight				
Day 4				
Male	10.0	10.0	10.9	-
Female	9.2	9.3	10.1	-
Day 17				
Male	16.7	16.8	17.7	-
Female	15.7	15.8	16.9	-
Day 14				
Male	34.9	35.7	36.5	-
Female	33.6	34.5	35.3	-
Day 21				
Male	55.0	56.9	58.4	-
Female	52.9	54.9	56.0	-

Six pups (Two pups from 2 control group dams # 0132 and 0144 and, 4 pups of 4 dams # 328, 332, 342, 350 and 356 of 60 mg/kg/day treatment group) were found dead during the study. Only pup # 144 (control group) had wavy thoracic rib. All of other dead pups were comparable with control group pups.

In conclusion, RS25259 produced a dose dependent decrease of the implantation index in animals treated with low and mid doses of the study. The highest dose of the study, 120 mg/kg/day was toxic in animals and the treated animals were infertile as the rate of copulation was markedly reduced and none of the female got pregnant. No effects on the reproductive and fertility of animals treated with 18 and 60 mg/kg/day dose were noted.

3. **Segment I. Fertility and Reproductive Performance Toxicity of Orally Administered RS-25259-007 in Female Rats:** (Study # 78-R-94/AT 6750)

Testing Laboratory: Syntex Discovery Research, Palo Alto, CA.

GLP & QAU Requirements: The statement of compliance was included.

Date of start and Completion of Study: March 15, 1994 and September 9, 1994.

Animals Used: One hundred and twenty female Crl:CD-1^R (ICR)BRVAF/Plus strain rats approximately 3 to 4 months of age were used in the study.

Lot No. of RS-25259-007: Lot # PA 17555-40

Methods: These animals were divided in 4 groups (30/group) and were administered a single oral dose of either 0 (acetic acid and sod. acetate solution pH 5.0), 9, 30 or 60 mg of RS-25259-197/kg/day (in a volume of 5 ml/kg/day adjusted daily according to daily body weight) for 2 weeks prior to cohabitation with untreated males (1 male with 2 females). The treatment of female rats continued through gestation period 9. Females without evidence of mating were treated through 9 days after the end of the mating period. The dose selection of the study was based on the results of 1-month oral toxicity study in rats (Study # 16-R-92, AT 6329). In this study, a dose of 60 mg/kg/day was a 'no effect dose' and a dose of 180 mg/kg/day produced retardation in the body weight gain and abnormal histopathological changes in liver and thymus and ovarian cyst in females. The day 1 of pregnancy was an evidence of sperm plug in vaginal lavage. On day 15 of gestation, females with mating evidence were necropsied. Females with no evidence of pregnancy were necropsied 15 days after cohabitation period and number of implantation and corpora lutea counted. In the present study, female rats were observed daily for clinical observations, weighed on day 1 of pregnancy, twice weekly thereafter and at termination of the study. All of the surviving and rats died during the study were necropsied to determine the cause of their death. The number of implantation, corpora lutea, distribution of viable and resorbed implants/uterine horn determined and any abnormal conditions were recorded.

Results:

1. General Observational Effects on Dams: RS-25,259 up to a dose of 60 mg/kg/day did not produce any effect in dams. No significant retardation in the body weight gain was seen in animals belonging to 0, 9, 30 and 60 mg/kg/day treatment groups respectively. Three animals, i.e., 1 and 2 animals belonging to control and 9 mg/kg/day treatment groups died during the study. The percent of animals mated were 93, 86, 83 and 73 % in 0, 9, 30 and 60 mg/kg/day treatment groups respectively and the number of conceived were 85, 95, 83 and 73 % in animals belonging to 0, 9, 30 and 60 mg/kg/day treatment groups respectively. A trend of a decrease of number of matings and number of animals conceived was seen among animals included in 60 mg/kg/day treatment group. This was comparable with the animals included in the control group.

2. General Reproductive and Fertility Data of Dams: The number of corpora lutea and implantation were not affected by RS-25259 treatment (Table). The live mean litter size was 15.6, 13.1 and 13.6 in 9, 30 and 60 mg/kg/day treatment groups respectively vs 14.0 in the control group. The numbers of early resorptions were 0.8, 1.0, 1.1 and 1 in 0, 9, 30 and 60

mg/kg/day treatment groups respectively. The data is shown in the following table (Table taken from sponsor's submission at page 020.

Table 1
Segment I. Reproductive Performance Study of RS 25259 in Female Rats

Parameter Measured	Control 0	Low dose 9	Mid Dose 30	High Dose 60
Total # Dams used	29	28	30	30
Copulation Rate	93	86	83	73.3
Pregnancy Rate	85	95	83	73
Observation at C-Section				
Mean number of Corpora lutea	18.1	19.8	17.5	18.2
Mean Implantation	14.7	16.6	14.2	14.6
Mean Litter Size	14.0	15.6	13.1	13.6
Mean Early Resorptions	0.8	1.0	1.1	1.0
% Resorption Index	4.8	5.7	9.6	6.9
Implantation Index	18.21	12.15	20.39	24.57

In conclusion, RS25259 produced no effect on the fertility of female rats up to a dose of 60 mg/kg/day dose. Only a trend of a decrease of number of matings and conceived were seen at a dose of 60 mg/kg/day dose. The dose selection of the study appears to be not appropriate as it was a no effect dose in 1-month toxicity study. A dose of 180 mg/kg/day was toxic dose in the same study, therefore, MTD was not identified.

4. Oral Segment II Teratology Study with RS-25259-197 in Rats
(Report No. 67-R-94-25259-197-PO-TT)

Testing Laboratories: Syntex, Palo Alto, CA

Study Started: January 18, 1994

Study Completed: October 3, 1994

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: Sexually mature Crl:CD7BR VAF/Plus Sprague Dawley Rats, Females: approximately 15 weeks of age, 209-290 g in weight; Males: approximately 5 months of age, weight not indicated.

Drug Batch No.: PA17555-40ML

Methods: Three groups of female CD7Rats (25-26/group) were orally administered (by gavage) RS-25259-197 at doses of 18, 60, and 120 mg/kg (dissolved in vehicle and administered at a volume of 2 ml/kg) during day 7 through 16 of gestation. A forth group of 24 female rats were given 2 ml/kg of vehicle (13.2 mg/ml glacial acetic acid + sodium acetate 53.08 mg/ml in 1 ml of distilled water) alone and served as controls. Dose selection was based on an oral range-finding teratology study in rats where RS-25259-197 was administered at doses of 30, 90, or 180 mg/kg/ day. The 180 mg/kg dose produced reduced maternal weight gain and increased numbers of resorptions, but no treatment related external fetal abnormalities. Clinical observations were made daily and body weights were recorded on gestation days 1, 7, 10, 14, 17, and 21 of pregnancy. On gestation day 21, all dams were necropsied, with determinations of the numbers of corpora lutea, live fetuses (viable implants), resorptions (nonviable implants), and any abnormal uterine conditions were recorded. Fetuses were identified, weighed, examined externally and their sex was determined. Approximately one-half of the fetuses were examined for visceral abnormalities, with the remaining fetuses eviscerated and processed for skeletal examination.

Results: Treatment with RS-25259-197 produced no clinical signs of toxicity at any dose tested. One 120 mg/kg high dose female died on day 12; the cause of death was undetermined. Another 120 mg/kg female showed clinical signs of gasping, labored breathing, railing and swollen axilla/neck as a result of a gavage error. At the 120 mg/kg dose, RS-25259-197 suppressed body weight gains on gestation Day 17 (12%) and Day-21 (12%) relative to control gains of 74.6 and 132.8 g, respectively. Table 1 on the following page provides a tabulated summary of maternal and fetal observations at the Cesarean Section.

Table 1. Maternal and Fetal Observations in Rats at Cesarean Section

	Vehicle Control	RS-25259-197 (mg/kg) 18	60	120
No. of Litters	20	24	20	22
No. of Fetuses	251	322	284	299
No. Implantations[1] " SD	13.6 " 3.9	14.3 " 2.4	15.1 " 1.7	15.0 " 1.8
Viable[1] " SD	12.6 " 3.8	13.4 " 2.8	14.2 " 2.3	13.6 " 3.7

Non Viable[1] " SD	0	0	0	0
Resorptions				
Total	0	0	0	1
Early[1] " SD	1 " 1.6	0.9 " 1.1	0.9 " 1.2	1.4 " 3.1
Late[1] " SD	0.1 " 0.22	0.0 " 0.0	0.0 " 0.0	0.0 " 0.0
Corpora Lutea[1] " SD	15.6 " 3.7	16.6 " 1.6	17.4 " 2.8	17.1 " 3.1
Sex Ratio (M/F)	0.92	0.84	1.02	1.05
Fetal Body Wt.				
Males(g) " SD	3.72 " 0.21	3.67 " 0.21	3.5 " 0.21*	3.09 " 0.21*
Females(g) " SD	3.47 " 0.20	3.47 " 0.20	3.35 " 0.20	2.95 " 0.26*

* Significantly less than vehicle control ($p < 0.01$)
1 = Values indicate the mean value per litter

Table 1 indicates that 1 of 22 females examined at the 120 mg/kg dose had a total litter resorption, while reduced fetal weights were observed for males at the 60 and 120 mg/kg doses (6.2 and 17%, respectively) and for females at the 120 mg/kg dose (15%). Otherwise RS-25259-197 had no effects on maternal parameters or fetal viability.

Tables 2 and 3 on the following pages shows a tabulated summary of the incidence of external, visceral and skeletal variations and malformations.

Fetal Evaluations:

Table 2. Summary of the Incidence of Fetal External and Visceral Malformations and Variations

	RS-25259-197			
Dose groups (mg/kg)	0	18	60	120
No. Litters	20	24	20	21
No. Fetuses/Litter given a:				
External Examination:	251	322	284	299
Visceral Examination:	125	164	141	147
No. of Fetuses (No. of litters)				
Variations/Malformations:				
External				
-Arthrogryposis	0(0)	0(0)	0(0)	1(1)*
-Gastroschisis	0(0)	0(0)	0(0)	1(1)*
-Umbilical Hernia	0(0)	0(0)	0(0)	2(2)H
Visceral				
-Diaphragm absent	0(0)	0(0)	0(0)	1(1)*
-Gastroschisis	0(0)	1(1)	0(0)	1(1)*
-Hydronephrosis	0(0)	3(2)	2(2)	0(0)

-Hydroureter	2(2)	10(6)	1(1)	1(1)
-Omphalocele	0(0)	0(0)	0(0)	2(2)H
-Rotation of the heart	0(0)	0(0)	0(0)	1(1)*

* Seen in the same animal (Male fetus # 07 litter # 400)
H Seen in the same animal (Male fetus # 07 litter # 402)

Table 2 indicates that 2 fetuses, one each in separate litters showed multiple malformations; none of which were common to both fetuses. Thus, the low incidence and the sporadic nature of the observed external and visceral malformations suggest they represent chance occurrences and are thus not considered related to treatment.

Table 3. Summary of the Incidence of Fetal Skeletal Variations

	RS-25259-197			
Dose groups (mg/kg)	0	18	60	120
No. Litters	20	24	20	21
No. Fetuses/Litter Examined:	125/19	158/24	142/20	152/21
No. of Fetuses/No. of litters				
Skeletal Variations:				
Sternebrae				
-Dismorphic	38/15	48/23	60/19	62/20
-Unossified	31/10	62/22	70/19	111/21
3 or more Sternebrae				
-Reduced Ossification	5/4	7/6	11/6	49/18
-Unossified	0/0	0/0	1/1	10/8
Pubis				
-Reduced Ossification	2/2	2/2	1/1	11/9
Thor. Vertebral Centrum				
-Reduced Ossification	9/9	6/6	8/7	17/12
Cranium				
Frontal				
-Reduced Ossification	0/0	2/2	1/1	6/4
Interparietal				
-Reduced Ossification	9/6	15/9	21/12	38/15
Parietal				
-Dysmorphic	1/1	1/1	1/1	4/1
-Reduced Ossification	3/3	8/3	4/4	16/9
Occipital				
-Dysmorphic	13/8	25/13	18/12	49/18
-Reduced Ossification	2/2	1/1	1/1	9/5

Table 3 Shows that RS-25259-197 produced no skeletal malformations. However, a greater incidence of reduced skeletal ossification was seen in fetuses at the 120 mg/kg dose. This was correlated with the reduced fetal weights at the 120 mg/kg dose.

In conclusion, RS-25259-197 at the 120 mg/kg dose showed evidence of maternal toxicity (i.e. reduced maternal weight gain). In addition, reduced fetal weights were also observed at the 60 and 120 mg/kg doses and reduced skeletal ossification was observed at the 120 mg/kg dose. However, no treatment-related teratogenic effects were evident in the current study.

5. **Oral Segment II Teratology Study with RS-25259-197 in Rabbits**
(Report No. 66-B-94)

Testing Laboratories: Syntex, Palo Alto, CA

Study Started: January 18, 1994

Study Completed: October 3, 1993

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: Naturally Mated Female New Zealand White Rabbits (Hra:(NZW)SPF), 6 months of age, 2.629-3.850 kg in weight.

Drug Batch No.: PA17555-40 ML

Methods: Pregnant New Zealand White Rabbits (20/group) were orally administered (by gavage) RS-25259-197 at doses of 0.0 (vehicle control), 18, 60, and 120/90 mg/kg during day 7 through 19 of gestation. (Note because of mortality the 120 mg/kg high dose was lowered to 90 mg/kg after 1 to 4 days of dosing).
RS-25259-197 was dissolved in glacial acetic acid 13.2 mg/ml; sodium acetate, 53.08 mg/ml; pH to 5.0 using 1 N NaOH or 1 N HCl and administered in a volume of 2 ml/kg. Dose selection was made on the basis of an oral teratology range findings study in which pregnant rabbits were given 10, 30, or 100 mg/kg RS-25259, with decreased fetal weights observed at the 100 mg/kg dose. Clinical observations were made daily and body weights were recorded on gestation days 1, 7 (before dosing), 13, 19 (post dosing), 22, and 29. On gestation day 29, all dams were necropsied, with determinations of the numbers of corpora lutea, live fetuses (viable implants), resorptions (nonviable implants), and any abnormal uterine conditions were recorded. Fetuses were identified, weighed and examined externally. Live fetuses were sacrificed and then examined for visceral abnormalities and sexed. All fetuses were examined for skeletal abnormalities.

