**Physical Signs** - There were no treatment related physical signs during the lactation and postweaning periods.

**Body Weight** - There was a 10-13% decrease in average pup body weights on PND 14 and 21 at 15 mg/kg/day. A statistically significant decrease [5%] in the average female body weights on PND 14 at 10 mg/kg/day was considered by the Sponsor to be unrelated to treatment. Body weights and body weight gain of all treated groups tended to be less than those of the control group throughout the postweaning period, although the body weight difference was generally <10%. There were no treatment-related effects on $F_1$ maternal body weights or body weight gain.

**External Examination** - Three fetuses from a single dam administered 15 mg/kg/day exhibited multiple malformations. The Sponsor considers these malformations to be unrelated to treatment since they occurred in only 1 litter and were "to some degree, ... likely secondary to the death of the fetuses". These findings for all 3 included nasal dysplasia, cleft palate, protruding tongue, micromelia and local edema. One animal also had a shortened torso.

**Developmental Signs** - There were no treatment-related effects on vaginal canalization or preputial separation.

**Ophthalmologic Examination** – All findings were considered by the Sponsor to be incidental. Findings were not tabulated.

**Behavioral Assessment** - There were no treatment-related effects on passive avoidance, auditory startle habituation, or open field motor activity.

**Reproductive Performance** - There were no treatment-related effects on time to mating, mating index, fecundity, fertility, gestation length, and implants/pregnant female.

III. $F_2$ Generation

**Mortality** - There were no treatment-related effects on percent postimplantation survival and live pups/litter.

**Body Weight** - There were no treatment-related effects.

**External Examinations** - There were no treatment-related effects.

**Sponsor's Conclusions [numbered] and Reviewer's Comments**

1. Maternal toxicity based on mortality was ≥10 mg/kg/day. Gross and histopathological evidence of GI ulceration/peritonitis was observed at ≥5 mg/kg/day. There were no effects on reproductive performance. **Reviewer's Comment** – In general, the Reviewer concurs. The relevance of the statistically significant increase in gestation length observed at ≥5 mg/kg/day is not known. The NOAEL for maternal toxicity was not determined but is <5 mg/kg/day. However, only 1 female was affected at this dose.

2. $F_1$ toxicity occurred during prenatal and preweaning exposure. This toxicity was characterized by an increase in pup deaths PND 0 at ≥5 mg/kg/day and PND 1-3 at 15 mg/kg/day. A decrease in pup weights PND 14 and 21 was also observed at 15 mg/kg/day. **Reviewer's Comment** – The Reviewer concurs. The NOAEL for fetotoxicity and postnatal toxicity was not determined but is <5 mg/kg/day.

3. There were no treatment-related effects on external morphology, postweaning survival or growth, development, behavior, ophthalmologic exams, or $F_1$ reproductive performance. **Reviewer's Comment** – The Reviewer concurs.

7.5.4. MK-0966: Oral Study in Rats to Assess Effects on Fetal Ductus Arteriosus [Vol. 1.27; p. C-1900]

**Study Identification:** TT #96-718-0
**Site:** Merck Research Laboratories, West Point, PA
**Study Dates:** May 6-31, 1996
**Formulation and Lot No.:** L-748,731-000R027[redacted]
Vehicle - 0.5% methylcellulose
Positive control - Indomethacin
**Certificate of Analysis Submitted: No (X)** Assayed for uniformity and concentration [timing for assays not provided]; assays were within acceptable limits, according to the Sponsor
**Final Report:** Oct. 22, 1996
**GLP and QA Statements Signed: Yes (X)** [used a draft SOP]
**Objective:** "To evaluate the potential of MK-0966, an inhibitor of cyclooxygenase 2, to reduce the diameter of the fetal ductus arteriosus in rats".

| Test Material/ Group Designation | Dose and Regimen# | | | | N | Sex | Species/ Strain |
|---|---|---|---|---|---|---|---|
| | mg/kg | ml/kg | Route | # of doses | | | |
| Group 1 -VH Control | - | 5 | oral gavage | GD 21 between 6:00 to 7:05 am | 10 | F | Sprague-Dawley - [Crl:CD®(SD)BR] |
| Group 2 - MK-0966 | 3 | | | | | | [redacted] |
| Group 3 - MK-0966 | 30 | | | | | | App. 10 wks at study start |
| Group 4 - MK-0966 | 300 | | | | | | 222-289 g |
| Group 5 - Indomethacin | 10 | | | | | | |

#fed *ad libitum*

| Parameter Evaluated | Time Point(s) |
|---|---|
| Clinical observations | GD 0, 7, 14, and 21, 1-5 hours post dosing on GD 21 |
| Body weight | GD0,7, 14, and 21 |
| Fetal Examination - Pulmonary trunk and ductus arteriosus evaluation - 4/litter [6 hours post dosing] | GD 21 |

**Results -**

**Mortality** - There were no deaths or abortions during this study.

**Clinical Observations** - There were no treatment-related effects.

**Maternal Body Weight** - There were no treatment-related effects.

**Fetal Examination** - There were no treatment related effects on the diameter of the pulmonary trunk. There was a marked decrease [approximately 50-60%] in the diameter of the ductus arteriosus and the ductus arteriosus/pulmonary trunk ratio in all treatment groups. A dose dependent relationship was not apparent. The table below demonstrates these findings.

| Parameter | Dose [mg/kg] | | | | |
|---|---|---|---|---|---|
| | MK-0966 | | | | Indomethacin |
| | 0 | 3 | 30 | 300 | 10 |
| Ductus arteriosus diameter | 0.32 ± 0.02 | 0.16 ± 0.04 | 0.14 ± 0.02 | 0.14 ± 0.02 | 0.14 ± 0.02 |

**Reviewer's Comments [Study Design and Data Presentation]** – For the stated objective, study design and data presentation were adequate.

