In 3-month oral (via diet) toxicity study in Wistar rats doses of 10, 20 and 40 mg/kg/day were used. In this study only in high dose treated females, absolute as well as relative, weights of pituitary were reduced by 27-28% compared to control values. No treatment related histopathological abnormalities were evident in this study. The systemic exposure of GR 68755 at 40 mg/kg/day dose level was about 24-89 fold higher than the anticipated human exposure ($AUC_{0\text{-}24\ hr}$ ~ 396.4 ng.hr/ ml, 0.32 mg/kg/day [8 mg b.i.d.], 50 kg body wt. assumed). Based on multiple of human exposure, sponsor selected 40 mg/kg/day as the top dose for the carcinogenicity study in rat and the mid and low doses were set at 6.5 and 1.0 mg/kg/day respectively.

In 3-month oral (via gavage) toxicity study in Wistar rats doses of 10, 20 and 20 (days 1-7)/40 mg/kg/day were used. In this study, increase in liver weights were seen in all treated males (10-13%) and in high dose treated females (28%). Histopathological examinations revealed periacinar hepatocytic hypertrophy and foci of "pre-basophilic" hepatocytes in some of the high dose treated females (and none in the control). Data indicated that 40 mg/kg/day was the maximum tolerated dose in rats when drug was given via gavage.

In both dietary and gavage 3-month dose ranging study in rats, the systemic exposure of GR 68755 at 40 mg/kg/day dose level was at least 24 fold higher than the anticipated human exposure ($AUC_{0\text{-}24\ hr}$ ≈ 396.4 ng.hr/ ml, 0.32 mg/kg/day [8 mg b.i.d.], 50 kg body wt. assumed). Based on multiple of human exposure, sponsor selected 40 mg/kg/day as the top dose for the carcinogenicity study in rat and the mid and low doses were set at 6.5 and 1.0 mg/kg/day respectively. The selection of top dose is appropriate (see the result of main carcinogenicity study in rat).

In 104-week oral (via diet) carcinogenicity study in Wistar rats doses of 0, 1, 6.5 and 40 mg/kg/day were used. In this study, highest tested dose is the maximum tolerated dose since at this dose level body weight in males and females were 6% and 9% lower than the control body weights respectively. Furthermore, based on AUC values, high dose treated rats (both sexes) were exposed to 123-141 fold higher levels of GR 68755 than human [$AUC_{0\text{-}24\ hr}$ = 396.4 ng.hr/ml; 8 mg b.i.d. = 0.32 mg/kg/ day, 50 kg body weight assumed]. Hence, dose selection was appropriate. Treatment had no significant effect of intercurrent mortality rates. Survival rates at the end of treatment period were comparable in all groups. Increased incidences of basophilic foci in the liver of high dose treated females and increased incidences of clear cell foci in liver of high dose treated males were seen. No treatment related neoplastic findings were evident in this study. Hence, GR 68755 has no carcinogenic potential in Wistar rats.

In oral Segment I. fertility and general reproductive performance study in rats, doses of 0, 1, 6.5 and 40 mg/kg/day were used. There were no abnormal effects on the fertility and mating performance of the treated male and female rats at doses up to and including 40 mg/kg/day of GR 68755C.

In oral Segment II. teratology study in rats, doses of 0, 1, 6.5 and 40 mg/kg/day were used. No teratogenic effects at dosage up to 40 mg/kg/day was seen in rats. However, the highest tested dose was maternotoxic (decreased body weight gains and food intakes) and fetotoxic (increased incidence of supernumerary ribs). The postnatal development and the fertility of the offspring were comparable in all groups.

In oral Segment II. teratology study in rabbits, doses of 0, 1, 6.5 and 40 mg/kg/day were used. No teratogenic effects at dosage up to 40 mg/kg/day was seen in rabbits.

No mutagenic potential was demonstrated when GR 68755 was tested in 5 different tests: Ames Test, in vitro chromosomal aberration test in human lymphocytes, L5178 Y/TK mouse lymphoma mutation assay, ex-vivo UDS assay in rat hepatocytes and in vivo rat micronucleus test.

GR 2202X is an intermediate in the synthesis of GR 68755C. It is also present in the final drug substance as an impurity. GR 2202X is mutagenic in Ames test. It should be noted here that GR 68755 (which contained GR 2202X as impurity) has no carcinogenic potential in Wistar rats. In human after administration of 16 mg b.i.d. the level of GR 2202 was below 1 ng/ml (report # WBP/91/099). Hence, finding associated with GR 2202 has no clinical significance. Sponsor further indicated that in tablet formulation GR 2202 will not exceed more than 0.1% (w/w).