Results: Treatment with RS-25259-197 produced no clinical signs of toxicity at any dose tested. One rabbit each in the vehicle control, 18, and 60 mg/kg dose groups and 11 rabbits in the 120/90 mg/kg dose group died during the dosing interval. Another rabbit at the 18 mg/kg/day

dose was killed because of a suspected vertebral fraction. Surviving rabbits at the 120/90 mg/kg showed suppressed body weight gains (78%) on gestation Day 13, relative to gains of 89.9 g from mean Day 1 body weights of 3315.6 g in vehicle controls. However, weight gains in all treated groups were comparable to control gains of 202.1, 265.3, and 354.4 g on days 19, 22, and 29, respectively. Gross pathological signs were limited to the animals, which died, and the 18 mg/kg doe, which was euthanized, showed lung and tracheal changes characterized as froth in the trachea and bronchi, red or purple discoloration, and moist non-collapsed lungs. The individual rabbits which died in the vehicle control, the 18 and 60 mg/kg dose groups and 2 of the 11 rabbits which died in the 120/90 mg/kg dose group also showed focal gastric mucosal discoloration. Table 4 below provides a tabulated summary of maternal and fetal observations at the Cesarean Section.

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Table 4. Maternal and Fetal Observations in Rabbits at Cesarean Section

	Vehicle Control	RS-25259-197 (mg/kg) 18	60	120/90
No. of Litters	17	16	13	8
No. of Fetuses	120	126	98	63
No. Implantations[1] " SD	7.5 " 1.7	8.1 " 2.0	8.0 " 1.5	8.8 " 1.5
Viable[1] " SD	7.1 " 1.6	7.9 " 2.0	7.5 " 1.4	7.9 " 2.5
Non Viable[1]" SD	0	0	0	0
Resorptions				
Total	0	0	0	0
Early[2] " SD	0.4 " 1.0	0.2 " 0.5	0.5 " 0.8	0.9 " 1.1
Late[1] " SD	0.1 " 0.33	0.0 " 0.0	0.0 " 0.0	0.0 " 0.0
Corpora Lutea[1] " SD	8.9 " 1.7	9.1 " 1.4	9.0 " 1.9	10.4 " 2.7
Sex Ratio (M/F)	1.4	1.2	0.83	0.97
Fetal Body Wt.				
Males(g) " SD	36.7 " 3.81	35.3 " 3.84	33.9 " 5.81	34.4 " 2.47
Females(g) " SD	35.6 " 5.48	37.2 " 5.34	35.3 " 5.11	33.6 " 3.16

* Significantly less than vehicle control ($p < 0.01$); " = ±;

1 Values indicate the mean value per litter

Analysis of the data in Table 4 showed a slight but statistically significant increasing trend for early resorptions in treated groups vs vehicle controls. However, pair-wise comparisons of the incidence of early resorptions in treated groups versus vehicle controls were not statistically significant and no effects on mean litter size were evident. Thus, the slight increasing trend for early resorptions is not considered to be a biologically significant effect. All other maternal and fetal parameters were comparable between treated and control group.

Tables 5 and 6 on the following pages show a tabulated summary of the incidence of external, visceral and skeletal variations and malformations.

Fetal Evaluations:

Table 5. Summary of the Incidence of Fetal External and Visceral Malformations and Variations in Rabbits

	RS-25259-197			
Dose groups (mg/kg)	0	18	60	120/90
No. Litters	17	16	13	8
No. Fetuses/Litter given:				
External Examination:	120	126	98	63
Visceral Examination:	120	126	98	63
No. of Fetuses (No. of litters) Variations/Malformations:				
External				
-Arthrogryposis	0(0)	0(0)	1(1)	0(0)
-Domed Head	0(0)	0(0)	0(0)	1(1)
Visceral				
-Agonadal	1(1)	0(0)	0(0)	0(0)
-Asplenia	0(0)	0(0)	3(1)	0(0)
-Cardiomegaly	0(0)	0(0)	1(1)	0(0)
-Dysplasia	0(0)	0(0)	0(0)	1(1)
-Ectopic Kidney	0(0)	1(1)	0(0)	1(1)
-Gall Bladder Agenesis	0(0)	0(0)	1(1)	1(1)
-Gall Bladder Hypoplasia	0(0)	0(0)	1(1)	0(0)
-Hydrocephaly	0(0)	0(0)	1(1)	0(0)
-Microsplenia	0(0)	0(0)	1(1)	0(0)
-Oligopulmonism	2(1)	1(1)	1(1)	0(0)
-Septal Defect	0(0)	0(0)	0(0)	1(1)

The incidence of external and visceral variations/malformations (listed in Table 5) was limited. There was no single type of variation/malformation, which occurred in more than one litter, and none of the findings appeared related to dose. Thus, the observed incidence of external and

visceral malformations probably represents chance occurrences and was not considered related to treatment.

Table 6. Summary of the Incidence of Fetal Skeletal Variations

	RS-25259-197			
Dose groups (mg/kg)	0	18	60	120/90
No. Litters	17	16	13	8
No. Fetuses Examined	120	126	98	63
Skeletal Variations:	No. of Fetuses (No. of litters)			
APPENDAGES				
Astragalus				
Nonossified	2/2	0/0	5/1	0/0
Reduced ossification	3/1	1/1	0/0	5/1
BODY				
1 or 2 Sternebrae				
-Dysmorphic	11/8	15/10	15/7	14/7
-Fused Branched	0/0	1/1	1/1	2/2
-Unossified	116/17	123/16	90/13	57/8
-Reduced Ossification	70/17	79/16	65/13	40/8
3 or more Sternebrae				
-Dysmorphic	2/2	2/2	1/1	5/3
-Fused Branched	0/0	0/0	0/0	2/1
-Unossified	1/1	3/1	7/3	3/2
-Reduced Ossification	0/0	1/1	1/1	1/1
Lumb. Vertebral Arch				
-Reduced Ossification	1/1	3/1	2/2	5/5
Pubis				
-Reduced Ossification	9/5	6/4	17/8	10/4
Thoracic Rib				
-Dysmorphic	1/1	1/1	2/2	4/1
-Fused/Branched	1/1	0/0	1/1	1/1
Cranium				
Frontal				
-Reduced Ossification	0/0	1/1	1/1	0/0
Hyoid				
-Dysmorphic	0/0	1/1	0/0	2/2
-Reduced Ossification	18/10	41/11	39/11	24/7

Note: Variations, which occurred at a greater incidence in control groups or which occurred only at the low or mid dose, were not included.

Table 6 shows that treatment of pregnant rabbits with RS-25259-197 during the period of organogenesis resulted in no treatment related increased incidence of skeletal malformations or variations relative to vehicle treated control rabbits.

In conclusion, administration of RS-25259-197 at doses of 0 (vehicle), 18, 60, or 120/90 mg/kg/day during the period of organogenesis was maternally toxic at the 120/90 mg/kg dose producing suppressed body weight gains (78%, relative to control gains on Days 1 through 13) and maternal mortality. However, RS-25259-197 showed no evidence of teratogenic effects in the F1 offspring of surviving dams at any dose tested.

6. **Oral Prenatal and Postnatal Development study with RS-25259-197 in rats:** (Report. No. 1063/7-D 154; PALO-99-13)

Testing Laboratories:

Study Started: June 3, 1999

Study Completed: August 22, 2000

GLP Requirements: A Statement of compliance with the GLP regulations and quality assurance unit was included.

Animals: SD Female Rats approximately 10 to 12 weeks old, weighing >160 g,

Drug Batch No.: 30893-P105/Lot #2

Methods: RS-25259-197 was administered orally by gavage at the doses of 0 (vehicle), 1, 9, 30 or 60 mg/kg/day to timely mated 4 groups of female rats (24/group) from gestation day 6 to day 21 of post-partum (41 days). The compound solution was prepared in glacial acetic acid and the final pH was 5.0±0.2 and RS-25259-197 and vehicle were administered in total volumes of 5 ml/kg. According to sponsor, the dose selection was based on previous reproductive toxicity studies in rats. The highest dose could cause adverse effect with out mortality and mid dose was the approximately midpoint between low and high dose. The females were allowed to litter and rear their offspring and the offsprings animals were maintained untreated for 12 weeks postweaning. Twenty F1 animals/sex/group were selected and paired for 15 days or till pregnant for examining the reproductive and fertility parameters. Mated females were killed on day 13 and the litter size, the number of corpora lutea and the sex of fetuses (viable implants on day 1, 4, 7, 14 and 21), resorptions (non-viable implants) and abnormal conditions were determined. The general condition was assessed daily, overt toxicity and mortality (twice daily). The female F0 body weights were determined on day 4, 6, 7, 8, 9, 12, 15, 18 and 20 of gestation and, on day 1, 4, 7, 14 and 21 postpartum. The food consumption was determined for day 4-6, 6-7, 7-8, 8-9, 9-12, 12-15, 15-18 and 18-20 gestation and also over days 1-4, 4-7, 7-14, and 14-21 postpartum. The food consumption of F1 females was determined weekly prior to pairing and for F1 females over days 0 to 3, 3 to 6, 6 to 10 and 10 to 13 of gestation. The changes in the functional tests and physical development of F1 groups animals noted during the different stages of development were determined. The ovaries and uteri removed and number of corpora lutea, # intrauterine

position of implantations, live embryos, early and late intrauterine deaths recorded. The F1 males were euthanized, discarded and no gross examinations were conducted.

Results: Three males and 22 females belonging to 60 mg/kg/day treatment group showed piloerction and paddling. Two, 3, 2 and 3 out of 24 females in each of 0, 9, 30 and 60 mg/kg/day treatment groups were reported with total litter loss on day 21 postpartum. The number of live pups, sex ratio and viability of F1 pups on post-partum day 21 was similar in control and treatment groups of animals. The body weight gain in control and treated animals was similar and the body weights on gestation day 20 of F0 were 367, 366, 370 and 363 g, respectively in 0, 9, 30 and 60 mg/kg/day treatment groups. An increased mortality was seen among pups born to high dose treatment group animals. No treatment related histopathological changes in the animals were seen. Postimplantation survival index were 89.5, 94.6, 92.5 and 98.5% in control and 3 treatment groups animals. Briefly, the data in table show that treatment of RS-25259-197 at doses up to 60 mg/kg had no effect on the pregnancy rate, No. of corpora lutea and implantations of F0 rats.

Table **Summary of Reproductive Indices in Female Rats Examined**

Group	Vehicle	RS-25259-197 Dose (mg/kg)		
		9	30	60
Variable				
# Females	24	24	24	24
# Preg.(%)	24 (100%)	24 (100%)	23 (95.8%)	24(100%)
# Died During Lactation	0	0	0	2
# w/Live Pups (%)	22 (91.7%)	21(87.5%)	20 (86.9%)	19 (79.2%)
Mean Body Wt. (F_0) in g:				
Gestation day 20	367	366	370	363
Lactation day 21	328	329	329	330
Mean Implantation Sites	14.0	13.7	13.2	13.1
Mean Live litter size	12.7	13.1	12.3	12.1
Live Birth Index (%)	96.5	98.7	97.9	94.3
Mean % Male Pups (F1)	51.5	48.6	50.9	51.9
Mean # Pups at Culling	8.0	8.0	7.8	7.8
(Day 4)				
(Day 14)	7.4	7.5	7.2	6.6
(Day 21)	7.4	7.5	7.2	6.5
F_1 Generation Data After Culling:				
Body wt (g) on day 1 Males	6.5	6.6	6.8	7.2*
Females	6.1	6.2	6.3	6.7
On day 21:				
Males	51.9	49.0	51.7	52.2
Females	50.4	47.1	49.8	

				49.8
Days of 100% Physical Developmental Parameters:				
a. Pinnea Unfolding	5	5	5	
b. Incisor Eruption	15	15	15	4
c. Eye Opening	17	17	17	14
				17

* Significantly different from control values P < 0.05
IMPLANTATION INDEX = (IMPLANTATIONS/CORPORA LUTEA) X 100; RESORPTION INDEX = (TOTAL RESORPTION/IMPLANTATIONS) X 100

Effects on F1 Pups: The abnormal position of the hind legs was seen in 1 mid dose and 2 high dose litters. Four male and 5 female pups of litter #80 (high dose treatment group) died on lactation day 1 and 1 died on day 2 of lactation. One pup of intermediate dose (litter #53) and 1 pup of low dose treatment group (litter #48) were affected by abnormal positioning of hind leg. The pups with this abnormality died during the study but a pup of intermediate dose treatment group recovered during the study. The physical development of F1 pups was comparable with the control group pups. The pinna unfolding, incisor eruption and eye opening parameters in pups of palonosetron treated animals was similar to the pups of control group animals. The functional tests of righting reflex (postpartum – PP day 1), air righting reflex (day 17 PP), grip strength (day 21 PP), pupillary reflex (day 21 PP) and auditory response and visual placing (day 21 PP) were also similar to the pups of control group animals. However, the vaginal opening in the pups of 3 treatment groups was significantly ($p<0.001$) increased than the control group animals (37 days in treated groups pups vs 35 days in control group animals). These were 100% in animals included in palonosetron treatment groups. The learning ability and motor activity were similar and not affected in treated animals.

Briefly, the study showed that treatment up to 60 mg/kg/day with RS-25259-197 did not produce developmental toxicity excepting abnormal positioning of hind legs was seen in pups in the initial stages of the study. The pups born with this abnormality died during the study and 2 pups (1/mid and low dose treatment groups survived and these were normal. The sponsor did not evaluate these further and no microscopic examination was done. Palonosetron up to 60 mg/kg/day dose during the development phase did not produce postnatal toxicity in rats. A significant reduction in the live litter size was observed, however it's relation to treatment is not apparent as no other gestational parameters showed treatment-related changes.