**Sponsor's Conclusions [numbered] and Reviewer's Comments-**

1. MK-0966 produces comparable effects on ductus arteriosus diameter as indomethacin, indicating that COX-2 "may play a role in the perinatal constriction of the ductus arteriosus in the rat." Reviewer's Comment - A NOAEL was not determined but is <3 mg/kg.

## 7.6 Summary of Reproduction Toxicology -

**Fertility Studies – Includes assessment of ovulation and cyclicity**

Administration of L-748,731 to rats, beginning either 14 or 20 days prior to mating and continuing through cohabitation until mating was confirmed or until GD 7, resulted in a decrease in the number of corpora lutea [CL] and preimplantation embryos and/or unfertilized oocytes/female. This was accompanied by an increase in the ovulation failure indices or partial inhibition of ovulation. A NOAEL was not determined but was <10 mg/kg/day. Effects on fertility and fecundity were variable. In three studies, no effects on fertility and fecundity were observed at doses up to 30 mg/kg. In one of these studies, in which doses of 10-300 mg/kg/day were administered, decreases in fertility and fecundity occurred at ≥100 mg/kg/day and reached statistical significance at 300 mg/kg/day. In two studies, there was a decrease in fertility and fecundity at 30 mg/kg. The decrease was statistically significant in one study. In this study, there was also a trend towards decreased fertility and fecundity at 10 mg/kg/day. In the three studies in which administration of L-748,731 continued until GD 7, there was a decrease in the number of implants and live fetuses/pregnant female. This decrease was associated with an increase in resorptions, peri/post implantation losses, and dead fetuses/female. The NOAEL for embryofetal toxicity was considered to be 3 mg/kg/day. Reversibility of compromised embryofetal survival was demonstrated following a 14-day recovery period. There were no treatment-related effects on estrous cyclicity or time to mating. The NOAEL for maternal toxicity [e.g. GI ulceration/peritonitis] was 3-10 mg/kg/day.

There were no effects on male fertility [mating performance, fertility indices, embryonic/fetal survival, sperm count and motility, testicular/epididymal organ weights, histolopathology] at doses up to 100 mg/kg/day.

**Implantation Study**

In rats administered L-748,731 GD 1-7, there was no change in the number of corpora lutea but there was a decrease in embryofetal survival at ≥10 mg/kg/day. There was a significant increase in pre/peri-implantation loss at 30 mg/kg/day and in postimplantation loss at ≥10 mg/kg/day. The NOAEL for embryofetal toxicity was not determined but was <10 mg/kg/day. The NOAEL for maternal toxicity [GI ulceration/peritonitis] was 30 mg/kg/day.

**Developmental Studies**

The data did not conclusively indicate a teratogenic effects in rabbits and in rats up to a dose of 50 mg/kg/day. Retrocaval ureter [malformation] was observed in fetuses for all the treatment groups but not in the control animals. A dose-dependent relationship was not observed in fetal incidence. The historical control data for retrocaval ureter in the MARTA data base was a mean of 0.324 ± 0.87% [maximum of 4.27%] and the mean of the Sponsor submitted historical controls was 1.28%. Fused kidney was seen in 1/141 [0.7%]. The MARTA database reports a fetal incidence of fused kidney as 0. The mean fetal incidence of this finding in Sponsor submitted historical controls was 0.02%. Since it was observed in only a single high dose fetus, however, the relationship to drug treatment is questionable

Based on recommendations of the Reproduction Toxicity Committee, vertebral malformations, including axis and atlas malformations, were combined for further analysis. The fetal [litter] incidence for all vertebral malformations was 1/115[1], 2/136[2], 2/126[2], and 5/141[4] at 0, 10, 25, and 50 mg/kg, respectively. Statistical analysis [Cochran-Mantel-Haenszel method], conducted by Dr. Baldeo Taneja, indicated that there was no trend for an increase in the incidence of vertebral malformations based either on fetal incidence [p=0.415] or on litter incidence [p=0.603]. The Sponsor states [submission dated April 19,

1999] that "the spectrum of malformations is different for each fetus and when broken down by incidence, according to region and description,...all values are within MARTA historical control range reference. The MARTA historical control range of vertebral malformations for related alterations is as follows: Cervical [including bipartite, fused, hemicentra, hypoplastic or misshapen] is 0-1.96%, Thoracic [including agenesis, bipartite, fused, hemicentra, hypoplastic or misshapen] is 0-2.65% and Lumbar [including bipartite or fused] is 0 – 2.63%". Based on these considerations, the evidence is not conclusive with respect to a drug-related effect. Additional information has been requested from the Sponsor [e.g. Sponsor's lab control data].

Other findings occurred sporadically, did not show a dose dependent relationship, were comparable to concurrent controls, or within MARTA historical controls.

In the rabbits, there was an increase in the litter and fetal incidence of incomplete ossification at ≥25 mg/kg/day (fetal incidence of 23[19%] vs. 37[33%] and 50[37%] at 0 vs. 25 and 50 mg/kg/day, respectively). This included incomplete ossification of the sternebra, metacarpus, and talus/calcaneus. The Sponsor considers the increased incidence of incomplete ossification to be of "minimal toxicological significance since the average number of sacrocaudal vertebrae, an indicator of overall fetal ossification, were similar across all groups". There was a minor increase in the incidence of incomplete ossification in the rats.

