No specific information is available on the treatment of overdosage with EMEND. Single doses up to 600 mg of aprepitant were generally well tolerated in healthy subjects. Aprepitant was generally well tolerated when administered as 375 mg once daily for up to 42 days to patients in non-CINV studies. In 33 cancer patients, administration of a single 375-mg dose of aprepitant on Day 1 and 250 mg once daily on Days 2 to 5 was generally well tolerated. Drowsiness and headache were reported in one patient who ingested 1440 mg of aprepitant.

In the event of overdose, EMEND should be discontinued and general supportive treatment and monitoring should be provided. Because of antiemetic activity of aprepitant, drug-induced emesis may not be effective.

Aprepitant can not be removed by hemodialysis.

Evaluation: No changes recommended.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Aprepitant (MK-0869/L-754, 030) is a neurokinin$_1$ (substance P) receptor antagonist and has been found to bind selectively and with high affinity to NK_1 receptors from different species. It causes inhibition of binding of [^{125}I]substance P to cloned human, rat and guinea pig NK_1 receptors, and to NK_1 receptors from dog and ferret cerebral cortex, with IC_{50} values in the nM range. It has >3,000-fold higher affnity for NK_1 receptors than NK_3 receptors and has higher affinity than other G-protein coupled receptors. After i.v. dosing of L-758, 298 (a phosphoramidated pro-drug) to rhesus monkeys, a good relationship between plasma active drug (MK-0869) concentration and central receptor occupancy (determined by PET assay) was observed. It caused inhibition of facilitation of the nociceptive spinal flexor reflex in a rabbit model. Oral or i.v doses of aprepitant caused dose-dependent increase in the latency of cisplatin-induced retching and vomiting and reduced numbers of retches and vomits. In a model of cisplatin-induced delayed emesis in ferrets, MK-0869 caused complete inhibition of retching and vomiting at oral doses of 2 and 4 mg/kg. When administered in combination with i.v. ondansetron (a 5-HT_3 receptor antagonist), i.v. aprepitant had additive effects on cisplatin-induced emesis in ferrets. Similar additive effects were observed when the drug was administered in combination with i.v. dexamethasone.

L-758, 298 had no effects on the blood pressure, heart rate or ECG parameters of anesthetized dogs at an i.v. dose of 1 mg/kg. Substance P-induced depressor response and tachycardia in anesthetized dogs were reversed by L-758, 298. It had no behavioral and central nervous system (CNS) effects in conscious mice at oral doses up to 100 mg/kg. L-758, 298 had no treatment-related effects on the respiratory function (peak expiratory flow, intrapulmonary pressure, tidal volume, airway resistance, respiratory rate and minute volume) and hemodynamics (mean arterial pressure, heart rate, systolic and diastolic blood pressures) of anesthetized dogs.

Pharmacokinetics/toxicokinetics studies were conducted with both the pro-drug, L-758, 298 and and the active drug, L-758, 030 (MK-0869), following i.v. and oral administration to rats, mice, dogs and ferrets. The absoprtion of the drug after oral dosing was rapid, and the maximum plasma concentration was reached in between 2-4 hours. The oral bioavailability of MK-0869 (L-754, 030)

was 43% in rats, 42.4% in mice and 45.4% in ferrets. The absolute bioavailability in humans was approximately 60%. MK-0869 is a weak substrate and inhibitor of P-glycoprotein (Pgp). Following i.v. dosing in rats, the the drug was not concentrated in any particular tissue. L-758, 030 is highly bound to plasma proteins from rat, dog and human >98%). MK-0869 can penetrate the blood brain barrier, and was detected in the brain of rats and ferrets after oral or i.v. administration. The drug was detected in the fetal plasma, when administered to pregnant animals, and it was excreted in the milk of lactating rats. Saturation of absorption of MK-0869 was achieved in rats at an oral dose of 125 mg/kg b.i.d., and in mice at an oral dose of 500 mg/kg/day.
N-dealkylation is the major pathway of metabolism of L-755, 030. After oral administration of [^{14}C]MK-0869 to rats, several nonpolar (L-755446, L-809861, L-826678, L-809771), polar (L-829615, L-819617) and very polar (L-596064, L-294569, L-770787) metabolites were identified in the plasma. In dog plasma, these metabolites and several additional nonpolar and polar metabolites were identified. After i.v. dosing of [^{14}C]L-758298 to humans, several, polar and very polar metabolites were identified in the plasma, which are similar to those found in rats. In the human liver microsomes, CYP3A4 was identified as the main CYP450 isozyme involved in the metabolism of MK-0869. Two other CYP450 isozymes, CYP1A2 and CYP2C19, were alsoinvolved in the metabolism of the compound.
Fecal excretion is the predominant excretory pathway in rats. Following oral administration of a 2 mg/kg dose of [^{14}C]MK-0869 to rats, 57.8% and 29.5% of the radioactivity were excreted in the feces and urine, respectively; following i.v. dosing, 53.8% and 33.7% of the radioactivity were excreted in the feces and urine, respectively. In dogs, fecal excretion was similar to that of urinary excretion; after a 2 mg/kg i.v. dose, 39.1% and 37.7% of dose was excreted in feces and urine, respectively, in 168 hours. After an oral dose, 43.1% and 40.5% of the administered dose was excreted in the feces and urine, respectively, during the same period.

Acute toxicity studies with L-758, 298 (a prodrug of MK-0869) were conducted in mice and rats after i.v. administration of 200 and 500 mg/kg doses and oral administration of a 500 mg/kg dose. The minimal lethal dose (MLD) by the i.v. route was 500 mg/kg in both mice and rats. There were no deaths of mice or rats receiving the 500 mg/kg oral dose; thus, the MLD by the oral route was not known. The clinical signs observed in mice after i.v. dosing included gasping, convulsions, bradypnea and loss of righting reflex that disappeared within 3 hours. In rats, the clinical signs included gasping and bradypnea.

In a 16-day intravenous toxicity study, rats received MK-0869 (— particle size) at doses of 0, 80, 160, and 240 µg/kg/day. The no effect dose appeared to be 240 µg/kg/day. Solubility of MK-0869 in the vehicle limited the amount of drug that could be administered by the intravenous route. Therefore, doses used appeared to be inadequate to assess the toxicity of MK-0869 when administered by the intravenous route. Body weight gains of female rats at 160 and 240 µg/kg/day were impaired by >10%; however, there were no effects on corresponding male treatment groups. A target organ of toxicity was not identified.

In a 5-week i.v. toxicity study in rats, MK-0869 doses of 9, 2, 5 and 10 mg/kg/day were used. Hepatocelluar hypertrophy was observed in both males and females at 5 and 10 mg/kg/day doses. The target organ of toxicity was the liver and the 2 mg/kg/day dose was the no effect dose.

In a 5-week oral dose range-finding study with L-754, 030 in rats, groups of animals received 0 and 250 mg/kg/day, and 0, 250, 500 and 1000 mg/kg b.i.d doses of the drug. Slight hepatocellular hypertrophy was observed in males and females of all treatment groups. For the thyroid gland, very slight to slight follicular cell hyperplasia were observed for treatment groups. A very slight to slight dose-dependent vacuolation of individual cells in the pars distalis of the pituitary gland was observed for all male treatment groups. This change may represent a degeneration or exhaustion of the TSH producing pituitary cells secondary to hepatic enzyme induction and increased catabolism of T_3 and T_4. The target organs of toxicity were the liver, thyroid gland and the pituitary gland, and the no effect dose was not established.

In a 5-week oral toxicity study with the two MK-0869 formulations (formulation M, [redacted] particle size; formulation NB, [redacted] particle size) in rats, 0 and 125 mg/kg b.i.d doses of formularion M and 0, 5, 125, 250, 500 and 750 mg/kg b.i.d doses of formulation NB were used. A no effect dose was not observed with either formulation M or NB. Histopathological changes were observed in the liver and the thyroid gland. Hypertrophy and diffuse vacuolation of the hepatocytes, and diffuse follicular cell hyperplasia of the thyroid gland were observed in males and females of all treatment groups. Benign parafollicular cell adenoma was observed in two animals, one receiving 125 mg/kg b.i.d of formulation M and the other receiving formulation NB at 250 mg/kg b.i.d. The target organs of toxicity were the liver and the thyroid gland. Plasma drug concentrations in females were higher than that of males. A plateau of plasma drug level was observed in both males and females receiving b.i.d doses of formulation NB.

In a 14-week oral dose range-finding study with L-754, 030 in rats, groups of animals received 0, 5, 25, 125 and 250 mg/kg b.i.d doses of the drug. Very slight to slight hepatocellular hypertrophy was observed in all male and female treatment groups. Very slight to slight diffuse hepatocellular vacuolation, with increased incidences in males, was observed in animals receiving the high dose. Very slight to slight diffuse follicular cell hyperplasia of the thyroid gland was observed in all treatment group males and females. Vacuolation of individual cells of pars distalis of the pituitary gland was observed in males receiving 125 and 250 mg/kg b.i.d doses. The change was characterized by enlargement of individual pituitary cells due to formation of large cytoplasmic vacuoles and occasional protein droplets. The target organs of toxicity were the liver, thyroid gland and the pituitary gland, and the no effect dose was not established.

In a 27-week oral toxicity study with the NB ([redacted] particle size) formulation of MK-0869 in rats, groups of animals received 0, 125, 250 and 500 mg/kg b.i.d doses of the drug. Treatment-related changes in the hematology (increased platelet levels in males, and increased platelets, decreased hemoglobin and hematocrit velues in females) and clinical chemistry (increased protein and cholesterol and decreased triglycerides in both sexes) parameters were observed in all treatment groups. Hepatocellular hypertrophy and thyroid follicular cell hyperplasia were observed in males and females of all treatment groups. The target organs of toxicity were the liver and the thyroid gland and the no effect dose was not established.

In the 53-week oral toxicity study with a 27-week interim necropsy in rats, L-754, 030 [redacted] particle size), doses of 0, 0.25, 25 and 250 mg/kg/day were used. The target organs of toxicity were the liver and the thyroid gland following treatment for either 26 or 52 weeks. Slight centrilobular hypertrophy in the liver and slight diffuse follicular cell hyperplasia of the thyroid gland were

observed in both males and females receiving 25 and 250 mg/kg/day doses for 26 or 52 weeks. The histopathological changes in the liver and the thyroid gland appeared to associated with an induction of cytochrome P-450. The no effect dose was 0.25 mg/kg/day.

