

group. If a statistically significant increases in proportion of structurally aberrant cells (without gaps) occurred at one or more concentrations compared to control and proportion of aberrant cells at such data points exceed the normal range then the compound is genotoxic.

Results: Irrespective of the presence or absence of metabolic activation, treatment with GR 68755C did not produce any significant reproducible increase in chromosomal aberration over the value obtained for the control group. The positive control gave expected results. Thus GR 68755C had no clastogenic activity in this in vitro cytogenetic test.

**Unscheduled DNA Synthesis in Primary Hepatocytes of
Male Rat (Ex-Vivo)
(Study # R12689)**

Testing Laboratories: Glaxo Group Research Ltd.,
Genetic & Reproductive Toxicology
Dept., Hertfordshire, UK.

Dates Studies Started and Completed: January 14, 1991 and
August 29, 1991

Animals: Male and female AHA rats (189.7-257.2 g).

Doses Used: 25, 50, 75 and 100 mg/kg in males and 10, 25
and 40 mg/kg in females.

Drug Batch No.: C10261120/1 & C1026/123/1

Solvent Control: Water

Positive Control: 2-Acetylaminofluorene (2-AAF: 75 mg/kg)
and 1, 2-dimethylhydrazine HCl (DMH: 20 mg/kg).

Methods: Groups (3/group) of rats were given a single dose of GR 68755C via gavage (25, 50, 75 and 100 mg/kg in males and 10, 25 and 40 mg/kg in females). The positive control group animals received 2-AAF or DMN and the negative control group rats received vehicle (water). The volume of administration was 10 ml/kg. Groups of animals were sacrificed at 2-4 hours after drug administration, and another group were sacrificed at 12-14 hours after the drug administration. Hepatocyte primary cultures from the liver

of the rats were obtained, and [³H] thymidine incorporation was measured. Incorporation was followed by _____ of the hepatocytes and grains were counted in 100 nuclei other than S-phase. Net increases in nuclear grains induced by each compound were determined. The test compound is considered positive when the mean nuclear grain count is $> = 0$ and 20% or more of the cells responding (a cell is regarded as being "in repair" when net grain is $> = 5$).

Results: No net increase in nuclear grain counts was observed in hepatocytes when rats were treated with GR 68755C at oral (gavage) doses up to and including 100 mg/kg in males and 40 mg/kg in females. The positive controls were genotoxic, while no repair was induced by vehicle (negative control). Thus results suggest that GR 68755C was not genotoxic in this test.

Thymidine Kinase Mutation Test in
Mouse Lymphoma L5178Y Cells
(Study # V13036)

Testing Laboratories: Glaxo Group Research Ltd.,
Genetic & Reproductive Toxicology
Dept., Hertfordshire, UK.

Dates Studies Started and Completed: September 2, 1991 and
December 29, 1991

Strain Employed: L5178Y TK^{+/}- mouse lymphoma cells.

Concentration Employed: 200-400 mcg/ml in the absence of
S-9 mix and 100-300 mcg/ml in the presence of S-9 mix

Solvent Control: Water

Positive Control: Methyl methanesulphate (MMS: 10 mcg/ml)
and dimethylbenzanthracene (DMBA: 2.5 mcg/ml).

Source of Metabolic Activation: Rat liver microsomal
enzymes.

Drug Batch No.: C1026/133/1

Methods: In the range-finding study, cells were incubated with various concentrations of GR 68755C in the absence (10-350 mcg/ml) and presence (10-400 mcg/ml) of S-9 mix. The data indicated that the drug was cytotoxic at 300 mcg/ml in the presence of S-9 mix (relative survival rate = 42.3%) and heavy precipitate was seen at 400 mcg/ml. In the absence of S-9 mix, highest tested dose (350 mcg/ml) had no effect on survival rate, however, 2 days after the treatment relative survival rate at the highest dose was decreased by 34%. Based on the above findings, GR 68755C concentrations selected for the main study were 200 - 400 mcg/ml in the absence of S-9 mix and 100 - 300 mcg/ml in the presence of S-9 mix. A total of 5 assays were performed (3 in the absence of S-9 mix and 2 in the presence of S-9 mix). Cells were incubated for 3 hours, then cells were washed, resuspended in media and viability rates and mutation frequency were determined at appropriate time. The test substance was considered to be mutagenic if the mutation frequency at 1 or more dose was significantly greater than that of the negative control and it was dose related.