Embryofetal toxicity was observed in both species. In the rabbit, a decrease in embryofetal survival at ≥75 mg/kg/day was associated with an increase in percent resorptions/implants and percent postimplantation loss, and a decrease in live fetuses/pregnant female. The NOAEL for embryofetal survival effects in the rabbit was 50 mg/kg/day. Decreases in fetal survival, according to the Sponsor, correlated with an increased incidence of vaginal bleeding. In rats, there was an increase in stillborn/dead pups on postnatal day 0 at ≥25 mg/kg/day when compared to controls [litter mean of 6[2.2%] vs. 41[18.5%] and 32 [13.4%] at 0 vs. 25 and 50 mg/kg/day, respectively]. Postnatal mortality was also increased Days 1-3 and 4-7 at ≥10 mg/kg/day. The cross-fostering study [TT #95-730-0] indicated that this postnatal mortality was related to both gestational and lactational exposure of the pups to L-748,731. Pup mortality postnatal days 1-7 was comparable in treated pups fostered to either control or treated dams but increased compared to control pups fostered to control dams. Pup mortality postnatal days 8-21 in control pups fostered to treated dams was increased compared to control pups fostered to control dams as well as compared to treated pups fostered to either treated or control dams.

In these studies, no to minimal maternal toxicity was observed in the rabbits up to a dose of 50 mg/kg/day. Maternal toxicity characterized by intestinal perforation/peritonitis was observed in the rats dosed at ≥10 mg/kg/day.

**Late Gestation including evaluation of lactational period and postweaning development**

Administration of L-748,731 from GD 15 through LD 6 or 20 resulted in increased pup mortality and decreased post implantation survival and percent live pups on postnatal day 0 and on postnatal day 1-3 at doses of ≥5 mg/kg/day. There was also an increase in pup mortality postnatal day 4 -7 in litters of dams administered 15 mg/kg. The NOAEL for fetal and postnatal toxicity was 1 mg/kg/day. There were variable effects on duration of gestation. In two studies [TT #94-733-0 and TT #95-706-5], there was no effect on the length of gestation at doses up to 50 mg/kg/day. However, there were minor effects on gestation length in four studies at doses ranging from 5 to 30 mg/kg/day [TT #92-721-0, TT #96-719-0, TT #94-733-5, and TT #95-706-0]. The increase in length of gestation ranged from 0.3 to 0.7 days. Due to the small magnitude of change, the biological significance of this finding is not known. The Sponsor, furthermore, indicates that delivery on GD 23 is within the normal range of control. There was also an increase in parturition duration ranging from 19-24 minutes at ≥5 mg/kg/day. As for length of gestation, the increase in parturition duration is of questionable biological significance due to the magnitude of the change. The NOAEL for maternal toxicity in females dosed through LD 6 or LD 20 was 15 and <5 mg/kg/day, respectively. It should be noted that gross and histopathological evidence of GI toxicity was observed in only a single female dosed at 5 mg/kg/day through LD 20.

Administration of a single dose of L-748,731 on GD 21 in rats, resulted in a significant decrease in the diameter of the ductus arteriosus. The magnitude of the decrease [approximately 50-60%] in the diameter of the ductus arteriosus was comparable at dose levels ranging from 3-300 mg/kg as well as being comparable to the decrease observed following a single dose of 10 mg/kg of indomethacin. A NOAEL was not determined for the decrease in the diameter of the ductus arteriosus but was <3 mg/kg.

## 8. Special Toxicology:

### 8.1 IRRITATION STUDIES

8.1.1 ,L-748,731: Exploratory Dermal Irritation Study in Rabbits [Vol. 1.47: p. H-12]
**Study Identification: TT #95-2701**
**Site:** Merck Research Laboratories, West Point, PA
**Study Dates:** Sept. 12-18, 1995
**Formulation and Lot No.:** L-748,731-000R025
**Certificate of Analysis Submitted: No (X)**
**Final Report (X)** Dec. 27, 1995
**GLP: No (X)** [Exploratory study]
**Objective:** "To determine the potential dermal irritation of L-748,731, a selective cyclooxygenase-2 [COX-2] inhibitor, when applied to the skin of rabbits for 24 hours.

| Test Material/ Group Designation | Dose | Sex | N | Species/ Strain |
|---|---|---|---|---|
| L-748,731 | 500 mg/site | M | 2 | New Zealand White |
| | | F | 1 | App. 31 weeks at study start 3.28-3.59 kg, individually housed |

There was a single dermal application to an area on the back, clipped 24 hours prior to drug application, of each rabbit. The area was occluded. After 24 hours, the dressings were removed and the area gently cleansed of residual drug.

| Parameter Evaluated | Timing |
|---|---|
| Clinical observations | Daily through Day 8 |
| Draize scoring | Beginning 24 hours after treatment, then daily except on weekends [Days 5 and 6] until Day 8. |
| Body Weight | Pretest and Day 7 |

**Results**

**Clinical Observations** –There were no signs of dermal irritation.

**Body Weight** – There were no changes that were considered treatment-related by the Sponsor.

**Reviewer's Comment (Study Design and Data Presentation)** – For the stated purpose, study design and data presentation were considered adequate.

**Sponsor's Conclusions (numbered) and Reviewer's Comments -**
1. L-748,731 was non-irritating when applied to the skin for 24 hours. **Reviewer's Comment** – The Reviewer concurs.