In the 5-week oral dose range-finding study in mice, 0, 500 and 1000 mg/kg b.i.d (0, 1000 and 2000 mg/kg/day) doses were used. The no effect dose was identified as1000 mg/kg/day (500 mg/kg b.i.d), and a target organ of toxicity was not identified. Body weight gains were impaired by >10% for frnales receiving the 500 and 1000 mg/kg b.i.d doses. Increased liver weights were observed in males and females of all treatment groups; however no histopathological changes were observed. Elevations of cholesterol and triglyceride levels were observed in both males and females receiving the drug.

In the 5-week oral toxicity and toxicokinetic study with MK-0869 in mice, groups of animals received formulation M ([redacted] particle size) at 0 and 500 mg/kg/day and formulation NB at 0, 25, 500, 1000, 1250 and 1500 mg/kg S.I.D, and 0, 12.5, 250, 500, 625 and 750 mg/kg b.i.d doses. Centrilobular hypertrophy of the liver was observed in both males and females receiving the drug. For the S.I.D regimen, centrilobular hypertrophy was observed for male mice that received formulation NB at doses ≥25 mg/kg/day and female mice that received it at ≥500 mg/kg/day. For the B.I.D regimen, centrilobular hypertrophy was observed in male mice at doses ≥12.5 mg/kg B.I.D and in female mice at doses ≥250 mg/kg B.I.D. The no effect dose in males was not established, and in females, it was 25 mg/kg/day. The plasma exposure levels in female mice were higher than that in males (<2-fold). A plateau in the exposure levels was observed at 250 mg/kg B.I.D or 500 mg/kg S.I.D doses. Plasma exposure levels of the parent drug after administration of formulation NB at 1500 mg/kg/day or 750 mg/kg B.I.D doses was ≤2 times higher than that achieved with formulation M (500 mg/kg/day).

In a 14-week oral dose range-finding study with L-754, 030 in mice, 0, 25, 125, 250, 500 and 1000 mg/kg/day doses were used. Centrilobular hepatocellulay hypertrophy was observed in both males (at ≥25 mg/kg/day) and females (at ≥125 mg/kg/day), and hydropic degeneration of tubules of the kidney was observed in females at 1000 mg/kg/day. The 500 mg/kg/day was the tolerated dose, and the target organs of toxicity were the liver and the kidney.

In a 5-week i.v. toxicity study with L-758, 298 in dogs, 0, 0.5, 2, 8, and 32 mg/kg/day doses were used. Hind limb swelling was observed at 8 and 32 mg/kg/day doses. The no effect dose was 2 mg/kg/day, and no target organ of toxicity was identified.

In a 5-week oral toxicity study in dogs, groups of animals received 0, 5, 25, 125, 250, 500 and 750 mg/kg b.i.d (0, 10, 50, 250, 500, 1000 and 1500 mg/kg/day) doses of formulation NB ([redacted] particle size). A plateau in the plasma exposure levels was observed at the 500 mg/kg b.i.d dose. The no effect dose was approximately 125 mg/kg b.i.d, and the target organs of toxicity were the testes, prostate and the thymus. Testicular degeneration and prostatic atrophy were observed in male dogs receiving 125 mg/kg b.i.d and higher doses. An increased incidence of thymic atrophy was observed in animals receiving ≥125 mg/kg b.i.d; although, a dose-response relationship was not evident. A plateau in the AUC values for MK-0869 was observed at doses ≥500 mg/kg b.i.d

In a 39-week oral toxicity study with MK-0869 Formulation NB ([redacted] particle size) in dogs, 0, 5, 25, 125 and 500 mg/kg b.i.d (0, 10, 50, 250 and 1000 mg/kg/day) doses were used. Suppression

of body weight gains was observed at all doses. Increased alkaline phosphatase and cholesterol levels were observed in treatment group animals. Prostatic atrophy and testicular degeneration were observed male dogs receiving 25 mg/kg b.i.d and higher doses. The target organs of toxicity were the testes and prostate, and the no effect dose was not established.

In a 53-week oral toxicity study with a 27-week interim sacrifice with L-754, 030 in dogs, 0, 4, 16 and 32 mg/kg/day doses were used. No treatment-related toxic effects were observed in any group. The no effect dose was 32 mg/kg/day and no target organs of toxicity were identified.

In a 17-day i.v toxicity study with MK-0869 in monkeys, groups of animals received 0. 80, 160 and 240 mg/kg/day doses of the drug. No drug-related toxic effects were observed in any group, and the 240 mg/kg/day dose was the no effect dose in this study.

In a 5-week i.v. toxicity study with L-758, 298 in monkeys, 2, 5 and 10 mg/kg/day doses were used. No treatment-related toxic effect was observed in any group. The no effect dose was 10 mg/kg/day, and a target organ of toxicity was not identified.

The genotoxic potential for L-758, 298 (a pro-drug of MK-0869) was examined by the bacterial reverse mutation assay (Ames assay), the rat hepatocyte DNA damage assay, the mutagenesis assay in TK6 human lymphoblastoid cells and the chromosomal aberrations assay in the Chinese hamster ovary (CHO) cells. It was not found to be genotoxic in any of the assays, either in the absence or presence of metabolic activation.
The genotoxic potential for L-754, 030 (MK-0869) was examined by the *in vivo* mouse bone marrow micronucleus assay and the mutagenesis assay in TK6 human lymphoblastoid cells. It was not found to have any genotoxic potential in these assays.

The sponsor conducted two 106-week oral carcinogenicity studies in Sprague Dawley rats and a 105-week oral carcinogenicity study in CD-1 mice with MK-0869. In the first carcinogenicity study in rats, oral doses of 0, 0.10, 0.50 and 2.0 mg/kg/day (0, 0.05, 0.25 and 1.0 mg/kg b.i.d.) were used. No treatment-related effects on the body weights or survival were observed in any group. Treatment with MK-0869 was associated with increased incidences of papilloma of the skin (Control 1, 0/50 [0%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 0/50 [0%]; high dose, 3/50 [6%]; P=0.042, Trend test) in the male animals. However, the incidence of skin papilloma is within the spontaneous incidences reported for this tumor in this strain of rat (0.87% to 6.0%, ·
On the basis of CDER statistical standard, the incidence for this tumor was not significant as the P-value (0.042) exceeded the required P-value of 0.005 for common tumors (incidences >1%). Thus, MK-0869 was not carcinogenic in male and female rats when administered by the oral route for 106 weeks at doses up to 2.0 mg/kg/day. Plasma exposure levels in the male and female rats at the high dose were approximately .019 and 0.086 times the exposure levels in humans at the recommended clinical dose, respectively.

In the second 106-week oral carcinogenicity study in rats, 0, 5, 25 and 125 mg/kg b.i.d (0, 10, 50 and 250 mg/kg/day) doses were used. Treatment with MK-0869 was associated with higher incidences of thyroid follicular cell adenoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid

dose, 1/50 [2%]; high dose, 3/50 [6%]; P=0.014, Trend test) and carcinoma (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 1/50 [2%]; mid dose, 1/50 [2%]; high dose, 2/50 [4%]; P=0.036, Trend test) in the **male** rats. On the basis of CDER statistical standard, the incidences for these tumors were not significant as the P-values (0.014 and 0.036) exceeded the required P-value of 0.005 for common tumors. The incidences for these tumors at the high dose are higher than the historical control incidences from the sponsor's laboratory (follicular cell adenoma, 0%-4%; follicular cell carcinoma, 0%-2%). The incidences of thyroid follicular cell adenoma and carcinoma in males were similar to the spontaneous incidences for these tumors in this strain of rat (follicular cell adenoma, 1.67% to 12%; follicular cell carcinoma, 0.87% to 3.85%; [redacted] Treatment group **females** had higher incidences of hepatocellular adenoma (control 1, 1/50 [2%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.003, Trend test), thyroid follicular cell adenoma (control 1, 3/50 [6%], control 2, 1/50 [2%]; low dose, 1/50 [2%]; mid dose, 4/50 [8%]; high dose, 6/50 [12%]; P=0.018, Trend test) and adenocarcinoma of the uterus (control 1, 0/50 [0%], control 2, 0/50 [0%]; low dose, 0/50 [0%]; mid dose, 0/50 [0%]; high dose, 2/50 [4%]; P=0.043, Trend test). On the basis of CDER statistical standard, the incidences of thyroid follicular cell adenoma and uterine adenocarcinoma were not significant as the P-values (0.018 and 0.043) exceeded the required P-value of 0.005 for common tumors. Historical control incidences for thyroid follicular cell adenoma and uterine adenocarcinoma in female rats from the sponsor's laboratory were 0% - 3% and 0% - 3.85%, respectively. The incidences of thyroid follicular cell adenoma and adenocarcinoma of the uterus at the high dose were higher than the spontaneous incidences reported in this strain of rat (thyroid follicular cell adenoma, 1.43% to 6.12%; uterine adenocarcinoma, 1.67%; [redacted]

In the 105-week oral carcinogenicity study in mice, 0, 2.5, 25, 125 and 500 mg/kg/day doses were used. Treatment with MK-0869 was associated with increased incidences of fibrosarcoma (Control 1 and 2, 0/50 [0%]; 2.5 mg/kg, 0/50 [0%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 1/50 [2%]; 500 mg/kg, 2/50 [4%]; P=0.018, Trend test) of the skin in the male mice. The incidence of fibrosarcoma at the high dose (4%) is higher than the historical control incidences from the sponsor's laboratory (0% - 1%, mean 0.09%) in this strain of mice and the spontaneous incidences reported by [redacted] (1.54% to 2.00%; mean 1.77%). Treatment group females had higher incidences of hepatocellular adenoma (control 1, 1/49 [2%]; control 2, 0/50 [0%]; 2.5 mg/kg, 2/50 [4%]; 25 mg/kg, 0/50 [0%]; 125 mg/kg, 4/50 [8%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test) and Harderian gland adenoma (Control 1, 2/49 [4%]; control 2, 1/50 [2%]; 2.5 mg/kg, 1/50 [2%]; 25 mg/kg, 2/50 [4%]; 125 mg/kg, 2/50 [4%]; 500 mg/kg, 4/50 [8%]; P=0.014, Trend test). On the basis of CDER statistical standard, the incidences of hepatocellular adenoma and Harderian gland adenoma in females were not significant, as the p values (0.014 for both) exceeded the required p value for common tumors (0.005). The incidences of hepatocellular adenoma at the two higher doses (8%) are higher than the historical control incidences from the sponsor's laboratory (1% - 4%, mean 2%), and similar to the range of spontaneous incidences in CD-1 mice, reported by [redacted]; (range, 0.85% to 7.84%). The incidences of Harderian gland adenoma is similar to the historical control incidences (4% - 6%, mean 5.27%) from the sponsor's laboratory and the spontaneous incidences reported (1.35% to 8.33%, [redacted] in this strain of mice.