MUTAGENICITY

1. Salmonella/mammalian-Microsome Preincubation Mutagenicity Assay (AMES) test and Escherichia Coli WP2 uvrA Reverse Mutation Preincubation Assay:

Methods: Tests for potential mutagenicity of RS-25,259-197 were conducted by exposing five specific histidine auxotrophs of Salmonella tryphimurium (TA-1535 and TA-100 which detect base pair substitutions and TA-1537, TA-1538 and TA-98 which primarily detect frame shift mutagens) to RS-25,259 (375-6000 ug/plate) in the presence or absence of a post-mitochondrial supernatant fraction (S-9) from rat livers induced with Aroclor 1254. The assay is based on the property of these five strains to undergo reversion from a histidine requiring state to protrophy following exposure to various classes of mutagens. Plates were scored by counting the number of revertant colonies present after 72 hours incubation at 37^0C.
The WP2 urva reverse mutation assay system measures reversion from trp($^-$) to trp($^+$) at a site blocking a step of tryptophan biosynthesis prior to the formation of anthranilic acid (Brusick et al., 1980). Tryptophan reversion occurs due to a base change at the originally mutated site or by a base change elsewhere in the chromosome causing the original mutation to be suppressed. Thus the specificity of the reversion is sensitive to base pair substitution mutations.

Results: In a dose range finding study IRS-25,259-197 at concentrations of 0.3 to 5000 ug/plate were tested. The results showed no precipitate but toxicity RS-25,259-197 at doses of 1000 to 5000 ug/plate. A dose range of 33-5000 ug/plate for RS-25,259-197 was therefore used in the mutagenicity assay. Test results from both mutagenicity assays showed that RS-25,259-197 (33-5000 ug/plate) produced no positive responses in any Salmonella strain or in the E. coli reverse mutation assay with or without metabolic activation. In contrast the positive controls, 2nitrofluorene (1 ug/plate), 2-aminoanthracene (1 ug/plate for Salmonella and 10,000 ug/plate for the WP2 uvra assay), sodium azide (1 ug/plate) and 9-aminoacridine (75 ug/plate) and methyl-methanesulfonate (1000 ug/plate for the WP2 uvra assay) elicited the expected increases in revertant colonies.

ADDENDUM BY REVIEWER
In the above review of AMES test, the reviewer (W. Shannon, Ph.D., HFD-180) did not provide the following information about the conduct of the study. These are given below.

Stdy # T929-Y-91-25259-197-MU-AMEC/Sponsor Study # AM0400
Conducting Lab: [redacted]
Batch # Used: Lot PA 15303-18
Dates of Initiation and Completion of Study: October 29, 1991 and January 16, 1992.

GLP and QAU Statement: A statement was included.

2. Chromosome Aberrations in Chinese Hamster Ovary (CHO) cells.

Methods: Metaphase preparations were prepared and stained for sister chromatid differentiation followed by evaluation for the percentage of first, second and third-division metaphase cells for estimation of the effect of the test article on cell cycle kinetics. In addition, metaphase CHO cells were microscopically examined for chromosome aberrations at either 24 hours; 16 hours

after 8 hour exposure to RS-25,259-197 (86 to 355 ug/ml) in the absence of an Aroclor-induced S-9 activation system or at 14 hours; 12 hours after 2 hour exposure to RS-25,259-197 (156 to 650 ug/ml) in the presence of the S-9 system.

Results: Toxicity, defined as inhibition of mitosis, was approximately 72% at a dose level of 355 ug/ml and approximately 53% at a dose level of 650 ug/ml in the activated and non-activated systems, respectively. Evaluation of the four highest groups which showed < 80 mitotic inhibition in the absence of the S-9 system (151, 201, 267, and 355 ug/ml) for chromosomal aberrations showed that RS-25,259 at concentrations of 201, 267, and 355 ug/ml significantly increased the percentage of cells with average structural aberrations of 11, 12 and 25%. In comparison, average % of aberrant cells in the untreated, vehicle treated and the positive control, triethylenemelamine (TEM), were 0, 1 and 47%, respectively. In the presence of the S-9 activating system, RS-25,259-197 significantly increased the % of aberrations only at the 650 ug/ml concentration. The RS-25,259-197-induced increase at the 650 ug/ml level averaged 9% compared to an average of 1, 0 and 15 % increase for the untreated, vehicle-treated and positive control (cyclophosphamide), respectively. Increased aberrations included chromatid breaks and isochromatid breaks, chromatid fragments, and chromatid exchange figures, including quadriradials, triradials and complex rearrangements), and chromosome breaks (including breaks, acentric fragments, and DIC, dicentric chromosomes). These studies suggest that RS-25,259 is clastogenic in this test system.

ADDENDUM BY THE REVIEWER:

In the above review of chromosomal aberration test with CHO cells, the previous reviewer (W. Shannon, Ph.D., HFD-180) assessed that palonosetron produced an increase in the percent aberrations at the highest concentrations. But from the submitted table with NDA (sponsor table 5.2.2.31; pp 249, vol 12 of 381), it was assessed that palonosetron treatment produced a dose related increase in % aberrations in the absence of S-9 activation system. An increase in the % aberrations was seen in the cultures containing the highest concentrations of palonosetron in the presence of S9 activation. Palonosetron was clastogenic in the study with and without activating systems.

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Table 5.2.2.31 Summary of Cytogenetic Analysis of CHO Cells Treated with Paliperidone

Treatment	S-9 Mix Activation	Harvest Time	Mitotic Index	Cells Scored	Aberrations Per Cell (Mean ± SD)	Cells with Aberrations (%)
Untreated cells		24	[illegible]	100	[illegible]	0
Water	+	24	[illegible]	100	[illegible]	1
Paliperidone						
191 µg/ml	+	24	[illegible]	100	[illegible]	2
281 µg/ml	+	24	[illegible]	100	[illegible]	11*
367 µg/ml	+	24	[illegible]	100	[illegible]	12*
555 µg/ml	+	24	[illegible]	100	[illegible]	2*
[illegible] µg/ml	+	24	[illegible]	100	[illegible]	47*
Untreated cells	+	14	[illegible]	[illegible]	[illegible]	1
Water	+	14	[illegible]	100	[illegible]	5
Paliperidone						
277 µg/ml	+	14	[illegible]	100	[illegible]	1
416 µg/ml	+	14	[illegible]	100	[illegible]	2
833 µg/ml	+	14	[illegible]	100	[illegible]	1
654 µg/ml	+	14	[illegible]	100	[illegible]	7*
[illegible] µg/ml	+	14	[illegible]	100	[illegible]	15*

[illegible]
[illegible]
[illegible]
[illegible]

In the above review the following information about the conduct of the study was also not given. These are given below.

Stdy # TA191.337031/Sponsor Study # AM0401
Conducting Lab: [redacted]

Dates of Initiation and Completion of Study: November 1, 1991 and March 2, 1992.

GLP & QAU Statement: A statement was included.

3. **Mutagenicity Test on RS-25,259-197 in an Vivo Micronucleus Assay.**

Methods: The ability of RS-25,259-197 to induce micronuclei in bone marrow polychromatic erythrocytes of ICR mice was examined following i.v. administration of either 1, 3, or 10 mg/kg. Bone marrow extracts from RS-25,259-197 were examined at 24, 48 and 72 hours post dosing.

Results: RS-25,259-197 did not induce a significant increase in micronuclei in bone marrow polychromatic erythrocytes (PCE) and was considered negative in the mouse bone marrow micronucleus test. In contrast cyclophosphamide (50 mg/kg elicited the expected increase in PCE micronuclei (0.76± 0.07; males; 1.36 ± 0.14; females).

ADDENDUM BY REVIEWER:
In the above review the following information about the conduct of the study was not given. These are given below.

Stdy #. 4946-0-455/Sponsor Study # AM0399
Conducting Lab:

Dates of Initiation and Completion of Study: January 16, 1992 and February 28, 1992
GLP & QAU Statement: A statement was included.

4. CHO/HGPRT Mutation Assay.

Methods: Chinese hamster ovary (CHO) cells were used to test the ability of RS-25,259 to induce a mutation at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus, thereby selecting for cells which are resistant to the cytotoxic effects of the purine analog, 6-thioguanine. Briefly, CHO cells were exposed to RS-25,259-197 for a period of 5 hours at doses of 300, 400, 500, 600, and 700 ug/ml or at doses of 200, 400, 600, 800 and 1000 ug/ml in the absence or presence of metabolic activation (Aroclor-induced rat liver S-9 fragment), respectively. Drug exposure was followed by continued culture for an additional is to 24 hours after treatment. Cell survival following treatment was evaluated in one group following subculture and an additional 7-9 days of incubation. Mutagenicity was assessed in a second treated group which, following treatment were subcultured at 2-3 day intervals for 7-9 days, followed replating in the presence of 10 uM 6-thioguanine where cells were allowed to grow for an additional 7-10 days. Following this period cells were fixed, stained and counted for both cloning efficiency and mutant selection. Ethyl methanesulfonate (EMS) was used as a positive control in the mutagenic studies in the absence of the S-9 activation system and Benzo α Pyrene (BαP) in the presence of the S-9 activation system.

Results: Concurrent cytotoxicities, as measured by cloning efficiencies relative to the solvent controls were 99, 115, 107, 94, 36 and 21% at doses of 300, 400, 500, 600, and 700 ug/ml without metabolic activation and 108, 111, 99, 105 and 61% at doses of 200, 400, 600, 800 and 1000 ug/ml, with activation, respectively. RS-25,259-197 produced no evidence of increased mutagenesis in terms of an increased frequency of mutant clonable cells at any dose tested with or without activation (i.e. none of the mutant frequencies exceeded 40 mutants/10^6 clonable cells). Both positive controls showed the expected increases in mutant frequencies (EMS = 73.9 mutants/10 clonable cells and BαP =46.3 mutants / 106 clonable cells).

In conclusion, RS-25,259-197 showed no evidence for mutagenicity when tested in ex vivo mouse micronucleus test, the AMES test 'the E. coli WP2 uvra reverse mutation assay', and the Chinese Hamster Ovary HGPRT mutation assay in the presence or absence of a metabolic activating system (S-9 fraction). However, RS-25,259-197 was seen to produce an increase in the percentage of Chinese hamster ovary cells with chromosomal aberrations in a dose related

manner in the absence of the S-9 metabolic activating system and produced significant increase at the highest concentration 650 ug/ml in the presence of the S-9 activating system. The treatment related aberrations included chromosomal and chromatid breaks, chromatid fragments and exchange figures. Positive results in this test suggest that RS-25,259 was mutagenic in this vitro test.

In the above review of CHO/HGPRT Mutation Assay the previous reviewer (W. Shannon, Ph.D., HFD-180) did not provide the following information about the conduct of the study. These are given below.

Stdy # TA191.337031/Sponsor Study # AM0402
Conducting Lab: [redacted]

Dates of Initiation and Completion of Study: November 1, 1991 and March 2, 1992.

GLP and QAU Statement: A statement was included.

5. Ex-Vivo Unscheduled DNA Synthesis (UDS) Test in Rat Liver Cells
(Test # 990696/Study #99-38)

Testing Laboratories: [redacted]

Dates of Study Start & Completion: March 20, 2000 and November 28, 2000

GLP Compliance: A statement of compliance with the GLP regulations was included.
QA Report: yes (X)

Test Article and Control: Palonosetron HCl (30893-P105)
Test System: Male CDF Fisher 344 rat weighing between 218 to 268 g
Compounds & Doses Used: A single intravenous dose of 7.5, 15 and 30 mg/kg palonosterone was administered (vol 3 ml/kg in 0.9% saline). Positive controls used were methylmethane sulfonate (MMS, batch # 59H3681) and 2-acetylaminofluorene (2AAF, batch # 44H6311. Unlabelled thymidine solution (0.25mM).

Methods: In the UDS test, a single dose of 0, 7.5, 15 or 30 mg/kg was administered in 4 test groups of rats (2 animals/time group). Two animals in each of the test 1 and test 3, were sacrificed 2 hr after dosing and, 2 animals in each of test 2 and 4 were sacrificed 16 hr after dosing. The animals sacrificed and in situ perfusion of the liver performed and hepatocytes were isolated by collegenase perfusion. The cells resuspended in complete Williams E medium with 10% calf serum. About $3X10^5$ viable cells/ml of the suspension were seeded on to the slide

cover slip in 6-well dishes. Triplicate sampling for each of the rats was prepared and incubated with 90 to 120 min for cells to attach. The medium containing methyl-^{3}H-thymidine was added to each well and plates incubated at 37°C for 3-4 hr. The cultures were washed with Williams E medium, then 2 ml of unlabeled thymidine added to wash the cultures and incubated overnight. The cells were washed with PBS and treated with 2 ml of 1% sodium citrate for 10 to 20 min to swell. The cultures fixed in 1:5 acetic acid:absolute alcohol or 30 min and this was repeated two more times. The slides were washed, dried and left for 17 hr. The slides were developed in dark room after 12 days. These were stained in Harris hematoxylin previously filtered for 2 to 4 min and 100 morphologically normal cells were scored. The data of 3 randomly counted slides were calculated and the test was positive if a statistically significant increase in cell number were seen. A cell is in repair when the net grain count is >=5. An animals or group is considered to yield positive results if the net grain count is >=0 and the # of repairs >=20.

Results: The animals treated with 30 mg/kg dose showed convulsions and shallow breathing up to 30 min of the administration of the dose. A slight ctotoxicity was observed in 30 mg/kg treated animals. Therefore, the slides obtained from the animals treated at the doses of 7.5 and 15 mg/kg were selected for examining UDS. There were no increase in the mean net values of UDS in the treated groups, i.e. the mean number of UDS were -6.93, -6.75 and –7.43 in animals of 0, 15 and 30 mg/kg treatment groups. At sampling time of 16 hr, these cells were also similar to that of the vehicle control animal, i.e, -7.25, 7.30 and –7.33 in animals of 0, 15 and 30 mg/kg treatment groups. In the positive groups, treated with MMS and 2-AA a significant increase in triated thymidine incorporation was seen, i.e., about 20% cells were under repairs. Palonosetron was not mutagenic in this test.