Results: Irrespective of the treatment with metabolic activation system (S-9 mix), no increase in mutant colonies was seen in this study. Thus, the drug is not mutagenic at the tk locus of L5178Y mouse lymphoma cells.

Rat Micronucleus Test
(Report # 115E/92)

Testing Laboratories: Glaxo Group Research Ltd.,
Genetic & Reproductive Toxicology
Dept., Hertfordshire, UK.

Dates Studies Started and Completed: March 1, 1989 and
July 27, 1989

Test Species: Male PVG rats

No. of Animals: 5 - 7/group

Route of Administration: Orally (gavage) or I.V.

Dose Levels: Oral: 50, 125 and 250 mg/kg (10 ml/kg),
I.V.: 6.25 or 12.5 mg/kg (5 ml/kg).

Drug Batch No.: C1017/133/1

Basis of Dose Selection: Dose levels are based on the preliminary toxicity study.

Solvent Control: 0.9% saline (10 ml/kg).

Positive Control: Cyclophosphamide (25 mg/kg, 10 ml/kg).

Methods: Animals were given a single dose at 24 or 48 hours prior to sacrifice and preparation of the bone marrow (positive control animals were sacrificed at 24 hr after cyclophosphamide administration). On the slides, 2000 polychromatic erythrocytes per animal were examined for the presence of micronuclei. The compound is considered positive if the number of micronucleated polychromatic erythrocytes at one or more doses are significantly greater than the negative control value and it is dose related.

Results: GR 68755C did not induce an increase of micronucleated polychromatic erythrocytes in rat bone marrow. In contrast, the % of micronucleated polychromatic erythrocytes in cyclophosphamide treated group was markedly higher than the negative control. These findings suggest that GR 68755C is not mutagenic in this test system.

Addendum: The oral gavage doses were 20 and 40 mg/kg.

Ames Test
(Study # V12468)

This test was conducted to assess the mutagenic potential of GR 62202X which is an intermediate in the synthesis of GR 68755C).

Testing Laboratories: Glaxo Group Research Ltd.,
Genetic & Reproductive Toxicology
Dept., Hertfordshire, UK.

Dates Studies Started and Completed: Not given (report date: December 14, 1990).

Strain Employed: Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537.

Concentration Employed: 50 - 5000 mcg/plate.

Solvent Control: Dimethyl sulfoxide (DMSO).

Positive Control: NaN_3 (2.0 mcg/plate), ICR-191 (1.0 mcg/plate), hycanthone (10.0 mcg/plate), 2-aminoanthracene (2.0-5.0 mcg/plate or 5 mcg/ml) and neutral red (10 mcg/plate).

Source of Metabolic Activation: Phenobarbitone & beta-Naphthoflavone induced rat liver microsomal enzymes (S-9 mix).

Drug Batch No.: C 1017/321/1

Criteria of Positivity: When Dunnett's test gave a significant response ($p < \text{or} = 0.01$) and the data set showed a significant correlation then the test substance is considered positive provided results were reproducible.

Methods: Ames was conducted to assess the mutagenic potential of GR 62202X (an intermediate in the synthesis of GR 68755C) by measuring its ability to induce reverse mutations at selected loci of several strains of Salmonella typhimurium [TA 98, TA 1537 and TA 1538 (frame shift); TA 100 and TA 1535 (base pair substitution)] in the presence and absence of S-9 activation.

Results: GR 62202X was mutagenic in tester strain TA 98 in the absence as well as in the presence of S-9 mix. Additionally, positive results were also seen in strains TA 1537 and TA 100 in the presence of S-9 mix. Increase in mutant colonies was noted in all microbial strains employed in the presence of positive control (with or without S-9 mix). Data indicated that GR 62202X is mutagenic in Ames test.