Reproductive and developmental toxicology studies were conducted with both the pro-drug, L-758, 298 and the active drug, MK-0869 (L-754, 030) by the i.v. or oral routes. In the i.v. Segment I fertility and reproductive performance study with L-758, 298 in male rats, 2, 5 and 10 mg/kg/day

doses were used. It had no treatment-related effects on the fertility and reproductive performance of the male animals at i.v. doses up to 10 mg/kg/day.

In the oral Segment I fertility and reproductive performance study with MK-0869 in male rats, 25, 125 and 250 mg/kg/day doses were used. MK-0869 had no effects on the fertility and reproductive performance of the male rats at oral doses up to 250 mg/kg/day.

In a third Segment I fertility and reproductive performance study in male rats, MK-0869 ([redacted] particle size, formulation NB), at an oral dose of 1000 mg/kg b.i.d (2000 mg/kg/day), had no effects on the fertility and reproductive performance of the animals.

In the i.v. Segment I fertility and reproductive performance study with L-758, 298 (pro-drug of MK-0869) in female rats, 0, 1, 2 and 4 mg/kg/day doses were used. L-758, 298 had no treatment-related effects on the fertility and reproductive performance of the female rats at i.v. doses up to 4 mg/kg/day.

In a second oral Segment I fertility and reproductive performance study with MK-0869 (127 nm particle size) in female rats, a 1000 mg/kg b.i.d (2000 mg/kg/day) dose was used. No treatment-related effects on the fertility and reproductive performance of the female rats were observed at the oral dose of 1000 mg/kg b.i.d.

In the i.v. Segment II teratogenicity study with L-758, 298 in rats, pregnant animals received 0, 1, 2 and 4 mg/kg/day doses of the drug from Gestation Day 6 through Gestation Day 20. Intravenous L-758, 298 had no teratogenic effects in rats at doses up to 4 mg/kg/day.

In the i.v. Segment II teratogenicity study with L-758, 298 in rabbits, pregnant animals received 0, 1, 2 and 4 mg/kg/day doses. There were no treatment-related teratogenic effects produced by i.v. L-758, 298 in rabbits at doses up to 4 mg/kg/day.

In a modified i.v. Segment II/III reproductive toxicity study with L-758, 298 in female rats, doses of 0, 1, 2 and 4 mg/kg/day were administered to pregnant animals from Gestation Day 6 through Lactation Day 20. There were no treatment-related effects on pregnancies of F_0 females, and no effects on the peri- and post- natal development and reproductive performance of the F_1 generation were observed.

In an oral Segment II/III reproductive toxicity study with MK-0869 ([redacted] particle size) in rats, pregnant females received 0 and 1000 mg/kg b.i.d. (2000 mg/kg/day) dose of the drug. MK-0869, at an oral dose of 2000 mg/kg/day, had no teratogenic effects. It had no effects on the peri- and post- natal development or the reproductive performance of the F_1 animals. Treatment of the F_0 females with MK-0869 had no effects on body weights or external malformations of the F_2 animals.

L-758, 289 (a pro-drug of MK-0869) caused minimal local irritation in rats when administered at i.v. doses up to 5 mg/kg/day for 7 days. Topical application of L-754, 030 was not irritating to the skin of rabbits, and it was mildly irritating to the eyes of rabbits. In an *in vitro* bovine corneal opacity and permeability assay, L-745, 030 was a severe irritant to the cornea. The nonpolar netabolite. L-755, 446 was also a severe corneal irritant in this assay. However, the significance of this finding is not clear, as in the toxicology studies with L-754, 030, it had no effects on corneal opacity, and in the eye irritation study, it was a mild irritant to the rabbits eye. L-758, 298 caused hemolysis of washed red blood cells from rats, dogs and humans. However, it did not cause any hemolysis in human whole blood. The effects of oral MK-0869 on the plasma T_3, T_4 and TSH levels, and thyroxine clearance were examined in rats. It caused an increase in the TSH levels in both males and females; thyroxine clearance was also increased in animals receiving MK-0869. The increases in the TSH levels may be related to the increased liver enzyme (glucuronyl transferase) ncreased metabolism of thyroid

hormones. The pro-drug, L-758, 298 caused moderate induction P_{450} enzyme activity (7-ethoxy-4-trifluromethylcoumarin-O-deethylase and fatty acyl-CoA oxidase activity) in the mouse liver, when administered orally. The liver enzyme inducing capability of the drug may also be related to the hepatocellular hypertrophy and thyroid follicular cell hyperplasia, observed in subchronic and chronic toxicology studies in rats.

Conclusions:

Substance P, a tachykinin, is present in the sensory nerve terminals, and is most likely involved in nociception. Substance P may have important role in emesis, as substance P-containing vagal afferent fibers innervate the brainstem nucleus tactus solitarius, a region in the CNS involved in emesis. Aprepitant (MK-0869 or L-754, 030) is a selective and highly potent NK_1 (substance P) receptor antagonist, as shown by its affinities for native and cloned receptors from diffreent species. In *in vivo* studies, it has been found to be very effective in preventing both the initial and delayed phases of cisplatin- induced emesis in ferrets. It had additive effects on the anti-emetic effects of ondansetron or dexamethasone in this animal model. The preclinical pharmacology studies indicate that aprepitant might be effective in preventing chemotehrapy-induced emesis in cancer patients. The bioavailability of MK-0869 in humans (about 60%) was higher than that in aniamls. Saturation of absorption was observed in rats and mice when administered by the oral route, and this may be related to the lower exposure in these animals.

The sponsor has conducted acute, subacute/subchronic and chronic toxicity studies with MK-0869 (or its pro-drug, L-758, 298) in different animal species. In oral acute toxicity studies in rats and mice, the minimal lethal dose was 500 mg/kg. In the subscute/subchronic and chronic toxicity studies in rats, the target organs of toxicity were the pituitary, liver and the thyroid gland. Hepatocellular hypertrophy and thyroid follicular cell hyperplasia were observed in both males and females in the 5-week, 14-week, 27-week and 52-week oral toxicity studies in rats. These changes may be related to the induction of liver enzymes (glucuronyl transferase) by the drug and are of little toxicological significance. Changes in the pituitary gland may be related to the exhaustion of TSH producing cells. Hepatocellular hypertrophy was also observed in the 5-week and 14-week oral toxicity studies in mice. In dogs, tubular degeneration of the testes and prostatic atrophy were observed at high doses (<125 mg/kg/day in the 5-week toxicity study and >10 mg/kg/day in the 39-week toxicity study. In 5-week i.v. toxicity study in the monkey, no toxic effects were observed at doses up to 10 mg/kg/day. Thus, from the results of the toxicology studies with MK-0869, it appears to have low toxicity profiles in the rodent and non-rodent animals. MK-0869 (or L-758, 298) was not genotoxic in a battery of genotoxicity assays. It had no effects on the reproductive performance or fertility of male and females rats, and it was not teratogenic effects in rats and rabbits when administered during pregnancy. No treatment-related effects on peri- and post- natal development of the F1 animals were observed when the drug was administered to F_0 females. Thus, the preclinical toxicology studies conducted with MK-0869demonstrate that the drug is generally well-tolerated in mice, rats and dogs.

General toxicology issues:

In the subscute/subchronic and chronic toxicity studies in rats, the target organs of toxicity were the pituitary, liver and the thyroid gland. Hepatocellular hypertrophy and thyroid follicular cell hyperplasia were observed in both males and females in the 5-week, 14-week, 27-week and 52-week oral toxicity studies in rats. Hepatocellular hypertrophy was also observed in the 5-week and 14-week

oral toxicity studies in mice. Hepatocellular hypertrophy may be related to the induction of cytochrome P-450 enzymes by the drug. Thyroid follicular cell hyperplasia in rats may be related to increased metabolism of thyroid hormones and subsequent increase in the TSH levels. The changes in the pituitary gland may be due to exhaustion of TSH producing pituitary cells. In dogs, tubular degeneration of the testes and prostatic atrophy were observed at high doses (<125 mg/kg/day in the 5-week toxicity study and >10 mg/kg/day in the 39-week toxicity study). Testicular and prostatic changes were not observed in any other species, and MK-0869 had no treatment-related effects on the fertility and reproductive performance of male rats.

Recommendations: MK-0869 was adequately studied in preclinical pharmacology and toxicology studies The preclinical studies conducted with MK-0869 support the safety of Emend Capsules at the proposed doses.

Labeling with basis for finding:
See the labeling part of the review.