Toxicity studies in rats and dogs of 6-month duration are used for safety assessment of the proposed clinical protocol. In 6-month oral toxicity study in rats, CNS (salivation, tense behavior, moist eyes, croaking, tiptoe gait, pushing at cage floor with forepaws and tremor) and liver (basophilic foci of cellular alteration) are the target organs of toxicities and 8 mg/kg/day was the no effect dose. No effect dose level is about 25 times greater than the highest proposed clinical dose (0.32 mg/kg/day). In 6-month oral toxicity study in dogs, highest tested dose (20/30/25 mg/kg/ day) produced CNS toxicities, increases in serum alkaline phosphatase (both sexes) and alanine aminotransferase activities (in males) without accompanying histopathological changes in liver and deaths. Mid dose level (5.5 mg/kg/day) could be considered as well tolerated dose since it only produced increases in plasma alkaline phosphatase levels. The well tolerated dose is about 17 times greater than the highest proposed clinical dose. Based on preclinical studies, the proposed study should be allowed to proceed.

RECOMMENDATIONS:

1. Based on preclinical studies, the proposed study should be allowed to proceed.

2. In mouse and rat carcinogenicity studies, dose selections were appropriate.

/S/ 4/16/96
Tanveer Ahmad, Ph.D.
Pharmacologist, HFD-180

cc:
Orig. IND
HFD-180
HFD-181/CSO
HFD-180/Dr. Ahmad
HFD-180/Dr. Choudary
HFD-180/Dr. Fredd
HFD-345/Dr. Viswanathan
HFD-150/CAC/Dr. DeGeorge
HFD-006/CAC/Ms. Olmstead

TA/hw/3/20/96

(1) Noted
(2) The opinion of the CDER's CAC Exec. Committee about the adequacy the employed doses in the mouse and rat carcinogenicity studies of [redacted] hydrochloride will be solicited.

/S/ 4/16/96

Attachments: Appendix I. Neoplastic and Non-neoplastic Findings in Rats

APPENDIX I.

RAT

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TABLE 10F

Print No: 0045

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

Group	:	1	2	3	4
Compound	:	Control	---	GR68755C	---
Dosage (mg GR68755X/kg/day):		0	1.0	6.5	40.0

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		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	120	60	60	60	120	60	60	60
** TOP OF LIST **									
ADRENAL CTX L&R	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--CORTICAL FATTY VACUOLATION		48	21	25	22	7	3	1	1
--CORTICAL HAEMORRHAGIC DEGENERATION		1	3	4a	4a	97	49	56a	46
--EXTRAMEDULLARY HAEMOPOIESIS		0	0	0	0	0	0	1	0
--CORTICAL BROWN ATROPHY		1	1	0	1	0	1	0	0
--FOCAL CORTICAL HYPERTROPHY		6	6	7	6	5	0	0	2
--FOCAL CORTICAL HYPERPLASIA		0	0	0	0	0	1	0	0
--FOCAL LYMPHOCYTIC INFILTRATION		0	0	0	0	0	0	1	0
--CORTICAL MINERALISATION		0	0	0	0	1	0	0	0
ADRENAL MED L&R	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--FOCAL MEDULLARY HYPERPLASIA		9	6	6	4	1	0	0	0
BRAIN X 3	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--DEPRESSION DUE TO ENLARGED PITUITARY		8	9	10	6	10	18c	7	10
--HAEMORRHAGE		0	0	0	1	0	0	0	1
--DILATED VENTRICLES		1	1	0	0	0	2	0	0
--CHOLESTEROL GRANULOMA		0	0	0	1	0	0	0	0
--OEDEMA		0	0	0	1	0	0	0	0
--FOCAL GLIOSIS		1	0	0	0	0	0	0	0
CAECUM	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--SUBMUCOSAL OEDEMA		0	0	0	0	1	0	0	0
--MUCOSAL ACUTE INFLAMMATION		0	0	0	1	0	0	0	0
--ULCER(S)		0	1	0	0	0	0	0	0
--SUBMUCOSAL CHRONIC INFLAMMATION		0	0	0	0	0	0	1	0
--ARTERITIS		0	0	0	0	1	0	0	0
COLON	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--DILATED		1	1	0	1	0	0	0	0
--SUBMUCOSAL GRANULOMA(S)		1	0	0	0	0	0	0	0

Significant when compared with Group 1: a - p<0.05; c - p<0.001

RAT

TABLE 10F - continued.