8.1.2. Effect of L-748,731 in the Bovine Corneal Opacity and Permeability [BCOP] Assay [Vol. 1.47: p. H-23]
**Study Identification:** TT #95-4272
**Site:** Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherché, Riom, France
**Study Dates:** Not provided
**Formulation and Lot No.:** L-748,731-000R025
**Certificate of Analysis Submitted: No (X)**
**Final Report (X)** Oct. 26, 1995
**GLP: No (X)**

**Objective:** To determine the ocular irritancy potential of L-748,731 when applied to bovine corneas *in vitro*.

Fresh bovine corneas [N=4] were incubated in either 20% [w/v] L-748,731 in Minimal Essential Medium plus 1% fetal bovine serum or medium only for 4 hours prior to evaluation.

| Parameter Evaluated* | Timing |
|---|---|
| Corneal Opacity | Following 4 hour exposure to drug |
| Corneal Permeability – ability of fluorescein to pass from one compartment to another across the corneal sample | Following drug exposure and 90 minute incubation with fluorescein solution |

*irritancy score is based on opacity and corneal permeability combined with drugs classified as either mild, moderate or severe irritants.

**Results** – L-748,731 resulted in slight corneal opacity and minimal effect on permeability. Therefore, L-748,731 was classified as a mild irritant.

**Reviewer's Comment (Study Design and Data Presentation)** – For the stated objective, the study design and data presentation were adequate.

**Sponsor's Conclusions (numbered) and Reviewer's Comments –**
1. L-748,731 was classified as a mild ocular irritant in the bovine corneal opacity and permeability assay. **Reviewer's Comment** – The Reviewer concurs.

8.1.3 L-748,731: Exploratory Primary Eye Irritation Study in Rabbits [Vol. 1.47; p. H-52]
**Study Identification:** TT#95-4273
**Site:** Laboratoires Merck Sharp & Dohme-Chibret, Centre de Recherché, Riom, France
**Study Dates:** Oct. 6-9, 1995
**Formulation and Lot No.:** L-748,731-00OR025
**Certificate of Analysis Submitted: No (X)**
**Final Report (X)** Dec. 28, 1995
**GLP: No (X)**
**Objective:** "To determine the potential primary eye irritation of L-748,731 in rabbits."

| Test Material/ Group Designation | Dose | Sex | N | Species/ Strain |
|---|---|---|---|---|
| L-748,731 | 100 mg into OS | M<br>F | 2<br>1 | New Zealand White<br>App. 22-23 weeks at study start<br>M =3.5 and 3.85 kg F = 3.95 kg,<br>individually housed |

Right eye was untreated. Drug was place into the conjunctival sac of the left eye. The eyelids were held together for 20 seconds, then released.

| Parameter Evaluated | Timing |
|---|---|
| Clinical observations | daily |
| Ophthalmic Examination – general exam in order to score ocular reactions based on Draize scoring system, direct pupillary and corneal reflex | 15, 120 minutes, 24, 48, and 72 hours, 4 and 7 days post dosing |
| Body Weight | Pretest and Day 7 |

**Results**

**Clinical Observations** – There were no treatment-related effects.

**Body Weights** – There were no treatment-related effects.

**Ophthalmic Examination – Ocular Reactions** – At 120 minutes post dosing, slight conjunctival redness and very slight discharge was observed in 2 and 3 animals, respectively. By 48 hours, all rabbit eyes were normal for the remainder of the study.

**- Direct Pupillary Reflex and Corneal Reflex** – These reflexes were normal throughout the study.

**Reviewer's Comment (Study Design and Data Presentation)** – For the stated objective, the study design and data presentation were adequate.

**Sponsor's Conclusions (numbered) and Reviewer's Comments -**

1. L-748,731 was minimally irritating to the eyes of rabbits. **Reviewer's Comment** – The Reviewer concurs.

## 8.2 PHOTOTOXICITY STUDY

### 8.2.1 Acute Oral Phototoxicity Study in Mice [Vol. 1.49; p. Q-41]

**Study Identification:** TT#95-2691
**Site:** Merck Research Laboratories, West Point, PA
**Study Dates:** Sept. 11 – 17, 1995
**Formulation and Lot No.:** L-748,731-000R009
Vehicle – 0.5% methylcellulose
Positive control – Chlorpromazine HCl
**Certificate of Analysis Submitted: No (X)** according to the Sponsor, assays for concentration and uniformity were considered to be within acceptable limits.
**Final Report (X)** March 31, 1996
**GLP and QA statement signed: Yes (X)**
**Objective:** "To determine the phototoxicity potential of L-748,731, a cyclooxygenase-2 inhibitor, after a single oral dose to female mice."

| Test Material/ Group Designation* | Dosing Regimen** | | | | Sex | N | Species/ Strain |
|---|---|---|---|---|---|---|---|
| | mg/kg | ml/kg | Route | days dosed | | | |
| Group 1 – VH control | - | 10 | po | 1 | F | 6 | Crl:CD-1® (ICR) BR strain |
| Group 2 – Pos. control - chlorpromazine | 80 | | | | | | App. 7 weeks at study start |
| Group 3 - L-748,731 | 100 | | gavage | | | | F = 21.6-26.9 g |
| Group 4 - L-748,731 | 600 | | | | | | housed up to 6/box |

*two additional groups were dosed with either chlorpromazine and L-748,731 and placed in the dark to serve as negative controls.
**1 and 6% solutions of drug

Two hours after drug administration, mice were exposed to UVB light for 5 minutes and UVA light and visible light for 4 hours

| Parameter Evaluated | Timing |
|---|---|
| Physical examination – degree of erythema, sloughing, and/or necrosis of the ears | Daily for 7 days |
| Body Weight | Pretest and Day 7 |

**Results**

**Clinical Observations** – There were no signs of phototoxicity with either L-748,731 or control mice throughout the study period. There were no signs of phototoxicity in mice that were kept in the dark

following administration of L-748,731 or chlorpromazine. Slight to moderate erythema was apparent by 3 hours after light exposure in 6/6 mice administered chlorpromazine.