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Summary Table of Standard Ames Test Data for GR62202 (base) in
a) the Absence and b) the Presence of a Metabolising System (S9-Mix)
(Report No. WPT/90/304)

a) Concentration of GR62202X µg(base)/plate	Salmonella Typhimurium Strain (Mean Number of Revertant Colonies/Plate)							
	TA 1535		TA 1537		TA 98		TA 100	
	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
0	16.0	9.8	7.4	23.4	27.2	130.4	124.4	
50	17.0	8.8	8.6	32.2	32.60	121.4	127.8	
150	16.6	12.6	9.4	26.8	50.0	128.6	126.0	
500	13.8	11.6	8.8	35.0	60.6	121.2	127.0	
1500	13.2	10.6	8.8	62.2	90.8	128.0	129.2	
5000	7.8	7.6	6.4	75.0	68.6	113.6	118.0	
Positive Controls	577.0	612.0	324.0	168.0	480.5	671.5	685.5	

b) Concentration of GR62202X µg(base)/plate	Salmonella Typhimurium Strain (Mean Number of Revertant Colonies/Plate)							
	TA 1535		TA 1537		TA 98		TA 100	
	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2	Test 1	Test 2
0	11.6	12.2	8.8	11.6	24.2	23.2	144.8	145.0
50	10.6	15.2	11.6	11.0	31.8	33.8	148.0	154.2
150	10.8	10.6	13.6	15.0	32.8	47.2	154.0	132.4
500	13.8	12.2	15.8	25.8	69.6	101.8	165.0	155.8
1500	9.4	12.6	15.2	18.8	168.0	256.2	166.2	160.8
5000	9.4	10.4	16.0	14.6	282.4	885.0	156.0	188.0
Positive Controls	308.0	394.5	400.5	518.5	1752	2001	714.5	1634

Addendum: The positive results were not observed in strains TA 100, TA 1535, and TA 1537. Therefore, GR 62202 was positive in the Ames test only in one strain of S. typhimurium, TA 98.

LABELING:

The labeling is according to 21 CFR, Subpart B. The following revisions in the labeling are recommended.

2 Page(s) Redacted

Draft

Labeling

SUMMARY AND EVALUATION:

Alosetron hydrochloride (GR 68755) is a selective serotonin 5-HT₃ receptor antagonist with pK_i of 9.4-9.8 in rat vagus nerve and entorhinal cortex and has a high affinity for 5-HT₃ receptor with IC₅₀ of 1.1 x 10⁻⁹ M and low to no affinity for other types of receptors. Irritable bowel syndrome is a functional disorder of the gastrointestinal (GI) tract characterized by abdominal pain, discomfort, and changes of bowel function (constipation or diarrhea). The serotonin 5-HT₃ receptor is thought to play an important role in the irritable bowel syndrome. Activation of 5-HT₃ receptor located in GI tract stimulates release of 5-HT which subsequently produces pain and increases motor activity of the gut. Therefore, by blocking 5-HT₃ receptor, alosetron would be therapeutically useful for treatment of the irritable bowel syndrome. The results of in vivo studies indicated that GR 68755 had no significant effects on the heart rate, blood pressure, and ECG following i.v. dose of 1 mg/kg in guinea pigs and dogs. This is consistent with the findings from the in vitro studies in which GR 68755 had no marked effects on the action potential duration of the isolated canine Purkinje fibers (up to 100 ng/ml) and delayed rectifying potassium currents in the isolated guinea pig cardiac myocytes (up to 10⁻⁶ M).

In the present NDA, sponsor is asking for approval to market alosetron for treatment of irritable bowel syndrome (IBS) in female patients with diarrhea predominance. In support of this NDA, the following studies were submitted: (1) pharmacology, (2) ADME, (3) acute toxicity studies in mice and rats, (4) 1-month i.v. toxicity studies in rats and dogs, (5) 34/35-day oral toxicity studies in rats and dogs, (6) 34/35-day oral toxicity studies in rats and dogs, (7) 12-month oral toxicity studies in rats and dogs, (8) 13-week oral (in drinking water) oral dose ranging study in mice, (9) 3-month oral (in diet) dose ranging study in rats, (10) 3-month oral (gavage) dose ranging study in rats, (11) 94/95-week oral (in drinking water) carcinogenicity study in B6C3F1 mice, (12) 104-week oral (in diet) carcinogenicity study in Wistar rats, (13) Segment I oral fertility and reproductive toxicity study in rats, (14) Segment II oral teratology studies in rats and rabbits, (15) Segment III oral pre and postnatal reproductive toxicity study in rats, (16) two Ames tests,

(17) in vitro chromosome aberration tests in human lymphocytes, (18) mouse lymphoma cell (L5178Y/TK⁺/-) forward mutation assays at tk locus, (19) unscheduled DNA synthesis in rat hepatocytes, and (20) rat micronucleus test.