Table 1

Results of Unscheduled DNA Synthesis in Rat Hepatocytes on the Palonosetron. (Test 1 & 2)

Drug/Dose mg/kg	Mean Net Value at sampling Time 12 h (Test # 1)						Mean Net Value at sampling Time 16 (Test # 2)					
	Mean net Value				Mean	SD	Mean Net Values				Mean	SD
Vehicle/0	-6.7	-6.7	7.6	6.7	-6.93	0.45	-7.8	7.4	-7	6.8	-7.25	0.44
Palono/15	-6.6	-6.7	-6.7	-7	-6.75	0.17	-7.1	-8	-6.8	-7.3	-7.3	0.51
Palono/30	-7	-6.8	-7.9	-8	-7.43	0.61	-9	-6.6	-6.6	-7.1	-7.33	1.14
Positive control	13.7 MMS 300	12.3	11.7	11.5	12.3***	0.99	6.1 2-AAF 50	-7.4	11.3	10.3	8.78***	2.43

*p 0.05. 0.01, ***p. 0.001

Table 2

Results of Unscheduled DNA Synthesis in Rat Hepatocytes on the Palonosetron (Test # 3 and 4)

Drug/Dose mg/kg	Mean Net Value at sampling Time 12 h Test # 3						Mean Net Value at sampling Time 16 Test # 4					
	Mean net Value				Mean	SD	Mean Net Values				Mean	SD
Vehicle/0	-7.1	-7.2	7.7	6.5	-7.13	0.49	-6.8	-6.5	-6.8	-7.1	-6.80	0.24
Palono/15	-7.9	-7.1	-7.1	-6.7	-7.2	0.50	-6.7	-6.6	-6.8	-6.8	-6.73	0.10
Palono/30	-6.9	-6.9	-8.1	-9.3	-7.80	1.15	-7.7	7.2	-6.9	-7.2	-7.25	0.33
Positive control	10.7 MMS 300	9.6	14	14.4	12.2***	2.39	15.8 2-AAF 50	16.8	10.7	8.4	12.9***	4.03

*p 0.05, 0.01, ***p, 0.001

SPECIAL TOXICITY STUDIES:

1. <u>Dermal Sensitization Study in Guinea pigs with a Transdermal Formulation Containing RS25259-007</u>: (Study No. AT 6279)

<u>Method</u>: The dermal sensitization potential of RS-25258-007 (free base) formulation was examined in 10 female guinea pigs. These animals were exposed to a single dermal application of vehicle control (solution containing sodium chloride and sodium phosphate, pH 8.2±0.2) or 10 mg/kg of RS-25259-007 formulation using ——— during preinduction phase. Two days later, induction phase began with a single topical application of 10 % sodium lauryl sulfate (SLS) followed by a single application of Freund's Complete Adjuvant (FCA). After this, animals were then challenged with test formulation. The occlusion was removed and application sites were evaluated for the signs of irritation 24 and 48 hr after removal of dressing.

<u>Results</u>: No changes at the site of application were seen in the concentrations selected in the preinduction, induction or challenge period of the study. RS-25259-007 did not produce sensitization in guinea pigs.

2. <u>Dermal Irritation Study in Rabbits with Transdermal Formulation Containing RS-25259-007</u>: (Study No. AT 6276)

Method: The aim of the study was to determine dermal irritation potential of transdermal application of RS-25258-007 (free base) formulation containing phosphoric acid and sodium phosphate at pH 8.2±0.2. Four sites (on the back of each rabbit) were clipped in 3 female New Zealand white rabbits, vehicle or test material in a volume of 0.5 ml were applied on the clipped areas and held in contact for about 24 hr, the application sites were wiped, soaked in water and examined for signs of irritation once daily for 3 days period.

Results: No changes at the site of application of vehicle, 5 or 10 mg/ml RS-25259 formulation were seen. A very slight erythema was present in 1 out of 3 rabbits 24 and 48 hr after exposure with 20 mg/ml of RS-25259. Therefore, RS-25259-007 at 20 mg/ml concentration was a slightly to mild irritant in rabbits.

3. **Ear Vein Irrtation Study in the Rabbit with an Intravenous Formulation of RS-25-259-197** (Study #PALO-99-30)

Methods: The potential of i.v. administered RS-25,259 to produce intravenous irritation was studied in rabbits. Rabbits were injected with RS-25,259-197 (10 mg/kg) in the right ear vein, while the left ear vein was injected with vehicle and served as the control. Veins were filled with test formulation (RS-25,259-197 or vehicle) then occluded with finger pressure for 10 seconds. Animals were sacrificed at 10, 30 and 60 min after drug exposure and examined grossly and histologically for evidence of intravenous irritation following euthanasia .

Results: Neither the RS-25,259 nor the vehicle formulation caused gross or microscopic changes in any injection vein.

4. **In Vitro Compatibility Testing of RS-25259-197 Using Human Blood:** (Study #CL 5911)

Methods: In vitro whole blood compatibility (Hemolysis and hemoglobin concentrations > 0.05 g/dl) and plasma compatibility (precipitate or coagulum) testing were performed on undiluted and saline-diluted (1:10 dilution) vehicle and 10 mg/ml RS~25,259-197 formulations. Triton X 100 (one volume of 0.075% or 2%) + nine volumes of whole blood served as a positive control for these studies.

Results: RS-25,259-197 and vehicle-treatment produced no evidence of hemolysis or gross change in the supernatants prepared from whole blood, suggesting that 10 mg/ml formulations of RS-25,259-197 are compatible in vitro with human blood. In contrast, Triton X 100 induced measurable hemolysis, producing hemoglobin concentrations of 1.06 and 9.2 at 0.75% and 2.0% concentrations.

LABELING

The annotated labeling of CGP 39393 generally conforms to the format specified under CFR 21, subpart B, 201.50 to 201.57 dated April 1991. Based on the present review, the changes in the following sections/categories of the proposed label are recommended. These changes are described by first giving the existing text of the proposed label, followed by the reviewer's comments and the changed text of the label.

1. The existing text under the category:

(5) *Carcinogenesis, mutagenesis, impairment of fertility*:
reads as:

PRECAUTIONS:

Carcinogenesis, Mutagenesis, Impairment of Fertility

2. REVIEWER'S COMMENTS:
The above version of the label should be changed and it should reflect that in 2-year carcinogenicity study in rats, to read as:

"(5) *Carcinogenesis, mutagenesis, impairment of fertility*:

PRECAUTIONS:

Carcinogenesis, Mutagenesis, Impairment of Fertility

OVERALL SUMMARY AND EVALUATION:

The chemotherapy induced nausea and vomiting is mediated by the release of serotonin from enterochromaffin cells of small intestines and this stimulate 5-HT_3 receptors located on afferent vagal nerve fibres of area postrema and chemoreceptor trigger zone. Palonosetron (RS-25259-197) a selective serotonin (5-HT_3)-receptor antagonist was effective in controlling the emesis in vivo chemotherapy induced emesis animal experimental models. It exerted a potent anti-emetic effect in cisplatin-induced emesis in ferrets (from 0.03 to 0.1 mg/kg p.o. dose) and dogs (0.1 ng/kg to 0.1 mg/kg). Ondansetron showed variable results in cisplatin-induced emesis. It was effective in controlling vomiting when administered 7 hr before cisplatin emesis and was demonstrated to be 4 to 7 times more potent than ondansetron and granisetron. Palonosetron binds with 5-HT_3 receptor sites in the rat brain stem nuclei, vagal dorsal motor nucleus and limbic area (pKi = 10.4 ± 0.2, rat brain cerebral cortex). In a vitro rat esophageal muscularis mucosa preparation, it did not show 5-HT_4 receptors antagonistic effect but a slight antagonistic effect was seen on substance P receptors of isolated guinea pig ileum. In in vitro guinea pig colon preparation, it did not produce any serotonin 5-HT_4 agonism but it exerted antagonistic effects. Palonosetron was effective by oral and intravenous routes of administration. The antiemetic effects of the compound were comparable with ondansetron (0.03 to 0.1 mg/kg, p.o/0.01 to 0.03 mg/kg iv) in emesis induced by actinomycin (0.15 mg/kg, iv) in dogs. It did not affect the emesis induced by apomorphine and copper sulfate. A bolus dose up to 1000 mg/kg, i.v. produced only a transient decrease in diastolic blood pressure in dogs and had no meaningful effects on the respiratory function. The cardiac physiology study with palonosetron showed that it prolonged action potential duration at concentrations of 0.3 and 3 μ M (100 and 1000 ng/ ml). It inhibited maximal rate of depolarization at 3 and 30 μ M in rabbit Purkinje fibers. The cardiovascular studies with palonosetron indicated that it inhibited fast sodium and potassium channels (hERG (Ikr) and hHNa (INa) currents) in HEK293 cells with IC_{50} of 1.9- 2.04 μ M and 6.5 μ M, respectively. Palonosetron inhibited hERG current by ~17% at the lowest dose tested (10 ng/ml). This concentration was about 10.9 times the maximum plasma level (0.92 ng/ml) of palonosetron attained by the administration of an intravenous dose of 0.25 mg (5 μ g/ kg if 50 kg body weight assumed) to subjects in clinical trials. M9 metabolite from 0.001 to 0.1 mg/ kg produced no effects on blood pressure, heart rate, and ECG in conscious dogs. The drug — of palonosetron produced no effects on blood pressure, heart rate, and ECG

up to the doses of 0.01 mg/ kg, however, this intermediate was withdrawn by the sponsor as it caused cardiac block in animals and Torse de Ponte in clinical studies.

Sponsor submitted preclinical pharmacology, absorption, distribution, metabolism and excretion studies in rats, dogs and monkeys, acute i.v./p.o. toxicity studies in mice, rats and dogs monkey, 4-week sc toxicity studies in juvenile rats (2 studies), 4-week iv toxicity study in juvenile dogs, 1-month i.v./p.o. studies in rats and dogs, 3-month oral toxicity study in rats and dogs, 26-week I.v. toxicity study in rats, 40-week i.v. toxicity study in dogs, 2-year oral carcinogenicity studies in mouse and rat, segment I. Male/female oral fertility studies, segment II. Teratology studies in rats and rabbits, segment III. Prenatal and postnatal toxicity study in rats, mutagenicity studies of Ames test, mammalian gene mutation assay in CHO cells, chromosomal aberration test in CHO cells, ex vivo unscheduled DNA syntheis in Fisher 344 rats, in vivo mouse micronucleus test, special toxicity studies to test acute vein irritation test in rabbits, in vitro compatability test in human whole blood, in vitro cytotoxicity in Balb/c3T3 cells, in vivo photoallergenicity test in guinea pigs, cytogenetic assay in Chinese hamster V79 cells with/without UVA and UVB light.

The present application is for the control of immediate and delayed phases of chemotherapy induced emesis. Sponsor did not conduct a study to show the efficacy of palonosetron on the delayed phase of emesis observed during the chemotherapy. But in clinical studies, palonosetron has been shown to act on the delayed phase of emesis.

Sponsor in a preclinical ADME studies in rats, showed that the intravenously administered compound attained plasma concentration of 75.7 ng.eq/ml and 114 ng.eq/ml after 5 min of administration with systemic clearance of 8 L/kg/hr and volume of distribution of 17.2 l/kg. The systmic clearance indog was 2.58 L.kg/hr in dog and the terminal half life in rat was 1.49 hr shorter than 2.3 hr in dog. The compound was disrtributed in bladder, ileum, lungs, adrenals, large and small intestines. Eight metabolites in the plasma of rat and 9 in the dog were detected and none of these conjugated. Metabolite 2, 3, 4, 1 and 5 (in order of rank) were isolated in rats and, metbolite 6 was the major metabolite in rats. It was excreted in feces up to 82% in first 24 hr (the excretion in urine complete in 8 hr and iin feces by 24 hr). The compound was transformed in M6 (33.6%), M3 (4.7%) and parent compound (4.43%). The chemical structure of metabolites identified after iv dosing (M1, 2, 3 and 6) were identified by sponsor. In monkeys, most of the administered compound by intravenous route was recovered in urine. Metabolite M9 at intravenous doses of 0.001, 0.01, and 0.1 mg/ kg had no effects on blood pressure, heart rate, and ECG in conscious dogs. In healthy volunteers following a single dose of 0.25 mg produced a plasma concentration of (Cmax) 0.92ng/ml and a steady state concentration of 29.8 ng.h/ml. Its half life was estimated as 47.2 hr.

The acute tolerance of the compound was tested in a single iv dose of 10, 30 and 100 mg/kg RS-25259-197 in rats and mice. In dogs, doses of 10 and 20 mg/kg were tested. It produced the common signs depression of CNS in these animals. The signs in the treated rats and mice were labored respiration, convulsions and inactivity. The CNS depression related salivation, labored respiration and tremors were seen in dogs. Both dogs collapsed and showed convulsions.

Minimum i.v. lethal doses were 30 mg/kg in rats and mice. A dose of 20 mg/kg was not lethal in dogs.

In 4-week intravenous toxicity study in rats, the 1, 3 and 10 mg/kg/day doses of the compound were used. No treatment related observed effects were seen in animals of 3 mg/kg/day treatment group, the dose was identified as the no effect dose for this study and the target organs of toxicity were not identified in the study.

In a 28- day subcutaneous toxicity study, neonatal/ juvenile rats (4 days old – day 4 PP) were treated at the subcutaneous doses of 0, 5, 15, and 25 mg/ kg/ day. Sponsor administered the compound by subcutaneous route instead of intravenous route in the clinical setting because of the small size of animals in the present study. Rats (i. e., offspring) were killed and necropsied on day after the last treatment. Parental female rats received no treatment and were sacrificed following weaning of offspring. AUC values for palonosetron in male and female animals on days 1 and 28 increased with increasing doses but non-dose proportional manner. The plasma AUC values for palonosetron were similar on days 1 and 28. The identified 'no effect dose' was 5 mg/ kg/ day. There was no treatment- related mortality. The incidences of male and female rats at 15 and 25 mg/ kg/ day with an absent pupillary reflex on day 21 postpartum were increased as compared to controls. Eye opening was slightly delayed for rats at 15 and 25 mg/ kg/ day. Target organs (or tissues) of toxicity were injection sites, optic nerves, and kidneys. For male and female rats at 15 and 25 mg/ kg/ day, histopathological changes at injection sites included mineralization, hemorrhage, acanthosis, dermatitis, and cellulitis. The incidence of neuropathy in the optic nerves in 25 mg/kg/day was increased in male and female rats. The incidences of focal nephropathy and renal papillitis were increased for female rats at 25 mg/ kg/ day.