**Body Weights** – There were no treatment-related effects.

**Reviewer's Comment (Study Design and Data Presentation)** – For the stated objective, the study design and data presentation were adequate.

**Sponsor's Conclusions (numbered) and Reviewer's Comments -**
1. L-748,731 did not induce phototoxicity under the conditions of this study. **Reviewer's Comment** – The Reviewer concurs.

## 8.3 SPECIAL STUDIES CONDUCTED WITH THE METABOLITE L-755,190

***The current Pharmacology/Toxicology Reviewer reviewed the following studies.***

### 8.3.1. L748,706; L-755,190; Ibuprofen; Exploratory Fifteen-Day Cyclooxygenase Inhibition Study in Female Rats [Vol. 1.49; p. Q-76]

**Study Identification:** TT #95-078-0
**Site:** Merck Research Laboratories; West Point, PA
**In-life Phase Study Dates:** Dec. 6 -20, 1995
**Formulation:** L-755,190-000H007
Vehicle control - 0.5% aqueous methylcellulose
Comparative controls – Ibuprofen
- L-748,70600G009 – This is an analog of L748,731 and is considered by the Sponsor to be selective for COX-2.
**Certificate Analysis: No (X)**
**Final Report** (X) April 1, 1996
**GLP and QA statements signed:** No (X) not GLP
**Objective:** "To determine the effects of a selective cylclooxygenase II [COXII] inhibitor [L-748,706 – an analog of 748,731], a metabolite of L-748,731 [L-755,190], and a non-selective cyclooxygenase inhibitor [ibuprofen] on gastrointestinal toxicity, prostaglandin levels, and cyclooxygenase activity."

| Test Material/ Group Designation | Dose* | | | | Sex | N | Species/Strain |
|---|---|---|---|---|---|---|---|
| | mg/kg | ml/kg | Route | # days dosed | | | |
| Group 1 - vehicle | - | 5 | oral gavage SID | 15 | F | 16 | Crl:CD®(SD)BR - Sprague-Dawley rats 73 days at study start, 205-277 g individually housed |
| Group 2 - ibuprofen | 100 | | | | | | |
| Group 3 - L-748,706 | 100 | | | | | | |
| Group 4 - L-748,706 | 300 | | | | | | |
| Group 5 – L-755,190 | 100 | | | | | | |

*fed *ad libitum*

| Parameter Evaluated | Time Point(s) |
|---|---|
| Physical examination/mortality | Daily |
| Body weight | pretest, 1X/ Drug Week 1, 2X/Drug Week 2 |
| Food consumption | 4-day period, 1X/week for Drug Weeks 1 and 2 |
| Necropsy -10/group; GI tract only | Day 15 |
| Histopathology - 10 group; stomach, small and large intestine, gross GI changes | Day 15 |
| Special procedures - 6/group; PG levels [$PGE_2$, 6-keto $PGF_1$], CO activity, L-748,731 concentration - samples conducted 2 hours post-dosing | Day 15 |

Results -

**Mortality** – There were no unscheduled deaths or premature sacrifices.

**Physical signs** – According to the Sponsor, there were no treatment-related clinical signs,

**Body weight** - There was approximately a 38% and 20% decrease in mean body weight gain in the animals administered Ibuprofen and L-755,190, respectively.

**Food consumption** - A decrease in food consumption was associated with the decrease in body weight gain.

**Necropsy** – In at least 2/10 rats per group, there was mucosal discoloration, thickening or ulceration.

**Histopathology** - The following histopathological changes were observed: [1] pyloric lesion [1/10 Group 2 rats] [2] small intestinal erosion/ulcer [3/10, 1/10, and 1/10 Group 2, 3, and 5 rats]; [3] cecal erosion/ulcer [3/10, 1/10, 2/10, 2/10 Group 2, 3, 4, and 5 rats] and [4] colon ulcer [1/10 Group 4 rats]. These lesions were often associated with focal peritonitis.

**Jejunal levels of L-748,731** – In Group 5 rats, jejunal levels of L-755,190 at 2 hours following dosing were a mean of 36.8 μg/g [range of 9.16 –110 μg/g]. L-748,731 was also present in these rats the intestinal tissue [2.8 μg/g; range of 2.29 – 4.02 μg/g].

**Special procedures** - There were no treatment-related effects on 6-keto PGF1α with L-748,706 or L-755,190. Ibuprofen resulted in a large decrease in basal 6-keto PGF1α levels [>99%]. There was a decrease in basal PGE2 levels with both L-755,190 and L-748,706 when compared to controls [approximately 40-50%] although the magnitude was less than that observed with ibuprofen.

**Reviewer's Comment - Study Design and Data Presentation** - For the stated objective, these were adequate.

**Sponsor's Conclusions (numbered) and Reviewer's Comments-**

1. These results are similar to those obtained with L-748,731. COX1 activity and basal PG levels in the intestinal tract were not significantly modified by treatment with L-755,190 or L-748,706 especially compared to the effects of Ibuprofen. Comparable mild decreases have been observed in three studies, and, therefore, suggests that this decrease is a treatment-related effect. **Reviewer's Comments** – In general, the Reviewer concurs. However, there was a 40-50% in intestinal PGE2 levels.