A. Reviewer signature: /S/

B. Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

C. cc: list:

NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Chakder
HFD-180/Dr. Choudary

R/D Init.: J. Choudary 3/5/03

X. APPENDIX/ATTACHMENTS:

Appendix 1: Nonneoplastic and Neoplastic Findings in Male and Female Rats Receiving MK-0869 for 106 Weeks (Study # 97-134-0; 0, 0.10, 0.50 and 2.0 mg/kg/day) - Page 298

Appendix 1A: Minutes of the Executive Carcinogenicity Assessment Committee Meetings For Dose Selection and Protocols for the Carcinogenicity Studies in Rats and Mice - Page 328

Appendix 2: Nonneoplastic and Neoplastic Findings in Male and Female Rats Receiving MK-0869 for 106 Weeks (Study # 98-047-0; 0, 10, 50 and 250 mg/kg/day) - Page 331

Appendix 3: Nonneoplastic and Neoplastic Findings in Male and Female Mice Receiving MK-0869 for 105 Weeks (Study # 98-016-0, -2) - Page 366

Appendix 1: Nonneoplastic and Neoplastic Findings in Male and Female Rats Receiving MK-0869 for 106 Weeks (Study # 97-134-0)

TABLE E-5. NK-6089 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-D
[redacted] OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
NUMBER NECROPSIED	50	50	50	50	50	50	50	50	50	50
WITH MALIGNANT NEOPLASMS	18	6	18	11	21	15	19	15	19	13
WITH BENIGN NEOPLASMS	40	37	45	38	40	36	46	37	42	33
WITH NEOPLASMS	48	39	46	42	49	41	48	44	47	38
OF MALIGNANT NEOPLASMS	19	6	20	12	25	15	21	16	22	14
OF BENIGN NEOPLASMS	75	49	67	58	64	57	65	49	54	48
OF NEOPLASMS	94	55	87	70	89	72	86	65	76	62
MOUTH										
NO. ANIMALS EXAMINED MICRO.	-	-	-	-	-	2	1	-	-	1
NUMBER NOT REMARKABLE	-	-	-	-	-	-	1	-	-	-
MUCOSA, PAPILLOMA	-	-	-	-	-	1	-	-	-	-
MUCOSA, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	1	-	-	-	1
SALIVARY GLAND										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	49	50	50	49	50	49	50	50	50	48
NEUTROPHILIC CELLULAR INFILTRATION	-	-	-	-	-	1	-	-	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	-	-	1	-	-	-	-	-	-
DUCT, HYPERPLASIA	-	-	-	-	-	-	-	-	-	1
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
TONGUE										
NO. ANIMALS EXAMINED MICRO.	-	-	-	-	-	-	-	1	-	-
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	1	-	-
ESOPHAGUS										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	50	49	45	50	49	48	50	48	49	49
ABSCESS	-	-	1	-	-	-	-	-	-	-
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	2	-	-	-	-	-	-	-
SEROSA, FOCAL FIBROSIS	-	-	-	-	-	-	-	-	1	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. NK-4869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTONORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
ESOPHAGUS										
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	1	-	1	2	-	2	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
STOMACH										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	33	24	26	25	12	23	33	25	31	23
SEROSA, METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
NEUTROPHILIC CELLULAR INFILTRATION	1	-	1	1	-	-	-	-	-	-
GLANDULAR MUCOSA, DEGENERATION	-	-	-	-	-	1	-	-	-	1
NONGLANDULAR MUCOSA, EOSINA	-	-	-	-	1	-	1	-	-	-
FOCAL EROSION	1	1	5	1	4	4	3	2	-	1
GASTRITIS	-	-	-	2	1	2	1	-	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	1	-	1	1	-	-	-	-
NONGLANDULAR MUCOSA, DIFFUSE HYPERPLASIA	11	24	12	19	10	18	13	22	14	25
NONGLANDULAR MUCOSA, FOCAL HYPERPLASIA	4	4	3	3	1	3	2	1	4	2
LEIOMYOMA	-	-	-	-	-	1	-	-	-	-
NONGLANDULAR MUCOSA, LIPOMA	-	1	-	-	-	-	-	-	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	1	-	-	1
MINERALIZATION	-	-	1	-	-	-	1	-	-	-
NONGLANDULAR MUCOSA, PAPILLOMA	-	-	-	1	-	-	-	1	-	1
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	-	-	1	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
GLANDULAR MUCOSA, ULCER	1	-	1	1	-	1	-	-	-	1
NONGLANDULAR MUCOSA, FOCAL VACUOLATION	2	-	-	-	1	-	-	1	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. NE-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 697-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SMALL INTESTINE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	50	47	46	47	48	48	48	48	48	47
SEROSA, METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
ENTERITIS	-	2	-	2	1	-	-	2	-	1
VILLUS, HISTIOCYTOSIS	-	-	-	-	-	-	-	-	1	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	1	-	1	1	-	-	-	-
EPITHELIAL HYPERPLASIA	-	-	1	-	-	-	-	-	-	-
SEROSA, FOCAL INFLAMMATION	-	-	-	-	-	1	-	-	-	-
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	1	-	1	1
OSSEOUS METAPLASIA	-	1	-	-	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	1	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
VASCULITIS	-	-	-	1	-	-	-	-	-	-
LARGE INTESTINE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	49	48	48	49	49	48	49	49	50	48
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	-	1	-	-	-	-
INFLAMMATION	-	2	1	-	1	1	1	1	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	-	-	1
VASCULITIS	-	-	-	1	-	-	-	-	-	-
LIVER										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	7	4	8	4	4	6	7	3	5	2
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
HEPATOCELLULAR ADENOMA	1	1	-	1	1	-	-	2	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
LIVER										
HEPATOCELLULAR CARCINOMA	1	-	-	-	-	-	-	1	-	1
ISLET, METASTATIC CARCINOMA (PANCREAS)	-	-	-	1	-	-	-	-	-	-
PARAFOLLICULAR CELL, METASTATIC CARCINOMA (THYROID)	-	-	-	-	-	-	-	1	-	-
BASOPHILIC CELLULAR ALTERATION	18	10	9	10	15	12	17	14	18	13
CLEAR CELLULAR ALTERATION	-	3	-	3	-	-	-	2	-	1
EOSINOPHILIC CELLULAR ALTERATION	13	23	13	16	13	16	12	17	15	30
CELLULAR INFILTRATION	2	6	3	5	3	5	5	5	1	4
CHRONIC CHOLANGITIS	-	2	-	-	-	1	-	-	-	-
BILE DUCT, CYST	5	1	4	-	4	1	5	1	5	-
CYSTIC DEGENERATION	1	14	1	10	-	7	1	9	1	10
HEPATOCYTE, CENTRILOBULAR DEGENERATION	1	-	-	1	1	1	1	-	-	-
BILE DUCT, DISTENTION	-	2	-	-	-	-	-	-	-	-
EXTRAMEDULLARY HEMATOPOIESIS	1	-	1	-	-	-	2	-	2	2
FOCAL FIBROSIS	3	1	1	-	-	1	-	-	-	1
PERIPORTAL FIBROSIS	1	9	1	5	1	7	5	9	5	7
SUBCAPSULAR FIBROSIS	-	3	1	3	-	2	1	1	2	1
SUBCAPSULAR FOCAL HEMORRHAGE	6	5	5	3	6	3	5	3	5	1
HEMOSIDEROSIS	-	-	-	1	-	-	-	-	1	-
HISTIOCYTIC SARCOMA	-	-	-	1	-	-	-	-	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	1	2	-	2	2	1	2	-	
BILE DUCT, HYPERPLASIA	20	27	26	25	22	26	21	31	26	32
KUPFFER CELL, HYPERPLASIA	-	-	1	-	2	-	-	1	-	-
HEPATOCYTE, PERIPORTAL HYPERTROPHY	1	-	1	1	5	1	2	-	1	-
ACUTE FOCAL INFLAMMATION	-	-	-	-	-	2	1	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE E-5. NE-0069 (L-764,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 097-124-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
LIVER										
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	2	-	1	1	1	1	1
MULTINUCLEATED CELLS	1	-	1	-	-	-	2	-	3	-
NECROSIS	-	1	1	4	2	2	3	3	-	3
CENTRILOBULAR NECROSIS	1	-	2	-	-	-	1	-	-	-
VESSEL, NECROSIS	-	1	-	-	-	-	-	-	-	-
SINGLE CELL NECROSIS	-	-	-	-	2	-	-	1	1	-
PERICHOLANGITIS	5	7	8	4	3	4	8	3	6	3
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
KUPFFER CELL, PIGMENTATION	-	-	-	-	1	-	2	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
TELANGIECTASIS	14	20	12	16	11	24	19	22	21	23
VESSEL, CHRONIC THROMBOSIS	-	-	-	1	-	-	-	-	1	-
HEPATOCYTE, VACUOLATION	5	4	9	3	7	4	6	7	8	8
PANCREAS										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	39	26	35	24	42	28	38	33	39	31
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	2	-	-	-	-	-	-	-
ACINAR ADENOMA	-	-	1	1	-	-	-	-	-	-
ISLET, ADENOMA	3	4	1	6	1	6	1	4		5
ACINAR ATROPHY	7	10	7	9	3	6	3	3	8	7
ISLET, CARCINOMA	-	1	-	2	-	1	-	2	-	1
ISLET, FIBROSIS	-	-	-	1	-	1	-	2	-	3
PERIDUCTULAR CONNECTIVE TISSUE FIBROSIS	-	1	-	1	2	-	-	-	1	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #97-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
PANCREAS										
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	1	-	1	2	-	-	-	-
ACINUS, FOCAL HYPERPLASIA	-	-	-	-	-	-	-	-	1	-
DUCT, FOCAL HYPERPLASIA	-	-	-	-	1	1	-	-	-	-
ISLET, HYPERPLASIA	1	12	4	10	2	10	4	8	2	14
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	1	1	-	1
ISLET, HEPATOCELLULAR METAPLASIA	-	-	-	-	-	-	1	-	-	-
FOCAL PANCREATITIS	-	1	-	-	-	-	1	-	-	2
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	1	-	-	-
ACINAR VACUOLATION	-	-	-	-	-	-	-	-	1	-
VESSEL, VASCULITIS	-	1	-	2	-	-	-	1	-	-
PERITONEUM										
NO. ANIMALS EXAMINED MICRO	1	3	1	5	1	2	1	3	1	1
NUMBER NOT REMARKABLE	1	1	-	-	-	-	-	1	-	1
FIBROSIS	-	-	-	1	-	-	-	-	1	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-			-	1	-	-	-	-
ADIPOSE TISSUE, NECROSIS	-	1	-	3	1	1	-	1	-	-
MALIGNANT SCHWANNOMA	-	-		1	-	-	-	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	1	-	-	-
FOCAL STEATITIS	-	1	-	-	-	-	-	-	-	-
VASCULITIS	-	-	-	1	-	-	-	2	-	-
ADRENAL										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	51	50	50
NUMBER NOT REMARKABLE	1	11	1	10	4	17	3	15	3	13
CORTEX, ADENOMA	2	1	-	2	2	-	2	2	-	-
CYST	-	-	-	-	-	-	1	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-756,930): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-114-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
ADRENAL										
CYSTIC DEGENERATION	9	3	11	-	10	-	9	-	6	1
EXTRAMEDULLARY HEMATOPOIESIS	-	-	2	-	1	-	1	-	-	-
HEMORRHAGE	-	-	-	-	1	2	-	-	1	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	-	-	-	-	-	-
CORTEX, FOCAL HYPERPLASIA	17	22	23	20	17	16	22	19	25	18
MEDULLA, HYPERPLASIA	4	9	7	8	3	8	5	7	6	9
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	1	-	1	-	1	1	1
NECROSIS	-	-	-	1	-	-	-	1	-	1
BENIGN PHEOCHROMOCYTOMA	-	2	-	2	-	3	-	2	-	2
MALIGNANT PHEOCHROMOCYTOMA	1	-	1	2	-	-	-	-	-	-
TELANGIECTASIS	41	5	35	4	33	2	36	5	37	1
CORTEX, FOCAL VACUOLATION	24	18	13	19	23	15	22	15	20	15
PARATHYROID										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	46	40	40	45	45	42	40	42	43	39
TISSUE NOT PRESENT IN SECTION(S)	2	7	7	3	4	6	8	5	6	6
ADENOMA	1	1	1	2	-	1	1	-	1	2
FOCAL HYPERPLASIA	-	2	2	-	1	1	1	3	-	1
VACUOLATION	1	-	-	-	-	-	-	-	-	2
PITUITARY										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	48	50	50
NUMBER NOT REMARKABLE	3	13	4	10	2	8	3	8	7	9
ADENOMA	44	27	41	31	44	31	44	30	39	39
ANOMALY	-	-	-	-	1	-	-	-	-	-
CELLULAR INFILTRATION	-	-	-	-	1	-	-	1	-	-
FOCAL CYST	2	10	2	2	2	11	2	9	3	8
GIANT CELL FORMATION	-	1	-	-	-	-	-	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #97-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PITUITARY										
PARS DISTALIS, HEMORRHAGE	-	-	-	1	-	-	-	-	-	-
PARS DISTALIS, HYPERPLASIA	1	4	4	10	4	5	3	6	3	7
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	1	-	-
TELANGIECTASIS	-	-	1	-	-	-	-	-	-	-
THYROID										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	28	31	35	34	34	34	30	28	37	30
PARAFOLLICULAR CELL, ADENOMA	5	6	5	4	2	5	3	3	2	3
FOLLICULAR CELL, ADENOMA	-	-	-	-	-	-	1	-	1	-
PARAFOLLICULAR CELL, CARCINOMA	-	-	-	-	2	2	-	2	-	-
FOLLICULAR CELL, CARCINOMA	-	-	-	1	-	-	-	-	-	-
CYST	7	6	6	3	4	4	8	5	5	7
EMBRYONAL REST	-	-	-	-	-	-	-	-	-	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	-	-	-
PARAFOLLICULAR CELL, HYPERPLASIA	10	10	5	9	3	4	13	12	7	12
FOLLICULAR CELL, HYPERPLASIA	1	-	-	-	-	1	-	-	-	1
VASCULITIS	-	-	-	-	-	-	-	1	-	-
KIDNEY										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	51	50	50	52	50	50
NUMBER NOT REMARKABLE	6	6	7	3	3	8	7	4	6	3
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
TUBULE, BASOPHILIA	7	20	9	26	6	22	12	23	9	18
CELLULAR INFILTRATION	5	2	6	4	6	1	5	1	9	3
TUBULAR CYST	4	4	2	2	4	4	4	1	1	1
TUBULE, DEGENERATION	-	-	2	-	1	1	-	1	-	-
TUBULE, DILATATION	4	4	1	3	6	3	3	3	2	1
PELVIS, DILATATION	4	1	1	1	2	1	1	2	3	