Print No: 0045

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

Group	:	1	2	3	4
Compound	:	Control	---	GR68755C	----
Dosage (mg GR68755X/kg/day):		0	1.0	6.5	40.0

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Schedule number: GLX 041

		--- NUMBER-OF-ANIMALS-AFFECTED ---							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	120	60	60	60	120	60	60	60
DUODENUM	NUMBER EXAMINED:	119	60	60	60	120	60	60	60
--SUBMUCOSAL CHRONIC INFLAMMATION		0	0	0	0	0	0	1	0
EPIDIDYMIDES L&R	NUMBER EXAMINED:	119	60	60	59	0	0	0	0
--REDUCED SPERM CONTENT		38	15	17	12	0	0	0	0
--ARTERITIS		3	0	0	0	0	0	0	0
FEMUR INC.JT X2	NUMBER EXAMINED:	119	60	60	60	120	60	60	60
--SCLEROSIS		0	0	0	1	0	0	0	0
--OSTEODYSTROPHIA FIBROSA		4	4	2	0	0	0	0	0
--ARTICULAR CARTILAGE PROLIFERATION		1	0	0	0	0	0	0	0
--MARROW HAEMORRHAGE		1	0	0	0	0	0	0	0
--HISTIOCYTIC INFILTRATION		0	0	0	1	0	0	0	0
HEART, AURICLE	NUMBER EXAMINED:	120	60	60	58	120	60	60	60
--ACUTE PERICARDITIS		0	0	1	0	0	0	0	0
HEART, VENTRICLE	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--CHRONIC MYOCARDITIS		52	30	24	21	19	11	4	4
--MYOCARDIAL MINERALISATION		1	3	0	0	0	0	0	0
--VASCULAR MINERALISATION		2	4	0	1	0	0	0	0
--VALVULAR THICKENING		2	0	0	0	0	0	0	0
--ARTERITIS		2	1	0	1	1	0	0	0
--CHRONIC ENDOCARDITIS		0	0	0	1	0	0	0	0
ILEUM	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--ULCER(S)		0	0	0	0	0	0	0	1
--VILLOUS STUNTING		0	0	0	0	0	0	0	1
--DILATED		0	0	0	0	0	0	0	1
KIDNEYS (L&R)	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--PROGRESSIVE (SENILE) NEPHROPATHY		107	58	53	41c	64	42#	31	23

** CONTINUED ON NEXT PAGE **

Significant when compared with Group 1: a - p<0.05; c - p<0.001

RAT

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TABLE 10F - continued.

Print No: 0045

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

Group	:	1	2	3	4
Compound	:	Control	---	GR68755C	----
Dosage (mg GR68755X/kg/day):		0	1.0	6.5	40.0

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	--- NUMBER OF ANIMALS AFFECTED ---							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION NUMBER:	120	60	60	60	120	60	60	60
** FROM PREVIOUS PAGE **								
KIDNEYS (L&R) ..... NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--PELVIC EPITHELIAL MINERALISATION	3	0	2	1	46	32	19	14
--CORTICAL MINERALISATION	0	3a	0	0	3	2	1	0
--MEDULLARY MINERALISATION	0	1	0	0	9	2	2	0
--TUBULAR DILATATION	1	0	0	0	0	0	0	0
--HYDRONEPHROSIS	9	4	5	5	0	0	2	1
--EOSINOPHILIC MATERIAL WITHIN CORTICAL TUBULAR CYTOPLASM	2	0	1	0	1	0	0	1
--CORTICAL CYST(S)	3	4	2	0	1	1	1	1
--ACUTE PYELITIS	3	1	3	0	0	1	0	0
--PURULENT NEPHRITIS	1	0	0	0	0	0	0	0
--TRANSITIONAL CELL HYPERPLASIA	8	1	2	5	10	4	3	8
--ACUTE PYELONEPHRITIS	0	0	0	0	1	0	0	0
--PAPILLARY MINERALISATION	1	0	0	1	2	1	0	2
--CHRONIC INTERSTITIAL NEPHRITIS	0	0	0	0	1	0	0	0
--VACUOLATION AND/OR NECROSIS OF PROXIMAL TUBULES	0	0	0	0	0	1	1	0
--CORTICO-MEDULLARY MINERALISATION	0	0	0	0	2	1	1	1
--PELVIC HAEMORRHAGE	1	0	0	0	0	0	0	0
--PYELONEPHRITIS	0	0	0	0	1	0	0	0
--ACUTE PAPILLITIS	0	0	1	0	0	0	0	0
L M MANDIBULAR ..... NUMBER EXAMINED:	116	60	58	57	120	59	60	60
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	3	1	4	1	3	3	1	2
--PLASMACYTOSIS	14	8	9	3	22	16	17	12
--ABSCESS(ES)	1	0	0	0	0	0	0	0
--LYMPHOCYTOLYSIS	1	0	1	0	0	0	0	0
--HAEMORRHAGE	1	1	0	0	0	0	0	0
--CHRONIC LYMPHADENITIS	1	0	0	0	0	0	0	0
--DILATED SINUSES	1	2	3	0	1	0	0	1
--SINUS HISTIOCYTOSIS	1	0	1	0	0	1	0	0
--NECROSIS	1	0	0	0	0	0	0	0
--PARAFOLLICULAR HYPERPLASIA	1	0	2	0	3	0	1	0
--HAEMOSIDEROSIS	0	0	0	0	0	1	0	0