***The initial Pharmacology/Toxicology Reviewer, Dr. Will Coulter, reviewed the following studies.***

8.3.2 Five-Week Oral Toxicity Study in Rats: TT#95-056-0 Study TT#95-056-0 [Vol. 1.49; p. Q-167]

**Note: This study was conducted with metabolite L-755,190**

Compound: L-755,190, lot L-755,190-000H007 (factor 1.0),
Formulation: Suspension in 0.5% methylcellulose.
Route: Oral, by gavage at 5 mL/kg
Diet: M were given 24 g and F 17 g of Certified Rodent Diet per day.

| Dose Levels: Groups: | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| mg/kg/day: | 0 | 2 | 5 | 10 |

Total of Doses: 29 in M, 30 in F
Strain: Crl:CD®(SD)BR albino rats, age 36 day-
Body Weight: M - 125-176 g, F - 114-135 g
Number: 15/sex/group
Control Treatment: 0.5% methylcellulose

N-21,042 Vioxx
Merck & Co. FINAL

Study Site: Merck Research Laboratories, West Point, PA.
Date: August 25, 1995 - March 4, 1996
GLP/QAU: Both present and signed.

This study was conducted to determine the toxicity of L-755,190 in rats after oral administration for five weeks. The animals were observed daily for **mortality** and **clinical signs**. **Food consumption** was observed twice/week. **Body weight** was determined pretest, once W1, and twice/week thereafter. All surviving control and high dose animals were examined by **ophthalmoscopy** (indirect and slit lamp). **Hematology** (erythrocyte count-Hct-leukocyte count-differential leukocyte count-platelet count-Hb- mean corpuscular volume-mean corpuscular Hb-mean corpuscular Hb concentration) and **serum biochemistry** (total protein-glucose-creatinine-AST-alk phos-triglycerides-K-total Ca-albumin-urea nitrogen-A/C ratio-ALT-cholesterol-Na- chloride-phos) determinations were conducted W2 and 4 on all surviving animals. **Urinalysis** (protein-bilirubin-glucose-occult blood-specific gravity-microscopic examination of sediment-ketones- urobilinogen-pH-volume) was done W4 on 10 rats/sex/group. **Plasma drug levels** were determined D28 and D29 on 3 or 4 rats/sex/drug-treated group at 0.5, 1, 2, 4, 8, 12, and 24 hours; however, it was stated that L-755,190 was unstable in plasma matrix. For that reason plasma samples were not analyzed for drug levels. Complete **gross examinations** were done on all rats, and **organ weights** (heart-spleen-brain-pituitary-kidneys-testes-prostate-thyroid-liver-adrenal-ovaries) were recorded for all animals. **Microscopic examination** (lung-heart-liver-kidneys-urinary bladder-spleen-thymus-lymph nodes-adrenals-thyroid (with parathyroid)-pituitary-salivary gland-stomach-small intestine-pancreas-spinal cord-peripheral nerve-eye (with optic nerve and Harder's gland)-skin (with mammary gland)-bone (including joint)-bone marrow-testes and epididymides-prostate-ovaries-uterus-brain-skeletal muscle-large intestine) on all animals in the control and high dose group, and all animals that died prior to study termination. Also, all gross changes and eye changes were examined microscopically. **Organ weights** (heart-spleen-brain-pituitary-kidneys-testes-prostate-thyroid-liver-adrenal-ovaries) were expressed as absolute, percent of body weight, and percent of brain weight.

## RESULTS AND DISCUSSION

- mortality: 1G4 M and 1G3 F died W2 and W4, respectively, following orbital bleeding-
- body weight: no treatment related effects-
- food consumption: "no treatment related effects"-
- ophthalmic examinations: no treatment-related changes were reported-
- hematology: no observable treatment related changes noted-
- serum biochemistry: no observable large changes in average values - slight ↑ in AP values occurring in all groups were above the last two year historic values-
- urinalysis: no changes in average values - bilirubin values of +1 were reported W4 in 1M G1, 1F G2, 2M and 1F G3, and 2 M and 1F G4-
- organ weights:
  - kidney: absolute wt M G4 ↑ 5%, also ↑ relative to body and brain weight-
  - adrenals: absolute wt M G4 ↓ 4%, also ↓ relative to body and brain weight-
  - testes: absolute wt MG4 ↑ 6%, also ↑ relative to body and brain weight-
- histomorphology:

Lesions Not Observed in Controls

| GROUP | 2 mg/Kg/day F | 2 mg/Kg/day M | 5 mg/Kg/day F | 5 mg/Kg/day M | 10 mg/Kg/day F | 10 mg/Kg/day M |
|---|---|---|---|---|---|---|
| **Large Intestine:** cecum, acute subepithelial inflammation | | | 1 | | | |
| cecum, lymphoid proliferation | | 1 | | | | |
| cecum, ulcer | | | | | 1 | |
| **Liver:** capsule, focal fibrosis | | | | | 1 | |
| diffuse vacuolation | | | | | 1 | |
| focal necrosis | | | 1 | | | |
| focal vacuolation | | | | | 1 | |
| **Pancreas:** focal cellular infiltration | | | | | 1 | |

| GROUP | 2 mg/Kg/day F | 2 mg/Kg/day M | 5 mg/Kg/day F | 5 mg/Kg/day M | 10 mg/Kg/day F | 10 mg/Kg/day M |
|---|---|---|---|---|---|---|
| **Kidney:** cyst | | | | | | 1 |
| pelvis, distension | | | | | | 1 |
| **Urinary Bladder:** distension | | | | | | 1 |
| **Lung:** focal histiocytosis | | | | | 2 | 2 |
| chronic focal pneumonia | | | | | | 1 |
| **Uterus:** focal cellular infiltration | | | | | 1 | |

All lesions were considered very slight or slight/small.