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. NK-0069 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
KIDNEY										
PAPILLA, EDEMA	-	1	-	1	-	-	-	1	-	-
CORTEX, FOCAL FIBROSIS	4	12	8	14	7	16	5	21	5	14
FOCAL HEMORRHAGE	-	-	-	1	-	-	-	1	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	-	-	2	-	-	-	-	-
TUBULAR HYALINE DROPLETS	1	1	1	2	1	1	-	2	-	3
PELVIS, EPITHELIAL HYPERPLASIA	33	13	26	12	37	21	36	13	32	7
TUBULE, HYPERTROPHY	6	3	2	6	4	1	5	5	2	-
CORTEX, FOCAL INFLAMMATION	-	1	-	1	-	1	-	1	-	1
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
LIPOSARCOMA	1	-	-	-	-	-	-	-	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	2	-	1	1	1	1	1
PAPILLA, OSSEOUS METAPLASIA	-	-	-	-	-	1	-	-	-	-
PELVIS, MINERALIZATION	31	6	25	4	12	12	11	7	28	5
CHRONIC NEPHROPATHY		8	1	9	-	2	1	5		6
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
PYELITIS	2	1	6	6	2	3	5	3	4	3
SUPPURATIVE PYELONEPHRITIS	-	3	1	1	1	2	1	1	1	2
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	-	1	-	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
TRANSITIONAL CELL CARCINOMA	-	-	1	-	-	1	-	1	-	-
TUBULE, EPITHELIAL FOCAL VACUOLATION	1	-	1	-	1	-	-	-	-	-
VASCULITIS	-	1	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.15 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-756,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
URINARY BLADDER										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	47	47	45	48	48	47	44	44	45	44
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
CELLULAR INFILTRATION	1	-	1	-	-	-	1	2	1	1
CYSTITIS	-	1	2	2	3	2	4	1	2	2
EDEMA	1	-	-	-	-	-	1	1	-	-
FIBROSIS	-	-	-	-	-	-	-	-	1	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	1	1	-	-	-	-
EPITHELIAL HYPERPLASIA	1	2	-	-	2	2	1	1	-	3
MUSCULARIS, FOCAL INFLAMMATION	-	-	-	-	-	-	-	1	-	1
METASTATIC SCHWANNOMA (UTERUS)	-	-	-	-	-	-	-	-	1	-
UROLITHIASIS	-	-	-	-	-	-	-	1	-	1
OVARY										
NO. ANIMALS EXAMINED MICRO.	50	-	50	-	50	-	50	-	50	-
NUMBER NOT REMARKABLE	18	-	21	-	24	-	23	-	18	-
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
ATROPHY	9	-	11	-	11	-	11	-	14	-
CYST	12	-	5	-	7	-	7	-	7	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	1	-	-	-	-	-
STROMAL HYPERPLASIA	23	-	24	-	22	-	20	-	29	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	-	-	-	-	1	-	-	-
BENIGN STROMAL TUMOR	-	-	-	-	1	-	1	-	-	-
MALIGNANT STROMAL TUMOR	2	-	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-8. ME-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 097-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
UTERUS										
NO. ANIMALS EXAMINED MICRO.	50	-	50	-	50	-	50	-	50	-
NUMBER NOT REMARKABLE	32	-	31	-	32	-	30	-	35	-
ADENOCARCINOMA	-	-	2	-	1	-	-	-	-	-
ENDOMETRIUM, ADENOMA	-	-	1	-	-	-	-	-	-	-
CYSTIC DILATATION	9	-	10	-	9	-	9	-	9	-
FIBROSIS	-	-	-	-	-	-	-	-	1	-
CERVIX, REGION GRANULAR CELL TUMOR	1	-	-	-	1	-	2	-	1	-
OVIDUCT, HEMANGIOSARCOMA	-	-	1	-	-	-	-	-	-	-
CYSTIC HYPERPLASIA	1	-	1	-	2	-	5	-	1	-
CERVIX, EPITHELIAL HYPERPLASIA	1	-	-	-	-	-	1	-	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	1	-	-	-
STROMAL POLYP	5	-	4	-	5	-	2	-	2	-
MALIGNANT SCHWANNOMA	-	-	1	-	2	-	1	-	1	-
CERVIX, REGION STROMAL TUMOR	-	-	-	-	1	-	-	-	-	-
VAGINA										
NO. ANIMALS EXAMINED MICRO.	3	-	1	-	3	-	3	-	3	-
NUMBER NOT REMARKABLE	-	-	-	-	1	-	-	-	-	-
CLITORAL GLAND, ECTASIA	2	-	-	-	1	-	1	-	2	-
EPIDERMOID CYST	-	-	1	-	-	-	-	-	-	-
MUCOSA, HYPERPLASIA	-	-	-	-	1	-	-	-	-	-
CLITORAL GLAND, INFLAMMATION	-	-	-	-	-	-	1	-	-	-
LEIOMYOSARCOMA	-	-	-	-	-	-	1	-	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	1	-
CLITORAL GLAND, METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
TESTIS										
NO. ANIMALS EXAMINED MICRO.	-	50	-	50	-	50	-	50	-	50
NUMBER NOT REMARKABLE	-	24	-	28	-	33	-	24	-	27
EPIDIDYMIS, CELLULAR INFILTRATION	-	2	-	2	-	4	-	2	-	2
SEMINIFEROUS TUBULE, DEGENERATION	-	17	-	10	-	11	-	12	-	9
EPIDIDYMIS, EDEMA	-	1	-	-	-	-	-	1	-	-
EPIDIDYMIS, EPIDIDYMITIS	-	-	-	1	-	-	-	1	-	-
EPIDIDYMIS, METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	1	-	-	-	-
INTERSTITIAL CELL, FOCAL HYPERPLASIA	-	-	-	2	-	1	-	1	-	2
HYPOPLASIA	-	1	-	-	-	-	-	-	-	-
BENIGN INTERSTITIAL CELL TUMOR	-	2	-	-	-	2	-	2	-	1
EPIDIDYMIS, METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	1	-	-
MALIGNANT MESOTHELIOMA	-	-	-	-	-	-	-	-	-	1
EPIDIDYMIS, SPERMATIC GRANULOMA	-	5	-	2	-	-	-	-	-	-
EPIDIDYMAL EPITHELIUM, VACUOLATION	-	13	-	16	-	8	-	15	-	15
VASCULITIS	-	-	-	1	-	-	-	2	-	-
PROSTATE										
NO. ANIMALS EXAMINED MICRO.	-	50	-	50	-	50	-	50	-	50
NUMBER NOT REMARKABLE	-	36	-	42	-	17	-	39	-	41
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
SUPPURATIVE PROSTATITIS	-	14	-	8	-	13	-	11	-	8