Sponsor conducted a repeat 4-week toxicity study in juvenile rats study on the request of the Agency (letter January 31, 011) as the previous study ([redacted] report #1063/18-D6154) was not complete and it lack the measurements of hematology and clinical chemistry parameters. The doses and the methods used in the present study were the same as used in the previous 28-day study in juvenile rats ([redacted] report #1063/18-D6154). In brief, the study included the assessment of the body weights changes, the developmental parameters of ear/eye opening (from day 3 to 6 for ear and from day 11 to 16 for eye opening), righting reflux (day 5), air righting reflex (three trials on day 22), startle response (on day 15), pupillary light reflex and opthalmoscopy (on day 33 day of age) were also observed. Subcutaneously administered palonosetron caused renal pelvic distension, extramedullary haemopoiesis of marked intensity in spleen and dermal reactions including myofibril degeneration/necrosis of moderate to marked intensity in animals of 15 and 25 mg/kg/day treatment groups. Eye lens opacity and structural abnormality of posterior synechia was seen in 1 of 12 male pups and, delay in development of lens suture line was seen in 1 of 12 female pups of 25 mg/kg/day treatment group. No incidences of optic nerve degeneration were seen. A dose of 5 mg/kg/day was a 'highest tolerable dose' and kidney, spleen and site of injection were the target organs of toxicity.

In a 4-week oral toxicity study in rats, RS-25259-197 was administered at 6, 18, 60, and 180 mg/kg/day. No treatment-related mortality was observed but mild decrease in hemoglobin and other hematology parameters and, liver enzymes were reported in animals included in 60 and 180 mg/kg/day treatment groups. The identified target organs of toxicity in males were liver (increased weights, hepatocellular swelling and glycogen deposition along with decreased liver enzymes) and testes (reduced weights and histological correlates of degeneration/necrosis of the seminiferous epithelium and immature spermatogenic cells in the epididymis) . In females, thymus (reduced weight, gross findings of small thymus and histological findings of thymic lymphoid atrophy was the identified target organ of toxicity. A dose of 18 mg/kg/day was the no effect oral dose in rats.

In 26-week intravenous toxicity study with 4 weeks of recovery period in rats, 0, 2, 7 and 14/10 mg/kg/day palonosetron (B. #1308911/30893-P105; vol. 1 ml/kg) was administered to determine the reversibility of treatment related toxicity. The initial high iv dose of 14 mg/kg/day produced convulsions, reduced activity and deaths among animals and the dose was adjusted to10 mg/kg/day. Palonosetron treatment produced non-proportional plasma concentrations in animals and bleeding was seen at the site of injection in a dose-related manner. The identified target organ of toxicity was site of injection and 10 mg/kg/day and 7 mg/kg/day were identified as the 'highest tolerable and 'no effect' doses, respectively.

In a 28- day intravenous toxicology study, neonatal/ juvenile dogs received palonosetron at doses of 0, 1, 3, or 6 mg/ kg/ day. At the start of treatment, animals ranged in age from 9 to 18 days with a mean age of 13 days. The dose of 6 mg/ kg/ day could be considered a highest tolerated dose. Plasma AUC values for palonosetron on days 1 and 28 were proportional to dose. Plasma AUC values for its metabolite, RS- 17825- 007, on day 1 were greater than proportional to dose. Plasma AUC values for RS-17825- 007 on day 28 were approximately proportional to dose. Plasma AUC values for palonosetron and RS- 17825- 007 on day 1 were greater than those observed on day 28, which may be the result of augmented clearance associated with repetitive dosing or increased maturity of animals. Cmax values for palonosetron on day 28 were greater than those observed on day 1.

In 1-month iv toxicity study in dogs, palonosetron was administered at 0, 1, 3 and 10 mg/kg/day. No treatment related effects other than salivation and/or red ear discoloration was seen in animals of 10 mg/kg/day treatment group. A dose of 3-mg/kg dose was identified as the 'no effect dose'. Sponsor did not measure the effect of drug on the conduction parameters.

In a 4-week oral toxicity study in dogs, RS-25259-197 was administered at doses of 2, 6, and 20 mg/kg/day. Only transient clinical signs of salivation, with no treatment-related mortality observed in animals of 6 and 20 mg/kg/day treatment groups. Reductions in absolute and relative weights for testes were observed at the 20 mg/kg dose, but had no gross or histological correlates. No target organs of toxicity were identified in the study and the highest dose of 20 mg/kg/day was considered as 'no effect dose' for the study.

In 3-month toxicity study, 40 (20/sex) dogs were administered daily oral dose of either 0, 2, 10 or 40 mg/kg/day of RS-25259-197 in capsules. RS-25259 attained a dose dependent plasma concentration up to a daily dose of 20 mg/kg. Sponsor estimated the plasma concentration after the first dose; the estimates after 10, 20 and 40 mg/kg doses could not be determined. The dose of 40 mg/kg/day of RS25259-007 was tolerated well by both male and female dogs. The plasma concentration of the compound after the highest dose of 40 mg/kg/day of the study was not determined during the study. Since the half-life of the compound was 2 hr, the spacing of two daily doses the compound should have been 2 hr instead of 6 hr. The highest dose could be greater than 40 mg/kg/day as the target organs of toxicity and MTD could not be identified in the study.

The 9-month intravenous toxicity study in dogs (20/sex) was done to investigate the reversibility of the toxicity in dogs. The 4 groups of animals were administered intravenous bolus dose (rate 5 ml/min) of 0, 1, 3 or 5/10/6 mg/kg/day palonosetron (volume 1 ml/kg). The animals in the 4th group (high dose treatment group) were given 5 mg/kg/day during build up phase (study week 1) and 10 mg/kg/day during the first 2 days of week 2. Because of convulsions, ataxia, vomiting and diarrhea, the dose was adjusted to 6 mg/kg/day on day 3 of week 2. Slight ataxia was seen from the time of injection to males and females included in 6 mg/kg/day treatment group and in 2 males of 3 mg/kg/day treatment group. Soft to loose feces was reported in 1 male of each of 3 and 6 mg/kg/day treatment groups during the treatment period. A dose of 3 mg/kg dose was considered as the 'no effect dose' in the present study. The EKG tracings were used to measure the heart rate of study animals.

The 3-month oral gavage study in mouse was conducted at daily oral dose of either 0, 30, 60, 90 and 120 mg/kg/day of RS-25259-197 (as a free base) in 5 groups of animals (10/sex/group). A treatment related hypersalivation and convulsions were seen in 90 and 120 mg/kg/day treatment group animals. A daily dose of 120 mg/kg of RS25259-197 was lethal in both male and female mice and a dose of 90 mg/kg/day was lethal in males. It produced a decrease in absolute weights of accessory male organs, pulmonic congestion and bleeding. Therefore lungs and male sex organs were identified as the target organs of toxicity in this study. A dose of 60 mg/kg/day produced only a minor change in absolute and relative weights of accessory sex organs without any histopathological alterations, therefore this dose was considered as a 'MTD' for males in the study. A dose of 90 mg/kg/day was non-lethal in females, therefore it was identified as MTD for the females in the proposed study.

The 104-week carcinogenicity study in mice was conducted by administering palonosetron by oral gavage route in CD-1 Mice. The dose selection of the study was based on the recommendations of CAC-Ex committee dated February 21, 1995 and Division letter dated March 9, 1995 (to the previous sponsor, Syntex of Palo Alto). Syntex initiated the study but did not complete it as the development of the drug was ceseased by them. The present sponsor initiated the mouse carcinogenicity study at the doses recommended earlier by Ex-CAC. The 5 groups of animals were administered doses of 0, 0, 10, 30 and 60 mg/kg/day (0, 0, 30, 90 and 180 mg/mm^2/day) palonosetron. The plasma concentrations of palonosetron were higher in

males and these persisted for a prolonged time in males than in females. Palonosetron treatment did not produce a dose or treatment related tumors in mice. Sponsor in the present application has proposed the use of palonosetron at the dose of 0.25 mg/day (i.e., 5 ug/kg/day or 185 ug/mm^2/day). The oral dose of 60 mg/kg/day palonosetron in mouse carcinogenicity study provided 150 to 289 times the plasma exposure (AUC = 29.8 ng.hr/ml) in clinical subjects receiving an i.v. dose of 0.25 mg/day.

A 3-month oral dose range-finding study in rats was conducted with RS-25259-007 to provide a basis for dose selection in a 2-year oral carcinogenicity study. RS-25259 was administered by gavage in 5 groups of rats at the doses of 0, 18, 60, 120 and 180 mg/kg for 3 months. The study was conducted in sufficient number of animals and it was a valid study. A dose dependent suppression of body weight gains was seen among study males and among 120 and 180 mg/kg/day treatment groups animals. A reduction in testicular weights and accessory sex organs associated with diffuse testicular tubular atrophy (2 of 15 rats), testicular aspermatogenesis (100%), and decreased spermatozoa in the epididymides (100%) was seen in 180 mg/kg/day treatment group animals. The doses of 120 and 180 mg/kg/day palonosetron were lethal in both sexes of animals. Lymphoid atrophy of the spleen was also seen in 60% of the males at the 120 mg/kg dose. In females, the dose of 60 mg/kg/day was a 'no effect dose' and the dose of 120 mg/kg/day was MTD as it was associated with only slight suppression of body weight gains (12%), slightly lower platelet counts, mild increases in total counts for leukocytes, neutrophils, and lymphocytes, increased triglycerides, increased weights for liver and spleen, and histological lesions limited to an increased incidence of chronic nephrotic syndrome (36% versus no controls). The next higher dose in females (180 mg/kg) produced tremors, convulsions, and mortality in 6 of 15 animals tested. Effects in surviving females at the 180 mg/kg dose included alterations in hematology and clinical chemistry and histopathological lesions including: bone marrow toxicity (hypocellularity and reductions in femoral metaphyseal trabecular bone), splenic lymphoid atrophy and necrosis, increased height of the follicular epithelium of the thyroid and hypertrophy of the adrenal glomerulosa cells, increased severity of chronic progressive necrosis and congestion of the liver.

The 2-year carcinogenicity study in rats was conducted on the doses recommended by the CAC-Ex dated October 4, 1994 to the previous sponsor, Syntex of Palo Alto. The previous sponsor initiated the study but did not complete it, as they did not develop the drug further. The present sponsor initiated the rat carcinogenicity study in 5 groups of animals at the doses of 0, 0, 15, 30 and 60 mg/kg/day palonosetron in males and, 0, 0, 15, 45 and 90 mg/kg/day in female rats. These doses were equivalent to 90, 180 and 360 mg/mm^2/day in males and 90, 270 and 540 mg/mm^2 in female animals. The study was conducted on adequate number of animals (male/female) and the doses recommended by CAC-Ex committee. The plasma concentrations in females were more than males of the treatment groups during the study. On study week 26, the exposure of the compound in male and female animals of high dose was 136.9 and 308.2 times the plasma concentration (AUC values) achieved after the suggested clinical dose of 5 ug/kg in man. The administered compound attained a non-dose proportional plasma concentrations of the parent compound and the metabolite RS-17825 (major human metabolite). The plasma concentrations

of treated females were more than males during the study. On study week 26, the exposure of the compound in male and female animals was 136.9 and 308.2 times the plasma concentration (AUC values) achieved after the suggested clinical dose of 5 ug/kg in man. Increased incidences of benign pheochromocytoma in male were seen. Increased incidences of combined benign and malignant pheochromocytoma and, pancreatic islet cell adenoma and combined incidences of islet cell adenoma and carcinoma were seen in male treatment groups. The adenoma of pars distalis incidences were significantly high in males of treatment groups. The incidences of hepatocellular adenoma and thyroid C-cell adenoma were increased in females of high dose treatment group.

Palonosetron was tested for mutagenicity in Ames test, rat bone marrow micronucleus test, HGPRT in Chinese hamster ovarian cells. It was negative in these mutagenicity tests. However, it was mutagenic in an *in vitro* chromosomal aberration test in Chinese hamster ovarian cells in the presence and absence of activating system.

In Segment I. Fertility and reproductive performance toxicity study in male rats, RS-25259-was given was at the single oral dose of either 0, 18, 60 or 120 mg/kg/day for at least 61 to 63 days prior to cohabitation and were mated with untreated females. RS25259 produced a dose dependent decrease of the implantation index in animals treated with low and mid doses of the study. The highest dose of the study, 120 mg/kg/day was toxic and the treated males were infertile as the rate of copulation was markedly reduced and none of the female got pregnant. No adverse effects on the reproductive and fertility parameters of animals treated with 18 and 60 mg/kg/day dose were noted.

In other Segment I. Fertility and reproductive performance toxicity study in female rats, 4 groups of animals were administered a single oral dose of either 0, 9, 30 or 60 mg of RS-25259-197/kg/day (in a volume of 5 ml/kg/day adjusted daily according to daily body weight) for 2 weeks prior to cohabitation with untreated males. Only a trend of a decrease of number of matings and of animals conceived was noted in 60 mg/kg/day treatment group.

In the oral Segment II reproductive toxicity study in rats, RS-25259-197 was administered by gavage to pregnant rats at doses of 0 (vehicle), 18, 60, and 120 mg/kg during the period of organogenesis. The 120 mg/kg dose showed evidence of maternal toxicity (i.e. reduced maternal weight gain), which could have contributed to the reduced fetal weights and reduced skeletal ossification also seen at 120 mg/kg dose. Reduced fetal weights were also seen at the 60 mg/kg dose in the absence of any evidence of maternal toxicity. However, no treatment-related teratogenic effects were evident at any dose tested.

In the oral Segment II reproductive toxicity study in rabbits, RS-25259-197 was administered by gavage to pregnant rabbits at doses of 0 (vehicle), 18, 60, or 120/90 mg/kg/day (120 mg/kg dose reduced to 90 mg/kg after day 4), during the period of organogenesis. The 120/90 mg/kg produced maternal mortality and suppressed body weight gains in surviving dams. However, RS-25259-197 showed no evidence of teratogenic effects in the F1 offspring.

In oral Segment III. Prenatal and postnatal study, RS-25259-197 was administered orally by gavage at the doses of 0 (vehicle), 1, 9, 30 or 60 mg/kg/day to timely mated 4 groups of female rats (24/group) from gestation day 6 to day 21 of post-partum (41 days). No developmental toxicity excepting abnormal positioning of hind legs in 2 pups (1/low and mid dose groups) died during the initial stage of the development of the pups was observed but these were isolated cases and sponsor did not conduct microscopic examination on these pups. Palonosetron at the doses up to 60 mg/kg/day did not produce postnatal toxicity in rats. A significant reduction in the live litter size was observed, however it's relation to treatment is not apparent as no other gestational parameters showed treatment-related changes.