There was no observed dose-related toxicity produced by oral gavage administration of 2, 5, 10 mg/kg/day L-755,190 to rats for five weeks. The study was not without GI toxicity, however, as one high dose female rat developed an ulcer in the cecum and one mid dose rat developed a region of acute subepithelial inflammation. Urinary bilirubin was seen in all groups in this study and was also noted in the 60 µg/kg/day IV15-day rat study reported earlier in this review. The NOEL in rats was at 2 mg/kg/day for oral administration of metabolite L-755,190.

8.3.3 Fifteen-Day Intravenous Toxicity Study in Rats With L-755,190: Study TT#95-070-0 [Vol. 1.50; Q-472]

**Note: This study evaluated the toxicity of L-755,190, the major metabolite of L-748,731 *in rats*.**

Compound: L-755,190-000H007 (factor 1.0),
Formulation: Solution in 0.9% sterile saline.
Route: IV via the tail vein at ~2 mL/min
Diet: F given ~17 g/day and M given ~24 g/day of Certified Rodent Chow

| Dose Levels: Groups: | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| µg/kg/day: | 0 | 20 | 40 | 60 |
| Dose Volume: mL/kg: | 12 | 4 | 8 | 12 |

Total No. of Doses: 14
Strain: Crl:CD®(SD)Br - albino rats-
Age: ~59 - 60 days old-
Body Weight: M - 234-305 g, F - 169-217.
Number: 15/sex/group
Control Treatment: 0.9% sterile saline
Study Site: Merck Research Laboratories, West Point, PA.
Date: October 18, 1995 to March 4, 1996
GLP/QAU Statement: Both present and signed.

This study was done to determine the toxicity and irritation potential of L-755,190 following intravenous administration to rats. The animals were observed daily for **clinical signs** and **mortality**. **Food consumption** was observed twice a week. **Body weight** was recorded pretest and once during each week. Indirect and slit lamp **eye examinations** were done on all surviving G1 and G4 rats during W2. **Hematology** examinations (erythrocyte count-Hct-Hb-mean corpuscular volume-mean corpuscular Hb-mean corpuscular Hb concentration-leukocyte and differential leukocyte count- platelet count), **serum biochemistry** determinations (total protein-glucose-creatinine-AST-ALT-alk phos-triglycerides-K-Ca-albumin-urea nitrogen-A/G ratio-cholesterol-Na+-Cl-phosphorus), and **urinalyses** (protein-bilirubin-glucose-occult blood-specific gravity-microscopic examination of sediment-urobilinogen-pH-ketones-volume) were evaluated on all surviving rats W2. **Necropsy** was conducted on all rats, and **organ weights** (adrenals-brain-heart-ovaries-testes-kidneys-liver-pituitary-prostate-spleen-thyroid) determined. **Microscopic examinations** were carried out on at least 36 tissues from G1 and G4.

RESULTS

- clinical signs: no treatment related signs were stated in the study-
- mortality: all rats survived to termination-
- body weight: mean weight increase was about the same in all groups-
- food consumption: no treatment related changes - minor fluctuations noted-
- ophthalmic examinations: no treatment related changes stated-
- hematology:
  - platelets: ↑ 6%-10% in F and 3%-7% in M groups (similar to historic controls)-
  - % neutrophils: ↑ 29% G3; ↑ 27%-39% G2-4 (none over historic control values)-
  - neutrophils (absolute values): ↑ F 29% G2, 35% G3; ↑ M- 39%-47% G2-4 - no values above historic controls-
- serum chemistry values:
  - ALT: ↑ 17% in F (60 µg/kg/day) due to one high dose F rat (No. 95-5983) with 3.2x increase over G1 average value-
- urinalysis:
  - bilirubin: ↑ 27% in M G4 - 3 year database was 21% - was considered by Merck to have been unrelated to test article administration-
  - occult blood: + 1 value in 1M G2, +3 value in 1 M G4 (considered by sponsor to be unrelated to drug administration)-
- organ weights:
  - liver: slight ↑ in absolute and relative weights of treated M -
- gross changes: injection site lesions - other lesions appeared not to be treatment related-
- histopathology: no changes appeared to be related to the treatment-
  - kidney: 1/15 F G4 mononuclear pyelitis (slight)-
  - injection site: lesions developed in both the control and G4-
  - liver: focal necrosis 2 M and 2F G1, 3 M G4 (all very slight)-

There was no definitive toxicity that could be related to the intravenous administration of metabolite L-755,190 to rats at 20, 40, or 60 µg/Kg/day for 14 days; however, there were a few hematological, serum chemistry, and urinalysis parameters that were high in the 60 µg/kg/day group. This could be the starting level for toxicity for this metabolite in rats.