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. IT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SEMINAL VESICLE										
NO. ANIMALS EXAMINED MICRO.	-	6	-	1	-	1	-	2	-	3
NUMBER NOT REMARKABLE	-	5	-	-	-	-	-	1	-	3
ECTASIA	-	-	-	1	-	-	-	-	-	-
EDEMA	-	1	-	-	-	-	-	-	-	-
ACUTE INFLAMMATION	-	-	-	-	-	1	-	1	-	-
PENIS										
NO. ANIMALS EXAMINED MICRO.	-	-	-	1	-	3	-	4	-	4
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	2	-	-
PREPUTIAL GLAND, ABSCESS	-	-	-	1	-	2	-	1	-	2
PREPUTIAL GLAND, ECTASIA	-	-	-	1	-	1	-	1	-	2
PREPUTIAL GLAND, INFLAMMATION	-	-	-	-	-	-	-	-	-	1
SKIN										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	48	41	49	41	45	40	48	38	48	41
SEBACEOUS GLAND, ADENOMA	-	-	-	1	-	-	-	-	-	-
MALIGNANT BASAL CELL TUMOR	-	-	-	-	-	-	-	-	1	-
EPIDERMOID CYST	-	4	-	1	-	-	1	5		2
FIBROMA	-	1	-	1	-	1	-	-	-	-
FIBROSARCOMA	-	1	-	1	-	-	1	1	-	-
HEMANGIOMA	-	-	-	2	-	-	-	-	-	-
HEMANGIOPERICYTOMA	-	-	-	-	-	1	-	-	-	-
HISTIOCYTIC SARCOMA	-	-	-	-	-	1	1	-	-	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	1	1	1	1	2	1	3	-	-
EPIDERMIS, FOCAL HYPERPLASIA	-	-	-	-		1	-	-	-	
ACUTE FOCAL INFLAMMATION	-	-	-	-	1	-	1	-	1	1
KERATOACANTHOMA	-	1	-	-	1	2	-	2	-	1
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT #97-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SKIN										
LIPOMA	-	2	-	1	-	-	-	1	-	-
LIPOSARCOMA	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	-	-	1
PAPILLOMA	-	-	-	1	-	1	-	-	-	1
FOCAL SCAR	-	-	-	-	-	-	-	-	-	1
MALIGNANT SCHWANNOMA	-	-	-	-	-	1	1	1	-	-
SQUAMOUS CELL CARCINOMA	-	1	-	-	-	-	-	-	-	-
MAMMARY GLAND										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	16	29	21	33	18	32	28	33	25	40
TISSUE NOT PRESENT IN SECTION(S)	4	15	-	14	3	16	1	10	1	9
ABSCESS	-	1	-	-	-	-	-	-	-	-
ADENOCARCINOMA	10	-	10	-	16	-	11	2	15	-
ADENOMA	4	-	1	-	1	-	1	-	1	-
FIBROADENOMA	9	-	11	-	4	-	7	1	7	-
GALACTOCELE	13	5	14	3	12	3	8	4	6	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	-	-	-	-	-	-
HYPERPLASIA	1				1					1
NOSE										
NO. ANIMALS EXAMINED MICRO.	-	-	-	-	-	-	-	-	-	1
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-	-	-
OLFACTORY EPITHELIUM, MALIGNANT NEUROBLASTOMA	-	-	-	-	-	-	-	-	-	1
LUNG										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	36	28	30	23	28	22	31	23	29	17
ABSCESS	-	-	1	-	-	-	-	-	-	-
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	2	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.15 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
LUNG										
METASTATIC ADENOCARCINOMA (MAMMARY GLAND)	-	-	-	-	1	-	-	-	2	-
ADENOMA	-	-	-	-	-	-	-	-	-	1
PARAFOLLICULAR CELL, METASTATIC CARCINOMA (THYROID)	-	-	-	-	-	1	-	-	-	-
PERIVASCULAR CELLULAR INFILTRATION	-	-	-	-	-	-	-	3	-	1
CONGESTION	-	2	-	1	-	1	-	1	-	1
EDEMA	-	-	-	-	-	-	-	1	-	-
FIBROSIS	-	-	-	-	-	-	-	1	-	-
FOREIGN BODY GRANULOMA	-	1	1	1	-	1	1	-	-	3
HEMORRHAGE	-	1	1	2	-	-	3	1	1	2
FOCAL HISTIOCYTOSIS	11	17	12	24	18	24	15	19	16	25
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	1	2	1	1	2	1	2	-	-
ALVEOLAR EPITHELIUM, FOCAL HYPERPLASIA	-	1	-	1	-	-	-	-	-	2
BRONCHIOLAR LYMPHOID TISSUE HYPERPLASIA	-	-	-	-	-	1	-	-	-	-
INFLAMMATION	-	-	-	-	1	-	-	1	1	1
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	2	-	-	1	1	1	1
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
FOCAL PLEURITIS	-	-	1	-	1	-	-	-	1	-
ACUTE PNEUMONIA	-	-	-	-	-	-	-	1	1	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	-	-	-	-	1	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TI #97-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
HEART										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	27	11	32	10	29	8	35	32	35	11
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
METASTATIC ADENOCARCINOMA (MAMMARY GLAND)	1	-	-	-	1	-	-	-	-	-
CELLULAR INFILTRATION	6	2	6	-	6	-	4	4	4	1
VALVULAR CYST	-	-	-	1	-	-	-	-	-	-
ACUTE ENDOCARDITIS	1	-	-	-	-	-	-	-	-	-
EPICARDITIS	-	-	1	-	1	-	-	-	-	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	2	1	-	-	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	1	-	-	-	1	-	1
MINERALIZATION	-	1	-	-	-	-	-	-	-	-
AORTA, MINERALIZATION	-	-	-	1	-	-	-	-	-	-
CHRONIC MYOCARDITIS	14	38	10	37	12	41	12	32	11	38
PERICARDIUM, PERICARDITIS	-	-	-	-	1	-	-	-	-	-
METASTATIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	1	-	-	-	-	-	-	-	-
MALIGNANT SCHWANNOMA	-	-	-	1	-	-	-	1	-	-
SPLEEN										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	4	28	5	29	3	23	8	21	6	26
LYMPHOID ATROPHY	-	-	-	-	1	-	-	-	-	2
CAPSULE, CYST	-	1	1	-	-	-	-	2	-	-
EXTRAMEDULLARY HEMATOPOIESIS	5	8	9	3	9	10	9	6	7	4
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-
HEMOSIDEROSIS	40	13	36	10	41	16	32	10	38	15
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	1	-	-
LYMPHOID HYPERPLASIA	2	-	2	-	2	-	3	2	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
SPLEEN										
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	2	-	1	1	3	1	1
FOCAL NECROSIS	-	-	-	1	-	1	-	1	-	-
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	1	-	-	-	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
LYMPH NODE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	45	37	39	40	43	38	44	41	47	37
METASTATIC ADENOCARCINOMA (UTERUS)	-	-	1	-	-	-	-	-	-	-
METASTATIC ADENOCARCINOMA (MAMMARY GLAND)	-	-	1	-	-	-	-	-	-	-
NEUTROPHILIC CELLULAR INFILTRATION	-	-	1	-	-	-	-	-	-	-
CYST	-	7	-	3	1	5	1	1	-	4
SINUSOID, DILATATION	-	3	2	3	1	1	-	1	-	1
EDEMA	-	-	-	1	-	-	1	-	-	-
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-
HISTIOCYTOSIS	-	-	2	-	1	1	-	1	-	1
METASTATIC HISTIOCYTIC SARCOMA (SKIN)	-	-	-	-	-	-	-	-	-	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	1	1	1	3	1	-	2	-	-
REACTIVE HYPERPLASIA	2	2	3	2	2	2	3	3	2	2
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	1	-	1	1	1	1	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. NE-0868 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
LYMPH NODE										
LYMPHOCYTIC NECROSIS	-	1	-	-	-	-	-	-	-	1
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
METASTATIC SCHWANNOMA (UTERUS)	-	-	-	-	-	-	1	-	-	-
METASTATIC SCHWANNOMA (SKIN)	-	-	-	-	-	-	1	-	-	-
METASTATIC SQUAMOUS CELL CARCINOMA (MOUTH)	-	-	-	-	-	1	-	-	-	-
THYMUS										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	28	40	26	42	22	33	27	40	30	37
TISSUE NOT PRESENT IN SECTION(S)	1	5	-	4	2	4	1	3	2	3
ATROPHY	15	4	17	3	19	9	16	6	11	7
CYST	2	-	4	-	4	-	2	-	5	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	1	1	-	-	-	-
EPITHELIAL HYPERPLASIA	8	-	7	-	10	2	7	-	9	-
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	1	-	1	1
LYMPHOCYTIC NECROSIS	-	1	-	-	-	-	-	1	-	1
BENIGN THYMOMA	-	-	-	1	-	1	-	-	-	-
BONE MARROW										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	42	42	45	49	40	41	47	45	41	44
HISTIOCYTOSIS	-	-	-	-	-	-	-	-	-	1
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	1	-	1	-	-	1	-	-
ERYTHROID HYPERPLASIA	6	8	2	1	8	6	1	1	7	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
BONE MARROW										
MEGAKARYOCYTIC HYPERPLASIA	1	1	-	-	3	1	-	-	-	-
MYELOID HYPERPLASIA	2	1	2	-	1	1	2	1	4	2
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	1	1	1	1	1
METASTATIC PHEOCHROMOCYTOMA (ADRENAL)	1	-	-	-	-	-	-	-	-	-
BONE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	48	48	49	44	48	46	49	45	49	40
CYST	-	-	-	-	-	-	-	1	-	-
MAXILLARY SINUS, VASCULAR CYST	-	-	-	-	-	-	-	-	-	1
STERNUM, DEGENERATION	1	-	-	-	-	-	-	-	-	-
FRACTURE	-	-	-	-	-	-	-	-	1	-
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	1	-	-	-	-
OSTEOARTHRITIS	-	1	1	6	1	3	1	5	-	7
OSTEOSARCOMA	-	-	-	-	-	-	-	-	-	1
OSSEOUS PROLIFERATION	-	1	-	-	1	-	-	-	-	-
SKELETAL MUSCLE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	47	45	47	40	47	45	46	43	47	39
ATROPHY	-	1	-	5	-	2	-	2	-	7
FOCAL CELLULAR INFILTRATION	-	1	-	-	-	-	1	-	1	2
DEGENERATION	1	2	2	5	1	1	2	4	-	2
FIBROSIS	-	-	-	-	-	-	1	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.25 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SKELETAL MUSCLE										
METASTATIC										
HISTIOCYTIC SARCOMA										
(PRIMARY SITE UNDETERMINED)	1	1	1	1	2	2	-	1	-	-
METASTATIC LYMPHOMA										
(PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	-	-	-
BRAIN										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	18	41	25	40	18	34	21	38	20	38
PERIVASCULAR										
CELLULAR INFILTRATION	-	1	-	-	-	-	-	-	-	-
COMPRESSION	30	9	22	10	32	11	27	7	28	5
OPTIC TRACT, AXONAL										
UNILATERAL DEGENERATION	-	-	-	-	-	1	-	-	-	-
MENINGES, FIBROSIS	-	-	-	-	-	-	-	-	-	1
MALIGNANT GLIOMA	1	-	1	-	1	2	1	2	1	2
FOCAL GLIOSIS	-	-	-	-	1	-	-	-	-	1
MENINGES, BENIGN										
GRANULAR CELL TUMOR	-	-	1	1	-	1	-	-	-	-
FOCAL HEMORRHAGE	1	-	-	1	-	-	1	2	-	-
METASTATIC										
HISTIOCYTIC SARCOMA										
(PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	-	-	-
MENINGES, METASTATIC										
GRANULOCYTIC LEUKEMIA										
(PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA										
(PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	1	1	1
MENINGES, METASTATIC										
LYMPHOMA										
(PRIMARY SITE UNDETERMINED)	1	-	-	-	-	1	-	-	-	-
FOCAL MINERALIZATION	-	-	-	-	-	-	-	1	-	-
FOCAL NECROSIS	-	-	-	-	-	-	-	1	-	-
METASTATIC NEUROBLASTOMA										
(NOSE)	-	-	-	-	-	-	-	-	-	1
VESSEL, THROMBOSIS	-	-	1	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.35 MG/KG BID
GROUP 4 = 0.35 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. ME-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-114-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
SPINAL CORD										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	48	49	49	48	43	48	47	45	46	48
AXONAL DEGENERATION	1	1	1	2	6	2	3	1	1	1
HEMORRHAGE	1	-	-	1	1	-	-	1	-	-
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	1	1	1
EYE										
NO. ANIMALS EXAMINED MICRO.	50	49	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	12	9	18	15	10	14	17	13	13	14
AXONAL DEGENERATION	37	40	31	35	38	34	33	36	37	35
HISTIOCYTIC SARCOMA	-	-	1	-	-	-	-	-	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	1	1	1	-	2	2	-	1	-	-
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
EYE										
NO. ANIMALS EXAMINED MICRO.	50	50	50	50	50	50	50	50	50	50
NUMBER NOT REMARKABLE	17	20	27	19	21	17	23	21	21	11
HARDERIAN GLAND, CELLULAR INFILTRATION	7	6	6	2	9	5	9	6	11	8
RETINA, DEGENERATION	16	12	11	7	18	9	19	13	16	15
LENS, DEGENERATION	-	-	-	-	-	-	-	-	-	1
RETINA, HEMORRHAGE	-	-	-	-	-	-	-	-	-	1
RETROBULBAR TISSUE, HEMORRHAGE	-	-	1	-	-	-	-	-	-	-
METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	1	1	-	-	-	-
HARDERIAN GLAND, METASTATIC HISTIOCYTIC SARCOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	1	-	-
HARDERIAN GLAND, FOCAL HYPERPLASIA	17	21	12	27	8	25	12	17	11	21
INFLAMMATION	-	-	-	-	-	-	1	-	-	2