Sponsor in the present application has requested to set the specification of % for two potential impurities of palonosetron, i.e., The estimated amount of impurities at the proposed specification with the intended dose of 5 ug/kg will be ug/kg. The safety of the impurities was determined by computing the amounts of the impurities in 'no effect doses' of 26-week IV toxicity study in rats (7 mg/kg/day) and 40-week IV toxicity study in dogs (3 mg/kg/day). Palonosetron batch # P30893-P105 was used in 26-week IV rat and 40-week IV dog toxicity studies and, this was analyzed to contain % of (attached certificate of analysis). The amount of impurities administered with the safe dose of 7 mg/kg/day in rat study were ug/kg/day of As a rule of thumb, one tenth of these doses are considered safe for humans. Thus the the amounts of and ug/kg/day in the clinical dose may be safe. The amount of impurities administered in dogs with the no effect dose of 3 mg/kg/day in 40-week dog study was 5.5 and 6.5 ug/kg/day, respectively. As a rule of thumb, one fifth of these doses are considered safe for humans. Thus the the amounts of ug/kg/day. the clinical dose may be safe. Available clinical data would be of more relevance in this context.

Sponsor has demonstrated adequately that palonosetron was effective in the prevention of acute nausea and vomiting associated with cisplain induced (and other anti-cancer agents induced) emesis in dogs and ferrets. Palonosetron did not produce tumors in mouse carcinogenicity study. In rat carcinogenicity study, increased gavage doses of 0, 0, 15, 30 and 60 mg/kg/day in males and, 0, 0, 15, 45 and 90 mg/kg/day in females. The administered compound attained a non-dose proportional plasma concentrations of the parent compound and the metabolite RS-17825 (major human metabolite). The plasma concentrations in females were more than males of the treatment groups during the study. On study week 26, the exposure of the compound in male and female animals was 136.9 and 308.2 times the plasma concentration (AUC values) achieved after the suggested clinical dose of 5 ug/kg in man. Increased incidences of benign pheochromocytoma in male and females were seen. Increased incidences of combined benign and malignant pheochromocytoma and, pancreatic islet cell adenoma and combined incidences of islet cell adenoma and carcinoma were seen in all treatment group animals. The adenoma of

par-distalis incidences were significantly high in males of treatment groups. The incidences of hepatocellular adenoma and thyroid C-cell adenoma were increased in females of high dose treatment group.

RECOMMENDATIONS:

1. From preclinical standpoint, the application is approveable.

2. The proposed label of the sponsor should be changed to reflect the suggested changes in the text of the review.

/S/

Yash M. Chopra, M.D., Ph.D.,
Pharmacologist, HFD-180

COMMENTS:

/S/

Jasti B. Choudary, B.V.Sc, Ph.D.,
Supervisory Pharmacologist, HFD-180

cc:
Original NDA
HFD-180
HFD-181/CSO
HFD-180/Dr.Chopra
HFD-180/Dr.Choudary
R/D Init.: J. Choudary 6/26/03

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APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

IND [redacted] November 1, 1994

Syntex Inc.
Attention: Martha Reitman, MD
3401 Hillview Avenue
Palo Alto, CA 94303

Dear Dr. Reitman:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(i) of the Federal Food, Drug, and Cosmetic Act for RS-25259-197 Injection.

We also refer to your amendments dated June 1, 1994, serial numbers 029 and 030, containing the report (AT 6665) of a 3-month dose-ranging study of RS-25259-007 in rats and a protocol (89-R-94-25259-197-PO-CA) for an oral carcinogenicity study of RS-25259-197 in rats. You requested Agency's agreement on the dose selection and protocol design.

We have completed the review of your submission, and have the following comments and recommendations:

A. Regarding the 3-month dose ranging study:

1. In the male rats, at 60 mg/kg/day, there was no treatment related mortality or significant target organ toxicity and the body weight gains were moderately retarded when compared to the body weight gains in the control male rats. The dose of 60 mg/ kg/day is the maximum tolerated dose (MTD) in male rats and, accordingly, your proposal to employ this dose as the highest dose is acceptable for male part of the proposed carcinogenicity study. The recommended mid and low doses are 30 and 15 mg/kg/ day, respectively.

2. In female rats, 60 mg/kg/day was the no effect dose. Therefore, your proposed highest dose of 60 mg/kg/day for the female rats is not acceptable. At 120 mg/kg/day, there was no treatment related mortality or significant target organ toxicity and the body weight gains were moderately retarded when compared to the body weight gains in the control female rats. A dose of 120 mg/kg/day is the MTD in female rats. However, since this dose is too close to the lethal dose of 180 mg/kg/day, we recommend that you employ 90 mg/kg/day as the highest dose in the female rats. The recommended mid and low doses are 45 and 15 mg/kg/day, respectively.

B. Regarding the carcinogenicity study protocol:

1. Consider having two control groups of 75 animals each/sex instead of one control group of 150 animals/sex. The availability of two control groups for each sex will provide a measure of background variability in the concurrent controls.

2. If the survival of a treated group decreases to 20% of the original starting size, consideration shoul4 be given to stop dosing that particular group. If 1 on the other hand, survival of the control group approaches 20% of the original starting size, all groups (control and treatment) of that sex should be terminated. Any plans to terminate or alter the course 0: any one group should be communicated to the Division for advice prior to implementation.

3. We recommend that the carcinogenicity protocol be amended to incorporate the following:

a. Periodic determinations of plasma concentrations of the drug in satellite animals to assure absorption.

b. Periodic microbial screens in sentinel groups for monitoring the health of animals.
c. Daily dosing without interruptions for stated holidays.
d. The free base (RS-25259-007) should be employed in the study since the dose-ranging study was conducted using the free base.

If you have any questions, please contact:

cc: Kati Johnson
Orig IND Consumer Safety Officer
HFD-180 (301) 443-0487
HFD-18 0 /JChoudary
HFD-180/CSO

Sincerely yours,

R/D init: JChoudary 10/31/94
SFredd 10/31/94
kj/October 27, 1994\cso\i\\
AD

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CAC Executive Committee Final Report

Meeting Date: October 4, 1994
Application: IND
Division: HFD-180
Reviewer: S. Williams
CAC Chairperson: Taylor, A.
Members: Choudary, Contrera, Farrelly

The CAC Exec Committee reviewed a 3-Month Dose-Ranging Study and a Rat Carcinogenicity Bioassay Protocol for IND (RS-25259-197)

Review of the 3-Month Oral Dose-Ranging Study with RS-25259 in rats indicated disparate toxicological profiles in males versus females, in that males appeared more susceptible to the toxicological effects compared to females. In males, a dose of 60 mg/kg was identified as the MTD, based on slight suppression of body weight gains and histological findings limited to diffuse testicular atrophy in 2 of 15 rats examined. The 60 mg/kg dose in males was in agreement with the maximum dose proposed in the carcinogenicity protocol. However, it was suggested that the proposed low and mid doses (mg/kg, respectively) be revised to 1/2 and 1/4 of the MTD (i.e. 30 and 15 mg/kg) for males in the carcinogenicity bioassay.

In females, a MTD of 120 mg/kg was identified, based on slight suppression of body weight gains and histological lesions limited to an increased incidence of chronic renal nephrosis syndrome (4 of 11 rats tested). The 120 mg/kg dose was higher than the dose of 60 mg/kg proposed as the maximum dose for females in the Rat Carcinogenicity Study Protocol. In this regard, CAC Exec. Committee members agreed that the 60 mg/kg dose was inappropriately low, but expressed concern that use of the 120 mg/kg dose could result in excessive mortality, since it was so close to the 180 mg/kg dose which was lethal in the 3-Month Dose Ranging Study. Therefore, the Committee advised using a 90 mg/kg dose as the maximum dose to be administered to females in the proposed rat carcinogenicity bioassay. Doses of 45 mg/kg and 15 mg/kg were also suggested for the mid and low doses for females, respectively.

Additional recommendations expressed by the Committee included the following:

1. Instead of terminating the sex in which excessive treatment-related mortality occurs, we recommend that the Sponsor end dosing only in that sex of the affected dose group. In addition, any plans to terminate any portion of the study should be communicated to the FDA for advisement, prior to termination.

2 Sponsor should divide control group into 2 separate groups, such that pair-wise comparisons against the two control groups can be made

3. Sponsor should incorporate an additional arm and sentinel rats for periodic measurement of plasma blood levels and microbial screens, respectively.

Report by Shannon P. Williams, Ph.D.

cc:
IND
HFD-180/div file
HFD-180/Williams
/Choudary
HFD-502/CAC file

IND

MAR 9, 1995

Syntex, Inc.
Attention: Gaetan Rouleux
3401 Hillview Avenue
Palo Alto, CA 94303

Dear Mr. Rouleux:

Please refer to your Investigational New Drug Application (IND) submitted pursuant to section 505(1) of the Federal Food, Drug, and Cosmetic Act for RS-25259-197 Injection.

We also refer to your amendments dated October 6 and 14, 1994, serial numbers 38 and 39, respectively. These submissions contained a report (AT 6751) of a 3-month oral dose-ranging study in mice and a draft Protocol (97-M-94-25 59-197-PO-CA) for an oral carcinogenicity study of RS-25259-197 in mice, respectively, and requested Agency agreement on the dose selection and protocol design.

We have completed the review of your submissions, and have the following comments and suggestions

1. In the 3-month oral dose-ranging study, RS-25259-197 was lethal at doses of 90 and 120 mg/kg/day in male mice and 120 mg/kg/day in female mice. The target organs of toxicity were lungs (histopathology findings of congestion and clinical signs at 90 and 120 mg/kg/day in both sexes), central nervous system (convulsions at 120 mg/kg/day in both sexes) and male accessory sex organs (significantly decreased weights at 120 mg/kg/day). A dose of 60 mg/kg/day was devoid of any clinical signs of toxicity or histopathology changes in both sexes. Your proposed high dose of 90 mg/kg/day for the carcinogenicity study is not acceptable due to the observed toxicity in both sexes and lethality in males. We recommend that you employ 60 mg/kg/day as the high dose for both sexes and carefully monitor animals, particularly males, for possible convulsions and mortality during the course of the study. In the event of such developments, the dose should be reduced to 45 mg/kg/day after prior consultation with the Division. Your proposed mid and low doses of 30 and 10 mg/kg/day, respectively, are acceptable.

2. Consider having two control groups of 75 animals/sex instead of 150 animals/sex. Availability of two concurrent control groups for each sex will provide a measure of background variability.

3. We recommend that you consult the Division if the number of surviving animals in any treated group reaches 20 to 30 prior to week 90 for decisions on early termination or cessation of dosing.

4. The carcinogenicity protocol should be amended to incorporate periodic microbial screens in sentinel groups for monitoring the health of animals.

If you have any questions, please contact:
Kati Johnson
Consumer Safety Officer
(301) 443-0487

Sincerely yours,

Stephen B. Fredd, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation I Center for Drug Evaluation and Research

cc:
Orig IND
HFD-180
HFD-180/JChoudary
HFD-180/CSO/Kjohnson
R/D init: KJohnson 3/6/95 JChoudary 3/7/95 SFredd 3/7/95
kj/March 6, 1995/c:\wpfiles\cso\i\ \Okj
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CAC Executive Committee Final Report

Application: IND (RS-25259-197)

Division: Gastrointestinal and Coagulation Drug Products (HFD-180)
Date: February 21, 1995
Reviewer: Dr. Y.M. Chopra
Chairperson: Dr. J.DeGeorge
Members: Drs. Choudary, Contrera and Jacobs

Mouse Dose-Ranging Study and Proposed Mouse Carcinogenicity Study Protocol for RS-25259-197:

The committee was Provided with Copies of (1) Pharmacology review of Dr. Y.M. Chopra, (2) Supervisory Pharmacologist addendum to Dr. Chopra's review and (3) memorandum of the Supervisory Pharmacologist to the CAC Exec. Comm. (Dr. DeGeorge)

In the 3-month oral dose-ranging study, RS-25259-197 was lethal at oral doses of 90 and 120 mg/kg/day in male mice and 120 mg/kg/day in female mice. The target Organs of toxicity were lungs (histopathology findings of congestion and clinical signs of gasping, labored breathing and ralings at 90 and 120 mg/kg/day in both Sexes), central nervous system (convulsions at 120 mg/kg/day in both sexes) and male accessory sex organs (significantly decreased weights in 120 mg/kg/day group males). A dose of 60 mg/kg/day which was devoid of any clinical signs of toxicity or histopathology changes was identified as the MTD for both sexes. Adequate information on plasma levels of drug in the mouse and man are not available, for dose determinations.

Conclusions:

(1) Sponsor proposed a dose of 90 mg/kg/day for the high dose in the carcinogenicity study. This dose is clearly lethal in males and toxic in females. The Division recommended 60 mg/kg/day as the high dose for both sexes and concurred with sponsor's proposed mid and low doses of 30 and 10 mg/kg/day. The CAC Exec. Comm. concurred with this. It also recommended that the sponsor should watch for possible convulsions and mortality at the high dose particularly in males since that dose is close to the lethal dose of 90 mg/kg/day. In the event of such a development, the sponsor should reduce the dose to 45 mg/kg/day after prior consultation with the Division.

(2) The Committee agreed with the Division's recommendation that sponsor should consider having two control groups of 75 animals/sex instead of 150 animals/sex to provide a measure of background variability in the concurrent controls.

(3) Sponsor should consult the Division if the number of surviving animals in any treated group reaches 20 to 30 prior to week 90 for decisions on early termination or cessation of dosing.

(4) Periodic determinations of plasma concentrations of the drug are not necessary since the dose selection is not based on AUC values and the inherent feasibility problems with mouse for frequent sampling make it less practical.

(5) Periodical microbial screens in sentinel groups is considered desirable for monitoring the health of animals. It is expected that most of the sponsors usually follow such measures.

(6) Sponsor's proposed dosing interruptions for non-routine holidays may not affect the outcome of the study.