Significant when compared with Group 1: a - p<0.05

RAT

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TABLE 10F - continued.

Print No: 0045

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

Group	1	2	3	4
Compound	Control	---	GR68755C	---
Dosage (mg GR68755X/kg/day)	0	1.0	6.5	40.0

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	--- NUMBER-OF-ANIMALS-AFFECTED ---							
SEX:	-------MALE-------				------FEMALE------			
GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION								
NUMBER:	120	60	60	60	120	60	60	60
L N MESENTERIC ..... NUMBER EXAMINED:	120	60	60	59	120	59	59	60
--PARAFOLLICULAR HYPERPLASIA	8	2	10	7	8	6	9	6
--SINUS HISTIOCYTOSIS	1	1	0	1	5	2	1	0
--LYMPHOCYTOLYSIS	1	0	1	0	0	0	0	0
--HAEMORRHAGE	2	0	0	0	0	0	0	0
--CHRONIC LYMPHADENITIS	1	0	0	0	0	0	0	0
--ERYTHROCYTES AND ERYTHROPHAGOCYTOSIS IN SINUSES	25	8	8	9	16	10	6	4
--ARTERITIS	1	0	0	1	0	0	0	0
--DILATED SINUSES	10	1	2	1	1	1	0	0
--PLASMACYTOSIS	1	0	0	0	1	0	0	0
--ANGIECTASIS	0	0	0	0	1	0	0	0
LEFT EYE ..... NUMBER EXAMINED:	114	60	60	57	120	60	60	60
--RETINAL FOLDS	0	0	0	0	0	0	1	0
--CHRONIC KERATITIS	3	2	1	0	0	0	0	1
--RETINAL DEGENERATION	2	0	0	0	1	0	0	0
--DISRUPTION/FIBROSIS	0	0	0	1	0	0	0	0
--ACUTE KERATITIS	1	1	0	0	0	0	0	0
--PUS IN ANTERIOR CHAMBER	1	1	0	0	0	0	0	0
--LENTICULAR DEGENERATION	1	0	0	0	0	0	1	0
LIVER X 2 ..... NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--BASOPHILIC FOCUS	7	2	0	3	19	6	15	7
--BASOPHILIC FOCI	1	0	3	3	34	13	16	38a
--CLEAR CELL FOCUS/FOCI	42	25	19	33a	16	6	7	8
--EOSINOPHILIC FOCUS/FOCI OF HEPATOCELLULAR ALTERATION	7	0	2	5	3	0	1	0
--PORTAL TRACT (SENILE) CHANGE INCLUDING PROLIFERATION OF BILE DUCTS, HYALINE DEGENERATION AND INFLAMMATION	63	31	31	35	57	23	19	13b
--EXTRAMEDULLARY HAEMOPOIESIS	1	0	1	0	5	2	2	1
--FOCAL NECROSIS	9	9	2	9	9	2	3	1
--PERIACINAR COAGULATIVE NECROSIS	1	0	0	1	2	0	0	0
--LOBAR (TORSION) NECROSIS	1	0	0	0	0	0	0	0

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Significant when compared with Group 1: a - p<0.05; b - p<0.01; c - p<0.001

TABLE 10F - continued.