GR 68755 was absorbed rapidly in mice, rats, rabbits, and dogs (T_{max} : ~0.5-0.75 hr) and nearly completely in dogs (bioavailability = 96%). Half life ($t_{1/2}$) was <0.25 hr in mice and ~1-1.5 hour in rats, rabbits, dogs, and humans. Irrespective of strains of rats, the systemic exposure of GR 68755 and/or its metabolites in females were significantly greater than in males. This difference was not seen in mice and dogs. In humans, the plasma level of GR 68755 was slightly higher in young females (AUC = 61.3 ng.h/ml) than that in young males (AUC = 49.4 ng.h/ml) following i.v. administration of GR 68755 at 2 mg. The higher plasma level of GR 68755 in female than in males (rats and humans) may be due to the sex difference in the clearances. For example, the plasma clearance of GR 68755 was 44.7 and 16.4 ml/min/kg in male and female rats, and 675 and 544 ml/min in male and female patients, respectively. In rats, administered radioactivity was widely distributed throughout the body, and concentrations in liver, kidneys and adrenals were significantly higher than blood. Radioactivity was also seen in the eyes of pigmented rats. In pregnant rats and rabbits, radioactivity crosses placental barrier and is widely distributed in fetuses. The radioactivity was also detected in the milk of the lactating rats. About 72-88% of GR 68755 were bound to the plasma proteins in mice, rats, rabbits, dogs, and humans. Irrespective of species, the drug is rapidly metabolized following oral or i.v. administration. More than 10 radioactive peaks were seen in urine and fecal samples and one of the peak was identified as GR 87620 (N-desmethyl analogue of GR 68755). It represented 3-6% of the dose in rat feces and urine and ~10-19% in dog feces and urine. A bis-oxidized metabolite of GR 68755 (GR 153732) which is present in human plasma and urine following oral administration of GR 68755 was also identified in rat's and dog's urine samples. This metabolite (GR 153732) has very low affinity for human 5-HT₂ receptors (pKi <6) as compared to GR 68755 (pKi ~9). Less than 10% of dose was excreted as unchanged drug. Irrespective of species, about 42-59% and 33-48% of administered radioactivity were excreted in urine and feces, respectively. In rats, about 27.6% of administered radioactivity were excreted in the bile.

changes in the high dose group were clinical signs of toxicity (tense behavior, "croaking", tiptoe gait, and tremor) and basophilic foci of hepatocellular alteration. Therefore, the central nervous system and liver were the target organs of toxicity.

In the 12-month oral toxicity study in rats, GR 68755 was given to rats by oral gavage at 0, 1, 6.5, and 20/40 mg/kg/day for 377/380 days. Central nervous system and liver were the target organs of toxicity as evidenced by clinical signs of toxicity (salivation, noisy breathing, "croaking", and hunched posture) and histopathological changes in the liver (multiple basophilic foci of hepatocellular alteration and fine, minimal fatty vacuolation of periacinar hepatocytes) associated with increased activities of alkaline phosphatase and alanine aminotransferase (49-91%). Treatment with GR 68755 decreased hearing acuity in the treated animals (both males and females) and resulted in loss of hearing in 2 high dose males.

In the 1-month i.v. toxicity study in dogs, dogs were treated intravenously with GR 68755 at 0, 1, 3.5, and 12.25 mg/kg/day for 35 or 36 days. The major treatment related changes were clinical signs of toxicity including salivation, head shaking, open mouth, partly closed and/or moist eyes and rhinorrhea, subdued behavior, licking lips, and pink ears and gums (more in the high dose group). The central nervous system was the target organ of toxicity based on the clinical signs of toxicity.

In the 35-day oral toxicity study in dogs, GR 68755 was given by oral gavage at 0, 1, 5.5, and 30 mg/kg/day for 35 days. The dose of 30 mg/kg for females was reduced to 20 mg/kg on day 6 and then increased to 25 mg/kg on day 10 and to 30 mg/kg from day 12 onward. High dose was lethal. The treatment related changes in the high dose group were clinical signs of toxicity (subdued behavior, half-closed eyes, trembling), decreased body weight gain (8-13.7%), and thymic involution. Therefore, central nervous system and thymus were the target organs of toxicity.