8.3.4 Sixteen-Day Intravenous Toxicity Study in Dogs: TT#95-073-0; Study TT#95-073-0 [Vol. 1.50; p. Q-608]

**Note: L-755,190 used in this study is the major metabolite of MK-0966 (L-748,731) *in rats***

Compound: L-755,190-000H007 [redacted]
Formulation: Solution of L-755,190 (factor 1.0) in 0.9% Sodium Chloride Injection, USP.
Route: Intravenous, via the cephalic vein at 28-33 mL/minute.
Diet: 350 g of PMI Certified Canine Diet was provided daily.

| Dose Levels: Group: | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| µg/kg/day: | 0 | 20 | 40 | 60 |
| Dose Volume: mL/kg: | 12 | 4 | 8 | 12 |

Total No. Doses Received: M = 14, F = 15
Strain: Beagle, 41 to 45 weeks old, body weight M 9.7-12.9 kg, F7.6-9.7 kg.
Number: 4/sex/group
Control Treatment: 0.9% NaCl Injection, USP
Study Site: Merck Research Laboratories, West Point, PA
Date: November 6, 1995 to March 14, 1995
GLP/QAU Statements: Both present with signatures.

The purpose of the study was to determine the toxic potential of compound L-755,190, the 5-hydroxy metabolite of MK-0966, when administered to dogs fifteen consecutive days by the intravenous route. The animals were observed daily for clinical signs. Food consumption was measured 3-4 times a

week during W1 and W2. **Body weight** was recorded pretest, once the first week, and twice during the second week. **Indirect ophthalmoscopy** and slit lamp examinations were done pretest and during W2. **Hematology**, (erythrocyte count-hematocrit-leukocyte count-leukocyte differential count-Hb concentration-mean corpuscular volume-mean corpuscular Hb concentration-platelet count-prothrombin time-activated partial thromboplastin time), **serum** [protein-albumin-glucose-urea nitrogen-creatinine-A/G ratio-AST-ALT-alk phosphatase-cholesterol-triglycerides-sodium-chloride calcium (total)-phosphorus], and **urinalysis** (volume-glucose-protein-occult blood-pH-specific gravity-ketone-urobilinogen) parameters were determined pretest and during Week 2 on all dogs. **EKGs** were recorded on all animals pretest and in Week 2. Complete **gross examinations** were done on all dogs. **Organ weights** (adrenals-brain-heart-kidney-liver-thyroid-ovaries-pituitary-prostate-spleen-testes) were recorded for all animals and expressed as absolute weight, as percent of body weight, and as percent of brain weight. **Histopathologic examinations** were evaluated on 32 different tissues on all animals in G1 and G4.

RESULTS AND DISCUSSION

- physical signs: none were reported-
- mortality: none prior to sacrifice-
- body weight: no important changes noted-
- food consumption: no noticeable changes noted-
- ophthalmic examinations: "none" reported- no data present-
- EKGs: no treatment related changes were said to occur, but no data-
- hematology: minor changes in several parameters of all groups - nothing significant-
- serum biochemistry: no meaningful changes-
- urinalysis: 1G2 M (No. 95-0368) and 1G4 M (No. 95-0384) +1 protein pretest and +2 at W2-
  1G1 F and 2G3 M with +2 (No. 95-036) and +1 (No. 95-0373) occult blood W2-
- gross examinations: "no treatment-related changes"-
- organ weights: no apparent gross changes that could be related to the treatment-
- histopathology: no treatment related lesions - injection sites showed focal perivascular collagen necrosis/fibrosis/hemorrhage/inflammation in all groups, and were related to the multiple trauma of the injections - lesions only in treated animals are noted below-
  - adrenals: cortex, focal cellular infiltration, slight or small, 1MG4 (No. 510135)-
  - urinary bladder: focal subepithelial cellular infiltration, very slight, 1F G4 (No. 510148)-
  - prostate: chronic focal inflammation, very slight, 1 M G4 (No. 510135)-
  - skin: focal acanthosis, very slight, 1 F G3 (No. 510147)-
  - heart: focal mineralization, very slight, 1 F G4 (No. 510148)-
  - spleen: extramedullary hematopoiesis, very slight, 1 F G4 (No. 510150) - focal hemorrhage, slight or small, 1 G3 F (No. 510145) - reticuloendothelial hyperplasia, very slight, 1 G4 F (No. 510148)-
  - brain: focal perivascular cellular infiltration, very slight in all animals, 2 G4 F (No. 510148, No. 510149) and 2 M G4 (No. 510132, No. 510135), very slight in all animals-
  - eye: focal dystrophy, very slight, 2 M G4 (No. 510132, No. 510135)-

There were no treatment-related changes associated with the intravenous administration of the major metabolite L-755,190 at doses of 20, 40, and 60 µg/kg/day for fifteen days. Histopathology lesions that were reported in the high dose group and not observed in the controls were classified as very slight and slight or small. As in the above rat study, 60 µg/kg/day may be the toxic dose low for this compound in dogs.

**8.4 SUMMARY OF SPECIAL TOXICOLOGY** - L-748,731 was did not result in dermal irritation following a single dermal application of drug in rabbits. L-748,731 was minimally to mildly irritating in both the *in vitro* bovine corneal opacity and permeability assay and the *in vivo* ocular irritation study in rabbits. Under the conditions tested, L-748,731 did not acutely induce phototoxicity.

Oral administration of 0, 2, 5, 10 mg/kg/day of the metabolite (L-755,190) to rats for five weeks produced no dose-related toxicity. Urinary bilirubin was seen in all groups, including the control, but developed in more mid and high dose animals. Urinary bilirubin was also reported in the 15-day IV toxicity study in rats with the metabolite. At 5 and 10 mg/kg/day, there were lesions in the cecum - a