KEY: GROUP 1 - CONTROL 1 BID
GROUP 2 - CONTROL 2 BID
GROUP 3 - 0.15 MG/KG BID
GROUP 4 - 0.25 MG/KG BID
GROUP 5 - 1 MG/KG BID

CONTINUED
TABLE B-5. NK-0869 (L-754,030): 104-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
EYE										
HARDERIAN GLAND, INFLAMMATION	-	1	-	-	-	-	-	-	-	-
METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
HARDERIAN GLAND, METASTATIC GRANULOCYTIC LEUKEMIA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	-	-	1
METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	1	-	-	-	-	-	-	-	-	-
CHOROID, METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	-	-	1	-	-
HARDERIAN GLAND, METASTATIC LYMPHOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	1	-	-
AMELANOTIC MALIGNANT MELANOMA	-	-	-	-	-	1	-	-	-	-
SCLERA, FOCAL MINERALIZATION	-	-	-	-	-	-	-	-	-	1
CORNEA, FOCAL MINERALIZATION	-	-	1	-	-	-	-	1	-	2
LENS, SUBCAPSULAR EPITHELIAL PROLIFERATION	1	-	-	1	-	-	-	-	-	-
FOCAL UNILATERAL RETINOPATHY	-	-	-	1	1	-	-	-	1	1
METASTATIC SCHWANNOMA (PRIMARY SITE UNDETERMINED)		-	-		-	1	-	-		
HARDERIAN GLAND, METASTATIC SCHWANNOMA (PRIMARY SITE UNDETERMINED)	-	-	-	-	-	1	-	-	-	-
EAR										
NO. ANIMALS EXAMINED MICRO	-	-	-	-	-	1	1	-	-	2
NUMBER NOT REMARKABLE	-	-	-	-	-	-	-	-	-	-
ZYMBAL'S GLAND, CARCINOMA	-	-	-	-	-	1	-	-	-	1
PINNA, NEUROFIBROSARCOMA	-	-	-	-	-	-	1	-	-	-
SQUAMOUS CELL CARCINOMA	-	-	-	-	-	-	-	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED
TABLE B-5. MK-0869 (L-754,030): 106-WEEK ORAL CARCINOGENICITY STUDY IN RATS. TT 897-134-0
SUMMARY OF HISTOMORPHOLOGY

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
PRIMARY SITE UNDETERMINED										
HISTIOCYTIC SARCOMA	2	1	2	1	3	2	1	2	-	-
GRANULOCYTIC LEUKEMIA	-	-	-	-	-	-	-	-	-	1
LYMPHOMA	1	-	-	2	-	1	1	1	1	1
MALIGNANT SCHWANNOMA	-	-	-	-	-	1	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