Print No: 0045

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

Group	:	1	2	3	4
Compound	:	Control	---	GR68755C	---
Dosage (mg GR68755X/kg/day):		0	1.0	6.5	40.0

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Schedule number: GLX 041

		--- NUMBER-OF-ANIMALS-AFFECTED ---							
	SEX:	-------MALE-------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	120	60	60	60	120	60	60	60
** FROM PREVIOUS PAGE **									
LIVER X 2	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--FOCAL CYSTIC DEGENERATION		25	10	6	7	5	2	2	1
--CENTRIACINAR HEPATOCYTIC FATTY VACUOLATION		9	6	3	3	6	3	2	6
--PERIACINAR HEPATOCYTIC FATTY VACUOLATION		3	2	4	3	0	1	0	0
--PANACINAR HEPATOCYTIC FATTY VACUOLATION		2	0	0	0	0	1	0	1
--FOCUS OF HEPATOCYTIC FATTY VACUOLATION		3	3	4	2	3	3	4	4
--MIDZONAL HEPATOCYTIC FATTY VACUOLATION		0	2	0	1	0	0	0	0
--FINE VACUOLATION OF SINGLE HEPATOCYTES		0	1	1	1	0	5b	2	2
--FOCAL TELANGIECTASIS		9	0	4	3	9	6	4	2
--INCREASED APOPTOSIS		0	0	0	1	0	0	1	0
--CAPSULAR FIBROSIS		0	0	0	0	1	0	1	0
--CONGESTION		0	2	2	0	5	2	0	0
--CHRONIC INFLAMMATORY CELLS WITHIN THE PORTAL AREA		1	0	0	0	0	0	0	0
--MEDIAN LOBE ANOMALY		1	1	0	1	1	0	0	1
--HAEMORRHAGIC NECROSIS		0	0	0	2	0	0	0	0
--DISTENDED BILE DUCT		5	4	2	3	2	1	1	0
--BILIARY CYST(S)		0	0	0	0	0	1	1	2
--PIGMENT LADEN HEPATOCYTES		0	0	0	0	0	0	0	1
--PIGMENT LADEN KUPFFER CELLS		1	0	0	1	1	0	0	0
--CHRONIC INFLAMMATION		0	0	0	0	0	0	1	0
--AREA OF VACUOLAR DEGENERATION		0	0	1	0	0	0	0	2
--PORTAL FIBROSIS		0	0	0	1	0	0	0	0
LUNGS X 2	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--ALVEOLAR HAEMORRHAGE		10	3	2	0#	18	5	8	9
--ACCUMULATION(S) OF ALVEOLAR MACROPHAGES		60	30	31	36	26	22#	18	21
--PERIBRONCHIOLAR LYMPHOCYTES		2	0	0	0	0	0	0	0
--FOCAL ALVEOLAR WALL EPITHELIALISATION		1	0	3	1	3	1	1	0
--ALVEOLAR WALL MINERALISATION		1	3	0	0	0	0	0	0
--GENERAL VASCULAR MINERALISATION		1	1	0	0	0	0	0	0
--CHRONIC PNEUMONIA		2	2	1	1	0	0	0	0
--GRANULOMA(S)		2	3	4	3	6	4	5	4

** CONTINUED ON NEXT PAGE **

Significant when compared with Group 1: a - p<0.05; b - p<0.01

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TABLE 10F - continued.

Print No: 0045

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

Group	:	1	2	3	4
Compound	:	Control	---	GR68755C	----
Dosage (mg GR68755X/kg/day):		0	1.0	6.5	40.0