Report by Jasti B. Choudary

cc:
IND
HFD-180/Dr. Choudary
HFD-180/Dr. Chopra
HFD-502/CAC File

JBC/hw/2/27/95
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APPENDIX I

Group Distribution of Non-Neoplastic Incidences in animals of 104-week Mouse Carcinogenicity

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TABLE 10F

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 1

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
** TOP OF LIST **											
ADRENAL CTX	NUMBER EXAMINED:	55	55	55	56	64	56	55	56	56	63
--SUBCAPSULAR CELL HYPERPLASIA		3	0	4	5	8	3	0	1	2	1
--SPINDLE CELL HYPERPLASIA		20	20	24	19	29	46	45	43	44	51
--CORTICAL HYPERTROPHY		10	8	12	11	18	1	1	0	1	0
--INFLAMMATION		0	0	2	0	0	1	0	0	2	2
--PERICAPSULAR INFLAMMATION		0	1	1	0	0	0	0	0	1	0
--CEROID ACCUMULATION		1	0	0	0	1	3	5	6	5	9
--X-ZONE - VACUOLATION		0	0	0	0	0	0	0	0	1	2
--ACCESSORY ADRENOCORTICAL TISSUE		0	1	2	1	4	4	3	7	4	7
--CORTICAL VACUOLATION		0	0	2	0	0	0	1	1	1	0
--CORTICAL CYSTIC/HAEMORRHAGIC DEGENERATION		0	0	0	0	2	0	0	0	1	0
--CORTICAL HYPERPLASIA, FOCAL		3	4	3	2	2	0	1	1	0	0
--CORTICAL FIBROSIS		0	0	1	0	0	0	0	0	0	0
--CYST(S)		0	0	0	0	1	2	0	0	0	0
ADRENAL MED	NUMBER EXAMINED:	55	55	55	56	64	56	55	56	56	63
--MEDULLARY HYPERPLASIA, FOCAL		0	2	1	1	5	1	2	3	3	0
AORTA	NUMBER EXAMINED:	56	56	56	55	64	56	55	55	55	64
--MEDIAL MINERALISATION		0	0	0	1	0	0	1	0	1	0
--ADIPOSIS		0	0	0	1	0	0	0	0	0	0
BRAIN X4	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--ARTERITIS		1	0	0	0	0	1	1	0	1	0
--DEPRESSION DUE TO ENLARGED PITUITARY		0	0	0	0	0	0	2	0	1	1
--PERIVASCULAR CUFFING		0	1	0	1	0	0	1	1	0	1
--INFLAMMATION		0	1	0	0	0	1	0	0	1	0
--MENINGITIS		0	0	0	0	0	0	1	0	0	0
--HAEMORRHAGE		0	0	0	0	0	0	0	2	0	0

TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Paloncestron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 2

Schedule number: BSH 002

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
CAECUM	NUMBER EXAMINED:	55	56	55	53	63	55	56	55	55	63
--MUCOSAL ATYPICAL HYPERPLASIA		0	3	4	4	1	1	1	2	0	0
--MUCOSAL ULCERATION		2	0	2	0	0	0	0	0	1	0
--SUBMUCOSAL OEDEMA		2	0	4	2	2	1	1	0	0	1
--DISTENSION		0	2	0	2	0	0	1	0	1	0
--PERITONITIS		0	0	3g	1	0	0	0	0	0	1
--ADHESION(S)		0	0	1	0	1	0	0	0	0	0
--SUBMUCOSAL INFLAMMATION		2	2	6	4	0	1	0	0	1	0
--CYST(S)		0	2	2	2	1	0	2	2	0	0
--NEMATODES		0	0	0	0	1	0	0	0	0	0
COLON	NUMBER EXAMINED:	56	56	56	56	64	56	56	55	56	62
--PERITONITIS		0	1	0	0	1	1	0	2	1	0
--INTUSSUSCEPTION		0	0	0	0	0	0	0	1	0	0
--NEMATODES		10	15	9	7	17	5	10	16bg	4	5
--MUCOSAL ULCERATION		0	0	0	0	1	2	0	2	1	1
--SUBMUCOSAL INFLAMMATION		1	1	1	0	0	2	0	2	1	1
--MUCOSAL ATYPICAL HYPERPLASIA		1	2	0	0	2	2	0	2	1	1
--DISTENSION		0	0	0	0	1	0	0	0	0	0
--SUBMUCOSAL OEDEMA		0	0	0	0	1	0	0	0	0	0
--INFLAMMATION		0	0	1	0	0	0	0	1	0	0
--CYST(S)		0	1	0	0	0	0	0	0	0	0
DUODENUM	NUMBER EXAMINED:	54	55	55	52	61	55	54	55	54	60
--PERITONITIS		0	0	0	0	0	1	0	0	1	0
--MUCOSAL ATYPICAL HYPERPLASIA		0	0	2	1	1	1	4	3	4	1
--VILLOUS HYPERPLASIA		1	0	1	0	0	0	0	0	1	0
--MUCOSAL ULCERATION		0	0	0	0	0	0	0	0	1	0
--SUBMUCOSAL INFLAMMATION		0	0	0	0	0	0	0	0	1	1

TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 3

Schedule number: NSH 002

ORGAN AND FINDING DESCRIPTION	--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:	MALE					FEMALE				
GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **										
DUODENUM ..... NUMBER EXAMINED:	54	55	55	52	61	55	54	55	54	60
--DIVERTICULUM	0	0	0	0	0	1	0	0	0	0
--MUCOSAL INFLAMMATION	0	0	1	0	0	0	0	0	1	0
EPIDIDYMIDES ..... NUMBER EXAMINED:	56	56	56	56	64	0	0	0	0	0
--DEGENERATE SPERMATOGENIC CELLS IN DUCT(S)	3	2	0	1	3	0	0	0	0	0
--SPERMATOCELE	5	3	4	8	4	0	0	0	0	0
--INFLAMMATION	6	5	5	3	7	0	0	0	0	0
--REDUCED NUMBERS OF SPERMATOZOA	19	12	16	14	11	0	0	0	0	0
--PERITONITIS	0	0	1	1	1	0	0	0	0	0
--HAEMORRHAGE	1	0	0	0	0	0	0	0	0	0
--DUCT DILATATION	1	2	0	0	1	0	0	0	0	0
EYES ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--RETINAL ATROPHY	1	4	1	5	3	0	0	4g	3g	4g
--INFLAMMATORY CELLS, ANTERIOR CHAMBER	2	1	2	1	4	0	3	1	1	2
--RETROBULBAR INFLAMMATION/FIBROSIS	0	0	0	0	0	0	1	0	0	1
--TRAUMATIC DISRUPTION	2	1	1	0	1	1	1	0	0	1
--SCLERITIS	1	0	1	0	0	0	1	3	0	0
--KERATITIS	3	1	2	1	3	0	2	1	1	2
--LENTICULAR DEGENERATION	1	1	0	0	1	2	3	3	1	3
--RETINAL DEGENERATION	0	3	1	0	2	0	4	2	0	0d
--CORNEAL EPITHELIAL HYPERPLASIA	0	0	0	0	2	0	0	0	1	0
--CORNEAL MINERALISATION	0	0	0	1	0	0	0	0	0	0
--CORNEAL ULCERATION	0	0	0	0	1	0	0	0	1	0
--RETINA - LOSS OF OUTER NUCLEAR LAYER	3	6	4	1	4	2	3	3	2	4
FEMUR(INC.JOINT) ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--MARROW - NECROSIS	0	0	0	0	0	0	0	0	1	0

TABLE 10F - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 4

Schedule number: HSN 002

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **											
FEMUR(INC.JOINT)	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--MARROW - MYELOFIBROSIS		1	1	0	0	0	1	2	1	0	0
--MARROW - FAT REPLACEMENT		0	0	0	0	0	5	4	2	1	4
--MARROW - FOAMY MACROPHAGES		1	0	1	0	0	0	0	1	0	0
--CHONDROID HYPERPLASIA		14	13	12	9	16	8	15	8	5d	4eg
--OSTEOARTHRITIS		0	0	1	0	0	0	0	0	0	0
--PERIOSTITIS		0	1	1	0	0	0	0	1	0	0
--EXOSTOSIS		2	0	0	0	1	2	0	0	1	1
GALL BLADDER	NUMBER EXAMINED:	52	52	53	50	56	54	51	53	52	58
--LUMINAL DILATATION		7	7	6	9	8	13	19	10	17	9
--NECROSIS		0	1	0	0	0	0	0	0	0	1
--PERICAPSULAR INFLAMMATION		1	0	2	1	0	0	1	0	0	1
--ADHESION		0	0	0	1	0	0	0	0	0	1
--EPITHELIAL HYPERPLASIA		1	4	1	2	1	0	1	1	1	0
HARDERIAN GLANDS	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	55	64
--PORPHYRIN CONCRETIONS		3	6	4	10	10	12a	2b	15eg	11a	14a
--INFLAMMATION		2	3	0	2	3	3	2	2	1	2
--ACINAR DILATATION		17	18	12	17	18	15	8	22eg	16	20d
--ACINAR HYPERPLASIA		5	0	1	1	1	1	0	1	0	1
--LYMPHOID AGGREGATES		1	2	3	2	9ah	5	8	14eg	11	13
--ACINAR DEGENERATION		10	7	7	10	8	3d	11a	9	4	6
HEART,AURICLE	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--ATRIAL THROMBUS		1	2	2	0	0	0	0	0	1	0
--MYOCARDITIS		2	0	0	0	0	0	0	0	0	0
--ARTERITIS/PERIARTERITIS		1	1	1	1	1	1	3	0	2	1
--VASCULAR MINERALISATION		0	0	0	0	0	0	1	0	0	0

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TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Paleonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 9

Schedule number: NEN 002

ORGAN AND FINDING DESCRIPTION	--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:	MALE					FEMALE				
GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **										
HEART,AURICLE ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--PERICARDITIS	0	0	2	0	1	0	0	2	0	2
HEART,VENTRICLE ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--MYOCARDITIS	17	10	5bg	1eai	3odh	4	0	3	1	1
--MYOCARDIAL VACUOLATION	1	0	0	0	0	1	1	0	1	3
--MYOCARDIAL NECROSIS	1	0	0	0	0	0	0	0	0	0
--ENDOCARDITIS	0	0	1	0	0	0	0	0	1	0
--PERICARDITIS	0	0	0	1	0	0	0	1	0	1
--ARTERITIS/PERIARTERITIS	3	2	0	1	1	1	2	1	3	2
--ADHESION	0	0	0	0	0	0	0	1	0	0
--VASCULAR MINERALISATION	0	1	0	0	0	0	0	0	0	0
--MYOCARDIAL MINERALISATION	0	0	0	0	0	0	0	1	0	0
ILEUM ..... NUMBER EXAMINED:	54	55	54	54	63	55	56	55	53	62
--PERITONITIS	0	0	1	1	0	0	0	0	0	0
JEJUNUM ..... NUMBER EXAMINED:	54	55	55	52	63	55	55	55	55	62
--DISTENSION	0	1	1	4g	0	0	1	1	0	0
--CYST(S)	0	0	0	0	0	0	1	0	0	0
--DIVERTICULUM	0	0	0	0	0	0	1	0	0	0
KIDNEYS ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--CHRONIC PROGRESSIVE NEPHROPATHY	33	36	23dg	34	37	18	16	21	21	17
--HYDRONEPHROSIS	2	3	2	1	2	1	0	1	1	0
--INTERSTITIAL INFLAMMATION	2	1	3	2	1	2	0	1	2	2
--CORTICAL TUBULAR DILATATION	3	2	5	4	4	2	0	3	5g	3
--CORTICAL TUBULAR BASOPHILIA	2	2	4	2	3	1	2	0	1	2
--CORTICAL TUBULES WITH HYALINE DROPLETS	2	1	4	1	3	6	3	3	4	4

TABLE 107 - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 6

Schedule number: SEN 002

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	---------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **											
KIDNEYS	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--CORTICAL SCAR(S)		11	7	4	8	5	1	2	2	2	3
--CORTICAL TUBULAR PIGMENT		1	1	0	2	1	0	4	1	3	0d
--CORTICAL CYST(S)		14	20	11	14	11d	6	3	3	4	2
--TUBULAR HYPERTROPHY		4	5	3	5	1	1	0	0	0	1
--MINERALISATION, CORTICOMEDULLARY		0	0	0	1	1	0	0	0	0	0
--MINERALISATION, CORTEX		4	3	0	2	0mg	0	0	0	0	0
--MINERALISATION, PAPILLA		0	0	1	0	0	1	0	0	1	0
--VASCULAR MINERALISATION		0	0	0	0	0	0	0	0	1	0
--TUBULAR CASTS		3	4	4	1	1	1	2	2	4	3
--PERIVASCULAR LYMPHOID AGGREGATIONS		19	23	18	16	23	7	11	13	11	14
--AMYLOIDOSIS		2	0	1	0	1	1	2	0	1	0
--PELVIS - INFLAMMATION		20	25	17	18	19	17	17	19	15	17
--PYELONEPHRITIS		0	2	1	1	0	0	0	0	0	0
--CAPSULAR ADHESIONS		0	0	1	0	0	0	1	0	0	1
--PERICAPSULAR INFLAMMATION		0	0	0	0	0	1	0	0	0	0
--MEDULLARY CYST(S)		0	0	0	0	0	0	0	0	0	1
LACRIMAL GLANDS	NUMBER EXAMINED:	56	56	55	56	64	55	55	56	55	63
--LYMPHOID AGGREGATES		10	21	11	8mah	10ah	7	13	14	9	11
--INFLAMMATION		1	0	1	1	0	0	0	0	0	0
--FIBROSIS		2	1	0	0	0	0	0	0	0	0
--PURULENTIFICATION		2	0	0	1	2	7	5	4	1	2
--CYST(S)		0	0	1	0	1	0	2	1	0	1
--MINERALISATION		0	0	2	0	0	0	0	0	0	0
LIVER X S	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--HEPATOCYTE NECROSIS, FOCAL		5	3	6	5	4	10	4	7	6	8
--HEPATOCYTE NECROSIS, LOBAR, TORSION		1	0	0	0	0	2	1	0	0	0

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Page 187

HSH 002/013059 0190

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TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 7