One-Hundred-Six-Week Oral Carcinogenicity Study in Rats

Report Number: TT #97-134-0

Study Period (Years): 1997 to 1999

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
NUMBER NECROPSIED	50	50	50	50	50	50	50	50	50	50
MOUTH										
MUCOSA, PAPILLOMA	-	-	-	-	-	1	-	-	-	-
MUCOSA, SQUAMOUS CELL CARCINOMA	-	-	-	-	-	1	-	-	-	1
STOMACH										
LEIOMYOMA	-	-	-	-	-	1	-	-	-	-
NONGLANDULAR MUCOSA, LIPOMA	-	1	-	-	-	-	-	-	-	-
NONGLANDULAR MUCOSA, PAPILLOMA	-	-	-	1	-	-	-	1	-	1
UNDIFFERENTIATED SARCOMA	-	-	-	-	-	-	-	-	1	-
SMALL INTESTINE										
UNDIFFERENTIATED SARCOMA	-	-	-		-	-	1	-	-	-
LIVER										
HEPATOCELLULAR ADENOMA	1	1	-	1	1	-	-	2	-	-
HEPATOCELLULAR CARCINOMA	1	-	-	-	-	-	-	1	-	1
PANCREAS										
ACINAR ADENOMA	-	-	1	1	-	-	-	-	-	-
ISLET, ADENOMA	1	4	1	6	1	6	1	4	-	5
ISLET, CARCINOMA	-	1	-	2	-	1	-	2	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
PERITONEUM										
MALIGNANT SCHWANNOMA	-	-	-	1	-	-	-	-	-	-
ADRENAL										
CORTEX, ADENOMA	2	1	-	2	2	-	2	1	-	-
BENIGN PHEOCHROMOCYTOMA	-	2	-	2	-	3	-	2	-	2
MALIGNANT PHEOCHROMOCYTOMA	1	-	1	2	-	-	-	-	-	-
PARATHYROID										
ADENOMA	1	1	1	2	-	1	1	-	1	2
PITUITARY										
ADENOMA	44	27	41	31	44	31	44	30	39	29
THYROID										
PARAFOLLICULAR CELL, ADENOMA	5	6	5	4	2	5	3	3	2	3
FOLLICULAR CELL, ADENOMA	-	-	-	-	-	-	1	-	1	-
PARAFOLLICULAR CELL, CARCINOMA	-	-	-	-	2	2	-	2	-	-
FOLLICULAR CELL, CARCINOMA	-	-	-	1	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1 FEMALES	GROUP 1 MALES	GROUP 2 FEMALES	GROUP 2 MALES	GROUP 3 FEMALES	GROUP 3 MALES	GROUP 4 FEMALES	GROUP 4 MALES	GROUP 5 FEMALES	GROUP 5 MALES
KIDNEY										
LIPOSARCOMA	1	-	-	-	-	-	-	-	-	-
TRANSITIONAL CELL CARCINOMA	-	-	1	-	-	1	-	1	-	-
OVARY										
BENIGN STROMAL TUMOR	-	-	-	-	1	-	1	-	-	-
MALIGNANT STROMAL TUMOR	2	-	-	-	-	-	-	-	-	-
UTERUS										
ADENOCARCINOMA	-	-	2	-	1	-	-	-	-	-
ENDOMETRIUM, ADENOMA	-	-	1	-	-	-	-	-	-	-
CERVIX, BENIGN GRANULAR CELL TUMOR	1	-	-	-	1	-	2	-	1	-
OVIDUCT, HEMANGIOSARCOMA	-	-	1	-	-	-	-	-	-	-
STROMAL POLYP	5	-	4	-	5	-	2	-	2	-
MALIGNANT SCHWANNOMA	-	-	1	-	2	-	1	-	1	-
CERVIX, BENIGN STROMAL TUMOR	-	-	-	-	1	-	-	-	-	-
VAGINA										
LEIOMYOSARCOMA	-	-	-	-	-	-	1	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
TESTIS										
BENIGN INTERSTITIAL CELL TUMOR	-	2	-	-	-	2	-	2	-	1
MALIGNANT MESOTHELIOMA	-	-	-	-	-	-	-	-	-	1
SKIN										
SEBACEOUS GLAND, ADENOMA	-	-	-	1	-	-	-	-	-	-
MALIGNANT BASAL CELL TUMOR	-	-	-	-	-	-	-	-	1	-
FIBROMA	-	1	-	1	-	1	-	-	-	-
SKIN										
FIBROSARCOMA	-	1	-	1	-	-	1	1	-	-
HEMANGIOMA	-	-	-	2	-	-	-	-	-	-
HEMANGIOPERICYTOMA	-	-	-	-	-	1	-	-	-	-
HISTIOCYTIC SARCOMA	-	-	-	-	-	1	1	-	-	1
KERATOACANTHOMA	-	1	-	-	1	2	-	2	-	1
LIPOMA	-	2	-	1	-	-	-	1	-	-
LIPOSARCOMA	-	-	-	-	-	-	-	-	-	1
PAPILLOMA	-	-	-	1	-	1	-	-	-	3
MALIGNANT SCHWANNOMA	-	-	-	-	-	1	1	1	-	-
SQUAMOUS CELL CARCINOMA	-	1	-	-	-	-	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
MAMMARY GLAND										
ADENOCARCINOMA	10	-	10	-	16	-	11	2	15	-
ADENOMA	6	-	1	-	1	-	1	-	1	-
FIBROADENOMA	9	-	11	-	4	-	7	1	7	-
NOSE										
OLFACTORY EPITHELIUM, MALIGNANT NEUROBLASTOMA	-	-	-	-	-	-	-	-	-	1
LUNG										
ADENOMA	-	-	-	-	-	-	-	-	-	1
HEART										
MALIGNANT SCHWANNOMA	-	-	-	1	-	-	-	1	-	-
SPLEEN										
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-
UNDIFFERENTIATED SARCOMA	-	-	-	1	-	-	-	-	-	-
LYMPH NODE										
HEMANGIOSARCOMA	-	1	-	-	-	-	-	-	-	-
THYMUS										
BENIGN THYMOMA	-	-	-	1	-	1	-	-	-	-
BONE										
OSTEOSARCOMA	-	-	-	-	-	-	-	-	-	1

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

CONTINUED

SUMMARY OF PRIMARY NEOPLASMS

	GROUP 1		GROUP 2		GROUP 3		GROUP 4		GROUP 5	
	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES	FEMALES	MALES
BRAIN										
MALIGNANT GLIOMA	1	-	1	-	1	2	1	2	1	2
MENINGES, BENIGN GRANULAR CELL TUMOR	-	-	1	1	-	1	-	-	-	
NERVE										
HISTIOCYTIC SARCOMA	-	-	1	-	-	-	-	-	-	-
EYE										
AMELANOTIC MALIGNANT MELANOMA	-	-	-	-	-	1	-	-	-	-
EAR										
ZYMBAL'S GLAND, CARCINOMA	-	-	-	-	-	1	-	-	-	1
PINNA, NEUROFIBROSARCOMA	-	-	-	-	-	-	1	-	-	-
SQUAMOUS CELL CARCINOMA	-	-	-	-	-	-	-	-	-	1
PRIMARY SITE UNDETERMINED										
HISTIOCYTIC SARCOMA	2	1	2	1	3	2	1	2	-	-
GRANULOCYTIC LEUKEMIA	-	-	-	-	-	-	-	-	-	1
LYMPHOMA	1	-	-	2	-	1	1	1	1	1
MALIGNANT SCHWANNOMA	-	-	-	-	-	1	-	-	-	-

KEY: GROUP 1 = CONTROL 1 BID
GROUP 2 = CONTROL 2 BID
GROUP 3 = 0.05 MG/KG BID
GROUP 4 = 0.25 MG/KG BID
GROUP 5 = 1 MG/KG BID

Appendix 1A: Minutes of the Executive Carcinogenicity Assessment Committee Meetings for Dose Selection and Protocols for the Carcinogenicity Studies in Rats and Mice

Executive CAC
January 12, 1999

Committee: **Joseph DeGeorge, Ph.D., HFD-24, Chair**
Joseph Contrera, Ph.D., HFD-901, Member
Albert DeFelice, Ph.D., HFD-110, Alternate Member
Jasti Choudary, Ph.D., B.V.Sc., HFD-180, Team Leader
Timothy Robison, Ph.D., HFD-180, Presenting Reviewer

Author of Draft: Timothy W. Robison, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendation. Detailed study information can be found in the individual review.

IND# [redacted]
Drug name: MK-0869 (L-754,030)
Sponsor: Merck Research Laboratories West Point, PA

Rat Dose Selection: The sponsor initiated the rat carcinogenicity study with L-754,030 in December of 1997; however, they are seeking concurrence on dose selection. The sponsor is performing two concurrent studies with rats. In the first study (TT #97-134-0), rats are receiving L-754,030 by oral gavage at doses of 0.05, 0.25 and 1 mg/kg/day-B.I.D. (total daily doses of 0.1, 0.5, and 2 mg/kg, respectively). In the second study (TT #98-047-0), rats are receiving L-754,030 by oral gavage at doses of 5, 25, and 125 mg/kg/day-B.I.D. (total daily doses of 10, 50, and 250 mg/kg, respectively). The Executive CAC reviewed a dose selection proposal for the rat carcinogenicity study with L 754,030 on July 22, 1997 that was based upon a saturation of absorption of the parent compound. However, metabolism studies were not available and the dose selection proposal was rejected due to a lack of evidence demonstrating saturation of systemic exposure to both the parent compound and its metabolites. Since July 1997, the sponsor has conducted studies to characterize the metabolism of L-754,030 in rats. In the ongoing studies, selection of the high dose was based upon a saturation of absorption that occurred at doses ≥ 125 mg/kg/day-B.I.D. in both male and female rats. Systemic exposure to the parent drug and its metabolites did not significantly increase with doses ≥ 125 mg/kg/day-B.I.D. Preliminary pharmacokinetic data in human male subjects at a clinical dose of 400 mg/day indicated an $AUC_{0\text{-}24hr}$ value of 39.7 µg*hr/mL for the parent compound, L-754,030. Based upon kinetic and metabolism with L-754,030 in formulation M in rats, the sponsor's data appears to support saturation of exposure. Systemic exposure (i.e., AUC) to L-754,030 in rats, however, is less than that observed in human subjects. The sponsor has selected the low dose for the low dose range study (0.05 mg/kg/day-B.I.D.) upon a lack of hepatocellular hypertrophy in male and female rats. Given the extremely low exposure achieved at this dose compared to that in humans at the clinical dose range, it is unclear how this information will be applied in assessing human risk.

Mouse Dose Selection: The sponsor initiated the mouse carcinogenicity study with L-754,030 in December of 1997; however, they are seeking concurrence on dose selection. The sponsor selected doses of 2.5, 25, 125, and 500 mg/kg/day administered by oral gavage for the mouse carcinogenicity study. Selection of the high dose was based upon a saturation of absorption that occurred at doses ≥ 500 mg/kg/day in both male and female mice. Systemic exposure to the parent drug and its metabolites did not increase with doses ≥ 500 mg/kg/day using formulation M. Selection of the low dose at 2.5 mg/kg/day was based upon a lack of observed hepatocyte hypertrophy in male or female mice. Based upon kinetic and metabolism information absorption of L-754,030 in formulation M in mice appears saturated.

Executive CAC Recommendations and Conclusions for Rat and Mouse Dose Selections:

1. Studies TT #97-035-0 and TT #97-036-0 in mice and rats, respectively, demonstrated that a smaller drug particle size [redacted] in a new formulation resulted in a doubling of systemic exposure. Also, based upon the data provided, it is not clear that the absorption is saturated at the same doses as occurs with formulation M. Based upon the findings of these two studies, the committee could not offer concurrence regarding the adequacy of study design and dose selection. The committee recognized that saturation was reached for the formulation used in the ongoing studies [redacted]

However, the committee finds it difficult to agree that a biologically based saturation of absorption (i.e. transport) was reached for the compound. Rather, it appears that saturation is dependent upon physical characteristics of the drug substance related to particle size (i.e. dissolution). This view is based on the results that a smaller drug particle size resulted in a doubling of systemic exposure, and that exposure did not appear to saturate over the tested dose ranges with the new formulation.

2. The committee was particularly concerned that the sponsor had not optimized drug exposure in toxicology studies. Systemic exposures to the parent compound observed in mice and rats were only slightly greater or actually less than exposure observed in human subjects, respectively. Low systemic exposures to the parent compound and metabolites limited by dissolution may prevent full elucidation of the drugs toxicity profile, including carcinogenic potential at relevant human exposures.

3. The Executive CAC and Division would be agreeable to discuss this further in a telephone conference call.

/S/ 1/20/99

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

Appendix 2: Nonneoplastic and Neoplastic Findings in Male and Female Rats Receiving MK-0869 for 106 Weeks (Study # 98-047-0)

INTENTIONALLY

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