In the 6-month oral toxicity study in dogs, GR 68755 was given by oral gavage at 0, 1, 5.5, and 20 (days 1-3)/30 (days 4-8)/25 (days 9 onwards) mg/kg/day for 28 weeks. High dose was lethal. The treatment related changes in the high dose group were clinical signs of toxicity (subdued behavior, vocalizing, partly closed eyes, open mouth,

In the acute toxicity studies in mice, the clinical signs of toxicity were subdued behavior, labored respiration, tremor, ataxia, and convulsions in both mice and rats. In addition, decreased activity was seen in mice and "croaking" and half-closed eye were found in rats. The minimal lethal oral dose was 15 mg/kg and 25 mg/kg for female and male mice, respectively. The minimal lethal i.v. dose was 8 mg/kg for male mice and the minimal lethal i.v. dose for female mice was not determined. In the acute toxicity studies in rats, the clinical signs of toxicity were subdued behavior, occasional "croaking", tremor, ataxia, half-closed eyes, labored respiration, and convulsion. The minimal lethal oral dose was 60 mg/kg for female rats. The minimal lethal oral dose for male rats was not determined. The minimal lethal i.v. dose was 20 mg/kg for male rats. The minimal lethal i.v. dose for female rats was not determined.

In the 1-month i.v. toxicity study in rats, rats were treated intravenously with GR 68755 at 0, 1, 3.5, and 12.25 mg/kg/day for up to 36 days. The major treatment related changes were clinical signs of toxicity including subdued behavior, low posture, moist eyes, bulging eyes, and "croaking" mainly in the high dose group. The central nervous system was the target organ of toxicity based on the clinical signs of toxicity.

In the 34/35 day oral toxicity study in rats, GR 68755 was given by oral gavage at 0, 1, 8, and 40 (days 1-5)/64 mg/kg/day for 34/35 days. The high dose was lethal. The treatment related changes in the high dose group were clinical signs of toxicity (bulging eyes, ataxia, labored respiration, piloerection, prostration, tremor, and reduction of body temperature), decrease in platelet counts, and increase in serum alkaline phosphatase and alanine aminotransferase activities. Thymus was also the target organ of toxicity as evidenced by histopathological changes (partial thymic involution).

In the 6-month oral toxicity study in rats, GR 68755 was given by oral gavage at 0, 1, 8, and 20 (days 1-4)/40 (days 5-7)/64 (days 8-54-55)/40 (days 55/56 onwards) mg/kg/day for 196 days. The high dose of 64 mg/kg was achieved by increasing dose of 20 mg/kg on days 1-4 to 40 mg/kg on days 5-7 and to 64 mg/kg on day 8. However, the high dose of 64 mg/kg was reduced to 40 mg/kg on day 55 due to excessive toxicity observed. The treatment related

ataxia, and tremor), decreased body weight gain (6-13.7%), and increased alkaline phosphatase and alanine aminotransferase activity. Therefore, central nervous system and liver were the target organs of toxicity.

In the 12-month oral toxicity study in dogs, GR 68755 was given by oral gavage at 0, 1, 5, and 20 (days 1-3)/25 (day 4 onwards) mg/kg/day for 12 months. High dose was lethal. The treatment related changes in the high dose group were clinical signs of toxicity (rotating motion of head, ataxia, stiff limbs, walking on tip-toe, abnormalities of movement and respiration, subdued behavior, and tremor) and increase in hearing threshold. Therefore, central nervous system was the target organ of toxicity.

The results of the special toxicity studies indicated that GR 68755 suspension (50% w/w) produced no skin irritant reaction, single application of 10 mg GR 68755 to the rabbit eye produced slight corneal, moderate iridal and conjunctival reactions, and GR 68755 (10% w/w) had no contact sensitizing potential in guinea pigs.

The results of the 29-day special toxicity study on the hearing in dogs revealed no treatment related effects on hearing threshold. The increased hearing threshold in the 1-year toxicity studies in rats and dogs were not observed in the short term studies (up to 6-month).

In the 13-week oral (via drinking water) toxicity study in mice, GR 68755 was given to mice (via drinking water) at 0, 20, 30 and 40 mg/kg/day for 13 weeks. Control mice received acidified (pH 5.5) water. GR 68755 was unpalatable in females when given via drinking water. In females, water intakes were 12%, 11% and 22% lower than the control values in low, mid and high dose groups respectively. During the study period, GR 68755 concentration in water was adjusted twice weekly, hence animal did receive the intended dosages. Based on this finding, sponsor selected 30 mg/kg (via drinking water) as the maximum tolerated dose in mouse carcinogenicity study.