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION	--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:	MALE					FEMALE				
GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **										
LIVER X S ..... NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--INCREASED MITOTIC ACTIVITY	4	4	1	1	3	3	1	6	2	1
--ANGIECTASIS, FOCAL	1	0	0	0	1	0	0	2	1	2
--LEUKOCYTOSIS	8	7	13	7	7	12	9	15	14	11
--GRANULOMATOUS INFLAMMATION	0	0	1	0	0	0	0	0	0	1
--INFLAMMATION, PORTAL	1	6	7	5	3	8	4	4	7	4
--FOCAL HYPERPLASIA	1	1	0	1	0	0	0	0	0	0
--HEPATOCYTE VACUOLATION, MIDZONAL	1	0	0	0	1	2	4	1	1	1
--HEPATOCYTE VACUOLATION, CENTRILOBULAR	2	6	1	1	1d	0	0	1	1	0
--HEPATOCYTE VACUOLATION, PERIPORTAL	1	0	0	0	1	3	1	0	0	0
--HAEMORRHAGE	0	0	0	0	0	0	0	0	1	0
--EXTRAMEDULLARY HAEMOPOIESIS	2	2	2	1	1	6	4	4	1	10
--EOSINOPHILIC FOCI	2	0	1	0	0	0	0	0	0	0
--BASOPHILIC FOCI	6	2	3	1	2	0	2	0	0	2
--PERITONITIS	0	0	1	0	0	0	0	0	0	1
--PIGMENTED HEPATOCYTES	1	0	0	0	0	2	0	0	0	2
--NODULAR HYPERPLASIA	5	3	1	2	3	1	0	0	1	1
--PIGMENT IN MACROPHAGES	3	4	4	2	0dg	9	4	8	8	5
--VASCULAR MINERALISATION	0	0	0	0	0	0	0	0	1	0
--CAPSULAR ADHESIONS	0	0	0	0	0	0	1	0	0	2
--BILE DUCT HYPERPLASIA	0	0	0	0	1	1	0	1	0	0
--GROWTH ANOMALY	2	3	0	1	0	1	0	0	1	0
--BILIARY CYSTS, SINGLE	0	1	0	1	0	0	0	0	0	0
--CLEAR CELL FOCI	0	2	1	1	0	0	0	0	0	0
--CYSTIC DEGENERATION	1	1	0	1	0	0	0	0	0	0
--PROMINENT EOSINOPHILIC NUCLEAR INCLUSION	2	1	0	0	0	0	0	0	0	0
--REGENERATIVE HYPERPLASIA	1	0	0	0	0	0	0	0	0	0

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 10F - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Paleonestron Hydrochloride		
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 8

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION	--- NUMBER-OF-ANIMALS-AFFECTED ---									
SEX:	MALE					FEMALE				
GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
NUMBER:	56	56	56	56	64	56	56	56	56	64
LN MANDIBULAR ..... NUMBER EXAMINED:	56	58	58	53	64	55	55	56	56	64
--PLASMACYTOSIS	0	1	3	0	2	1	0	1	0	0
--INCREASED CELLULARITY, GENERALISED	0	0	1	0	0	1	0	0	1	1
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	0	0	0	0	0	0	1	1	3	4
--INCREASED CELLULARITY, PARACORTEX	0	0	1	2	1	2	2	0	3	1
--SINUS HISTIOCYTOSIS	1	0	0	1	0	0	2	0	2	0
--DILATED/CYSTIC SINUSES	1	0	0	0	0	0	0	0	0	1
--HAEMOSIDEROSIS	17	15	17	20	18	11	10	14	17	14
--FATTY INFILTRATION	0	0	1	1	2	2	4	3	1	2
--EXTRAMEDULLARY HAEMOPOIESIS	0	0	0	4g	0	0	0	0	0	1
--REACTIVE HISTIOCYTOSIS	0	0	0	0	0	0	0	1	0	0
--SITE ONLY	0	2	0	0	1	0	0	1	0	1
LN MESENTERIC ..... NUMBER EXAMINED:	56	56	55	56	63	55	56	56	56	64
--DILATED/CYSTIC SINUSES	4	9	4	4	3	1	3	4	2	3
--SINUS ERYTHROCYTOSIS/ERYTHROPHAGOCYTOSIS	6	7	11	8	7	1	3	5	5	6
--ANGIECTASIS	3	9	7	10	11a	6	8	11	7	7
--PLASMACYTOSIS	6	3	6	5	8	3	2	5	7	3
--HAEMOSIDEROSIS	7	6	11	6	14	8	16	12	7	12
--INCREASED CELLULARITY, GENERALISED	0	0	1	0	0	0	0	0	0	1
--INCREASED CELLULARITY, PARACORTEX	1	1	2	5g	4	2	1	8	0	2
--REACTIVE HISTIOCYTOSIS	0	1	1	0	1	1	0	2	1	0
--FATTY INFILTRATION	3	2	1	4	6	2	3	3	1	7
--EXTRAMEDULLARY HAEMOPOIESIS	1	2	3	5	8	0	3	3	1	0
--LYMPHADENITIS	0	1	0	3	0	1	1	0	1	0
--NECROSIS	0	0	0	0	0	0	0	0	1	1
--FIBROSIS	0	0	0	0	0	0	0	0	1	0

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 10F - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 9

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION		MALE 1	MALE 2	MALE 3	MALE 4	MALE 5	FEMALE 1	FEMALE 2	FEMALE 3	FEMALE 4	FEMALE 5
		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	NUMBER:	56	56	56	56	64	56	56	56	56	64
LUNGS X 3	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--ALVEOLAR EPITHELIAL HYPERPLASIA		5	5	1	5	4	2	4	2	4	5
--PNEUMONITIS		2	3	4	3	2	1	2	0	3	2
--ALVEOLAR HAEMORRHAGE		4	4	5	3	6	2	6	1	4	4
--ALVEOLAR MACROPHAGES ASSOCIATED WITH NEOPLASIA		5	13	7	3d	6d	6d	0a	6d	2	5
--AGGREGATIONS OF ALVEOLAR MACROPHAGES		1	1	0	3	3	2	7	3	4	6
--BRONCHIOLAR EPITHELIAL HYPERPLASIA		0	1	0	0	0	0	1	0	1	0
--FOCAL BRONCHIOLAR FIBROSIS		0	0	0	0	0	0	0	0	1	0
--BRONCHOPNEUMONIA		0	1	0	1	1	0	0	1	0	1
--PERIVASCULAR LYMPHOID AGGREGATES		8	7	5	5	6	6	5	6	9	7
--PERIBRONCHIOLAR LYMPHOID AGGREGATES		0	3	0	0	0	1	0	3	3	1
--PIGMENTED ALVEOLAR MACROPHAGES		0	2	0	1	1	0	0	0	0	0
--PLEURAL INFLAMMATION		0	0	0	0	0	0	1	2	2	0
--PLEURAL FIBROSIS		0	0	0	0	0	0	0	1	0	0
--PLEURAL ADHESION(S)		0	0	0	0	0	0	0	1	0	0
--CHOLESTEROL CLEFT GRANULOMA(TA)		0	0	0	0	0	1	0	1	2	0
--BRONCHIOLITIS		0	0	0	0	1	0	0	0	0	0
MAMMARY A.CAUD	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--ULCERATION		0	1	0	0	1	1	0	0	0	0
--INFLAMMATION		0	0	0	0	1	1	2	1	2	1
--DUCTULAR DILATATION		0	0	0	0	0	2	2	2	1	2
--ACINAR HYPERPLASIA		0	0	0	0	0	0	1	1	1	0
--ATYPICAL HYPERPLASIA		0	0	0	0	0	0	0	0	1	0
OESOPHAGUS	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	63
--INFLAMMATION		0	1	1	1	0	1	0	1	1	1

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 10F - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 10

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
OPTIC NERVES ..... NUMBER EXAMINED:		54	56	55	55	64	54	56	52	56	61
--INFLAMMATION		0	0	0	0	0	0	1	0	0	0
--GLIOSIS		3	5	2	6	8	5	4	3	3	3
OVARIES ..... NUMBER EXAMINED:		0	0	0	0	0	56	56	56	56	64
--OVARIAN CYST(S)		0	0	0	0	0	46	44	42	46	51
--ATROPHY		0	0	0	0	0	1	2	2	1	3
--ARTERITIS		0	0	0	0	0	1	3	1	3	1
--HAEMORRHAGIC CYST(S)		0	0	0	0	0	9	10	9	8	3 mod
--HAEMOSIDEROSIS		0	0	0	0	0	1	2	3	1	0
--ABSCESS(ES)		0	0	0	0	0	0	0	1	0	0
--INFLAMMATION		0	0	0	0	0	1	2	2	3	1
--PAPILLARY HYPERPLASIA		0	0	0	0	0	1	0	0	0	2
--HAEMORRHAGE		0	0	0	0	0	1	1	2	0	0
--EPITHELIAL HYPERPLASIA		0	0	0	0	0	0	0	1	1	0
--THROMBUS/THROMBI		0	0	0	0	0	0	0	0	1	0
--MINERALISATION		0	0	0	0	0	0	0	1	0	0
--CONGESTION		0	0	0	0	0	0	0	1	0	0
PANCREAS ..... NUMBER EXAMINED:		56	56	56	55	64	55	56	55	56	64
--OEDEMA		2	2	4	1	4	9	7	2	2 mg	7
--HAEMORRHAGE		1	0	0	0	0	0	0	0	0	0
--PERIDUCTAL INFLAMMATION/FIBROSIS		6	8	4	4	6	11	10	7	4	7
--INFLAMMATION		0	3	2	1	1	2	3	6	1	3
--ARTERITIS/PERIARTERITIS		5	1	1	0	1	2	0	0	2	1
--THROMBUS		1	0	1	0	0	0	0	0	0	0
--ISLET CELL HYPERPLASIA		12	14	7	8	8	4	4	6	3	3
--ACINAR ATROPHY, FOCAL		0	1	0	0	1	1	1	1	0	0
--ACINAR CELL HYPERTROPHY, FOCAL		5	0	1	0	4	2	1	3	3	3

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 10F - continued.

Histopathology - group distribution of non-neoplastic findings for all animals

Print No: 0022

Group	1	2	3	4	5
Compound	Control	Control	Palonosetron	Hydrochloride	
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 11

Schedule number: SSS 002

ORGAN AND FINDING DESCRIPTION	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **											
PANCREAS ..... NUMBER EXAMINED:		56	56	56	55	64	55	56	55	56	64
--ACINAR REPLACEMENT BY ADIPOSE TISSUE		0	0	0	1	0	1	0	0	1	1
--NECROSIS		0	0	0	0	0	0	0	0	0	1
--PERI-ISLET PIGMENT		0	0	0	0	0	0	0	2	0	0
--PERITONITIS		0	0	0	0	0	0	1	0	0	0
--CYST(S)		1	1	0	0	0	0	2	0	1	0
--ACINAR CELL VACUOLATION		0	0	0	0	0	0	1	1	0	0
PARATHYROIDS ..... NUMBER EXAMINED:		49	42	41	47	58	42	44	42	42	56
--CYST(S)		0	0	2	1	0	1	0	1	0	0
--HYPERPLASIA		0	0	0	0	0	0	0	0	1	1
--LYMPHOID AGGREGATES		1	1	0	0	1	0	0	2	0	0
PITUITARY ..... NUMBER EXAMINED:		56	55	55	56	64	56	56	56	56	64
--MINERALISATION		0	0	0	0	0	0	0	0	1	0
--DEVELOPMENTAL CYST(S)		4	2	1	1	0a	1	0	2	0	0
--INFLAMMATION		0	0	1	0	0	0	0	0	0	0
--ANGIECTASIS		0	0	0	0	0	2	0	1	1	1
--HYPERPLASIA - PARS DISTALIS, FOCAL		1	0	0	0	0	0	0	0	0	0
--HYPERPLASIA - PARS INTERMEDIA, FOCAL		0	1	0	0	1	1	0	2	0	2
--HYPERTROPHY - PARS DISTALIS, FOCAL		0	0	0	0	0	1	1	2	2	3
--ABSCESS(ES)		0	0	0	0	0	0	0	0	1	0
--CONGESTION		0	0	0	0	0	1	0	1	0	1
PROSTATE ..... NUMBER EXAMINED:		56	56	56	56	64	0	0	0	0	0
--LYMPHOID AGGREGATES		0	5	3	2	1	0	0	0	0	0
--INFLAMMATION		6	7	3	6	5	0	0	0	0	0
--ABSCESSATION		0	2	1	1	3	0	0	0	0	0
--OEDEMA		0	1	1	0	0	0	0	0	0	0

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 107 - continued.

Print No: 0022

Histopathology - group distribution of non-neoplastic findings for all animals

Group	1	2	3	4	5
Compound	Control	Control	Paloncosetron Hydrochloride		
Dosage (mg/kg/day)	0	0	10	30	60

Printed: 04-DEC-01
Page: 12

Schedule number: HSH 002

ORGAN AND FINDING DESCRIPTION		--- NUMBER-OF-ANIMALS-AFFECTED ---									
	SEX:	MALE					FEMALE				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
	NUMBER:	56	56	56	56	64	56	56	56	56	64
** FROM PREVIOUS PAGE **											
PROSTATE	NUMBER EXAMINED:	56	56	55	56	64	0	0	0	0	0
--ACINAR DISTENSION		0	0	0	1	1	0	0	0	0	0
--THROMBUS/THROMBI		0	0	0	1	0	0	0	0	0	0
--ACINAR HYPERPLASIA, FOCAL		0	1	0	0	0	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	56	56	56	55	64	56	56	55	56	64
--PERITONITIS		0	0	2	0	0	0	0	0	0	0
--SUBMUCOSAL INFLAMMATION		0	0	0	0	0	0	0	1	1	0
--SUBMUCOSAL OEDEMA		0	0	0	0	0	1	0	0	1	0
--PROLAPSE		0	0	0	0	0	0	0	1	0	0
--MEGATODIS		0	0	0	0	1	0	0	0	0	0
S. MUSCLE THIGH	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--MYOFIBRE DEGENERATION/NECROSIS		0	0	0	2	0	0	0	0	1	0
--INFLAMMATION		2	1	1	1	1	1	1	3	2	1
--ARTERITIS/PERIARTERITIS		0	2	0	1	1	1	0	0	0	0
SALIVARY GLAND	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--LYMPHOID AGGREGATES		12	16	11	7	11	9	8	12	11	19
--OEDEMA		0	0	0	0	1	0	0	0	0	0
--ARTERITIS/PERIARTERITIS		0	1	0	0	0	0	0	0	0	0
--ACINAR ATROPHY		0	0	3g	0	0	1	1	0	0	0
SCIATIC NERVE	NUMBER EXAMINED:	56	56	56	56	64	56	56	56	56	64
--DEGENERATE FIBRES		16	16	16	19	13	20	27	21	20	28
--INFLAMMATION		0	1	0	0	0	1	1	1	4	0
SEMINAL VESICLES	NUMBER EXAMINED:	56	56	56	56	64	0	0	0	0	0
--INFLAMMATION		8	10	4	6	4	0	0	0	0	0

APPEARS THIS WAY
ON ORIGINAL

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