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Schedule number: GLX 041

		--- NUMBER OF ANIMALS AFFECTED ---							
	SEX:	-------MALE--------				------FEMALE------			
	GROUP:	-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	120	60	60	60	120	60	60	60
** FROM PREVIOUS PAGE **									
LUNGS X 2	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--ALVEOLAR FLOODING		0	1	0	0	0	0	0	0
--FOCAL BONE		4	2	1	0	0	0	1	0
MAMMARY A.CAUD	NUMBER EXAMINED:	120	60	60	60	119	59	59	60
--SECRETORY ACTIVITY		3	2	2	2	54	28	26	32
--ACINAR HYPERPLASIA		1	0	0	0	39	23	17	15
--GALACTOCOELE(S)		0	0	0	0	0	0	0	1
OESOPHAGUS	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--ACUTE INFLAMMATION		0	1	0	0	0	0	0	0
--NECROSIS		0	1	0	0	0	0	0	0
OVARIES (L&R)	NUMBER EXAMINED:	0	0	0	0	120	60	60	60
--HAEMORRHAGE		0	0	0	0	0	0	0	1
--NUMEROUS CORPORA LUTEA		0	0	0	0	1	0	0	0
--BURSAL CYST(S)		0	0	0	0	3	1	2	3
--SERTOLI CELL PROLIFERATION		0	0	0	0	2	1	0	0
--OVARIAN CYST		0	0	0	0	1	1	2	0
PANCREAS	NUMBER EXAMINED:	120	60	59	60	119	60	60	60
--ARTERITIS		18	7	3	5	1	0	0	0
--FOCAL EXOCRINE CELL HYPERPLASIA		17	12	13	13	2	3	6a	5a
--ISLET CELL HYPERPLASIA		0	2	1	0	3	1	1	0
--ACINAR ATROPHY WITH CHRONIC INFLAMMATION		2	0	1	1	0	1	1	1
--PERITONITIS		0	0	0	1	1	0	0	0
--HAEMORRHAGE		2	1	0	0	0	0	1	0
--VASCULAR MINERALISATION		1	1	0	0	0	0	0	0
--FIBROSIS		1	1	0	0	0	0	0	0
--DUCTULAR PROLIFERATION		1	1	0	0	1	0	0	0
--OEDEMA		0	0	0	0	0	2	0	0

Significant when compared with Group 1: a - p<0.05

RAT

TABLE 10F - continued.

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

Group	1	2	3	4
Compound	Control	---	GR68755C	----
Dosage (mg GR68755X/kg/day)	0	1.0	6.5	40.0

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		--- NUMBER-OF-ANIMALS-AFFECTED ---							
SEX:		-------MALE-------				------FEMALE------			
GROUP:		-1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
ORGAN AND FINDING DESCRIPTION	NUMBER:	120	60	60	60	120	60	60	60
PARATHYROIDS L&R	NUMBER EXAMINED:	108	57	57	57	116	54	56	56
--HYPERPLASIA		14	4	0b	4	0	0	0	1
PITUITARY	NUMBER EXAMINED:	116	60	60	59	120	60	60	60
--FOCAL HYPERPLASIA		15	4	8	8	8	2	3	1
--HAEMORRHAGE		0	0	0	0	1	1	1	0
--CRANIOPHARYNGEAL CYST		4	0	0	1	0	2	1	0
--DUCTULAR REMNANTS WITHIN PARS NERVOSA		0	1	0	0	0	0	0	0
--HAEMOSIDERIN DEPOSITION		0	0	0	0	0	0	1	0
--FOCAL HYPERPLASIA OF PARS INTERMEDIA		1	0	1	0	0	0	0	0
--DEGENERATION		0	0	0	0	1	0	0	0
--DIFFUSE HYPERPLASIA		0	0	0	0	1	0	0	0
PROSTATE	NUMBER EXAMINED:	120	60	60	60	0	0	0	0
--ACUTE INFLAMMATION		3	1	2	0	0	0	0	0
--CHRONIC INFLAMMATION		5	1	2	0	0	0	0	0
--HYPERPLASIA		3	3	4	3	0	0	0	0
--ABSCESS(ES)		0	0	1	0	0	0	0	0
RECTUM	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--SUBMUCOSAL ACUTE INFLAMMATION		1	0	0	0	0	0	0	0
--DILATED		0	1	1	0	0	0	0	0
SEMINAL VESICLES	NUMBER EXAMINED:	120	60	60	60	0	0	0	0
--LACKING SECRETION		14	4	6	7	0	0	0	0
--DILATED WITH SECRETION		2	3	1	0	0	0	0	0
--ACUTE INFLAMMATION		0	0	1	1	0	0	0	0
--CHRONIC INFLAMMATION		0	0	2	0	0	0	0	0
SKIN	NUMBER EXAMINED:	120	60	60	60	120	60	60	60
--SCAB(S)		0	1	0	0	0	0	0	0
--FOCAL COLLAGEN DEPOSITION		0	0	1	0	0	0	0	0

Significant when comared with Group 1: b - p<0.01