In the oral carcinogenicity study in mice, mice (60/sex/group) were treated with GR 68755 via drinking water at 0, 0, 1, 5.5, and 30 mg/kg/day for 94/95 weeks in males or 104/105 weeks in females. The dose selection was considered adequate in the Executive CAC meeting held on April 23, 1996. The high dose was maximum feasible dose. There were no treatment related clinical signs of toxicity.

Mortality rate was comparable in control and treatment groups. The terminal body weight in the high dose female was 91.4% of the control. Higher incidences of Harderian gland adenoma and liver cell tumors were found in the treated males and females, respectively. These increased incidences were not dose related. They are within the background incidence. Treatment with GR 68755 produced benign interstitial cell tumor of the testes in a dose dependent manner and a single incidence of malignant interstitial cell tumor of the testes in a mid dose male (none in the controls). The increased incidences were not statistically significant by the trend test. The increased incidences in each of the treatment groups were not significantly (pairwise test) different from the incidences in the vehicle control. Plasma level of GR 68755 was not different between males and females. Alosetron did not have tumorigenic potential in the mouse carcinogenicity study.

In the 3-month oral (in diet) dose ranging study in Wistar rats, groups of rats were given GR 68755 via diet at 0, 10, 20 and 40 mg/kg/day for 3 months. No treatment related changes were observed in this study except reduction of absolute and relative weights of pituitary by 27-28% as compared to control values. The systemic exposure of GR 68755 at 40 mg/kg/day dose level was about 24-89 fold higher than the anticipated human exposure ($AUC_{0-24 \text{ hr}} \approx 396.4 \text{ ng.hr/ml}$, 0.32 mg/kg/day [8 mg b.i.d.], 50 kg body wt. assumed). The dose 40 mg/kg/day was selected as the high 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 the 3-month oral (gavage) dose ranging study in Wistar rats, GR 68755 was given to rats by oral gavage at 0, 10, 20 and 20/40 mg/kg/day for 3 months. The major treatment related changes were increase in liver weight in all treated males (10-13%) and high dose females (28%) and histopathological changes in the liver (periacinar hepatocytic hypertrophy and foci of "pre-basophilic" hepatocytes in high dose group).

In 104-week oral (via diet) carcinogenicity study in Wistar rats doses of 0, 1, 6.5 and 40 mg/kg/day were used. This study was reviewed on April 16, 1996 (Pharmacology review) and discussed at the Executive CAC meeting on April 23, 1996. The dose selection was considered adequate and this study was acceptable. 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. Alosetron did not have tumorigenic potential in the rat carcinogenicity study.

In the Segment I fertility and reproductive performance study in rats, GR 68755 was given by oral gavage at 0, 1, 6.5, and 40 mg/kg/day to male rats for 71 days prior to mating, throughout mating and until termination and to female rats for 22 days prior to mating, throughout mating, gestation, and until ~22 days after postpartum (approximately half the females were sacrificed on day 21 of gestation). Toxicity on the central nervous system was observed in the high dose dams (subdued behavior, low posture, labored breathing, and budging eyes). The fertility and mating performance were not adversely affected.

In the Segment II teratology study in rats, GR 68755 was given by oral gavage at 0, 1, 6.5, and 40 mg/kg/day to pregnant rats from gestation days 7 to 16. Maternotoxicities were observed in the high dose group and these included clinical signs of toxicity (subdued behavior, labored breathing, half closed eyes, and "croaking"), decreased body weight gain (~25%), and increased post-implantation loss. The incidence of supernumerary ribs was increased in the high dose group. GR 68755 was not teratogenic.

In the Segment II teratology study in rabbits, GR 68755 was given by oral gavage at 0, 1, 6.5, and 40 mg/kg/day to pregnant rabbits from gestation days 8 to 20. GR 68755 was not teratogenic.

In the Segment III perinatal and postnatal reproductive toxicity study in rats, GR 68755 was given by oral gavage to pregnant female rats at 0, 1, 6.5, and 40 (days 1-3)/30 (day 4 onward) mg/kg/day during gestation day 17 through day 22 after delivery. GR 68755 at high dose produced maternal toxicity including death, decreased body weight gain (~24%) and food consumption (~21%). At the maternal toxic dose, following were observed in the offspring: clinical signs of toxicity (tip toe gait, hyperactivity, piloerection, and vocalization), decreased birth weight _____ g, control = _____ g), decreased body weight gain during days 28-64 (12%), and slightly delayed testes descent and vaginal opening. The clinical