Review and Evaluation of Pharmacology and Toxicology Data

Division of Analgesics, Anti-inflammatory, and Ophthalmic Drug Products
HFD-550
Reviewer: Susan D. Wilson, D.V.M., Ph.D.

Electronic File Number:

NDA Number: **21-042**

Serial Number:
Submission Date: November 23, 1998
Type of Submission: Original NDA

Information to Sponsor: Yes (X)

Completion Date: May 7, 1999

Sponsor or Agent:
Merck & Co., Inc.
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

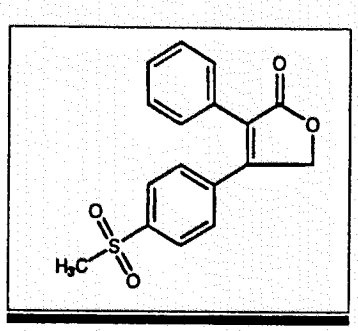
Manufacturer (if different) for drug substance:

Drug name:
1° - Vioxx™
2° - Rofecoxib
3° - MK-996, MK-0966, L-748,731

Chemical Name: 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5*H*)-furanone

CAS Number (if provided by sponsor):

Structure: $C_{17}H_{14}O_4S$



Molecular Weight: 314.36

Relevant IND/NDA/DMF: NDA 21-052

INDEX OF STUDIES

Drug Class: COX-2 Inhibitor

Indication: "Acute and chronic treatment of the signs and symptoms of osteoarthritis, relief of acute pain, and treatment of primary dysmenorrhea"

Clinical Formulation (and components): Tablet form in two strengths: 12.5 and 25 mg.

	12.5 mg dose	25 mg dose
MK-0966	12.50	25.00
Microcrystalline Cellulose		
Lactose		
Hydroxypropyl Cellulose		
Croscarmellose Sodium		
Yellow Ferric Oxide		
Magnesium Stearate		
Total		

Route of Administration: oral

Proposed Clinical Protocol: The maximum recommended dose for osteoarthritis is 25 mg daily. The maximum recommended dose for acute pain and dysmenorrhea is 50 mg daily for ≤5 days.

Studies Reviewed within this submission:

Report No.	Report Date	Study Title	Test Material Lot
PHARMACOLOGY STUDIES			
-	Nov. 1, 1994	F-21: Pharmacological studies of L-748,731 [Vol. 1.42; p. F-227]	-
-	Oct. 22, 1997	F-22: Additional In Vitro Biochemical Studies of MK-0966 [Vol. 1.42; p. F-356]	-
-	Oct. 22, 1997	F-23: Additional Pharmacological Studies of MK-0966 [Vol. 1.42; p. F-374]	-
-	Nov. 1, 1994	F-26: Effects of L-748,731 on Adjuvant-Induced Arthritis in Lewis Rats [Vol. 1.43; F-480]	
SAFETY PHARMACOLOGY STUDIES			
-	Oct. 31, 1994	F-24: Ancillary Pharmacology of L-748,731-000R, a Selective Cyclooxygenase II [COX-2] Inhibitor[Vol. 1.43; F-398]	-
-	Oct. 31, 1994	F-25: Effect of the Selective Cyclooxygenase II Inhibitors [COX-2], L-748,731-000R on Renal Function and Electrolyte Excretion in Conscious, Trained Dogs and Conscious Volume Depleted, Normotensive Rats [Vol. 1.43; F-424]	-
TOXICOLOGY STUDIES			
Single Dose Studies			
TT #94-2639 TT #94-2640 TT #94-2641 TT #94-2642	July 29, 1994	A-1: L-748,731: Acute Oral and Intraperitoneal Toxicity Studies in Mice and Rats [Vol. 1.7; p. A-21]	L-748,731-000R009

Report No.	Report Date	Study Title	Test Material Lot
Repeat Dose Studies			
Dog studies			
TT #94-020-0	May 6, 1994	B-1: L 748,731: Exploratory Fifteen-Day Oral Toxicity Study in Dogs [Vol. 1.8; B-125]	L-748,731-000R004
TT #94-040-0	Aug. 3, 1995	B-2: L-748,731: Fourteen-Week Oral Toxicity Study in Dogs [Vol. 1.9; B-183 and Vol. 1.10; B-339]	L-748,731-000R009
TT #95-003-0	June 19, 1996	B-3: L-748,731: Fifty-Three-Week Oral Toxicity Study in Dogs with a 27-Week Interim Necropsy: Final Report [Vol. 1.10; B-474 and Vol. 1.11; B-782]	L-748,731-000R014
TT #95-077-0	Apr. 25, 1996	B-18: L-748,731: Sixteen-Day Intravenous Toxicity Study in Dogs [Vol. 1.20; p. B-4232]	L-748,731-000R014
Rat studies			
TT #93-149-0	Mar 2, 1994	B-4: L 748,731: Exploratory Fifteen-Day Oral Toxicity Study in Rats [Vol. 1.11; B-910]	L-748,731-000R003
TT #94-615-0	Aug. 31, 1995	B-5: L-748,731: Fourteen-Week Oral Toxicity Study in Rats [Vol. 1.11; B-100 and Vol. 1.12; B-1184]	L-748,731-000R009
TT #95-614-0	May 2, 1996	B-6: L-748,731: Fourteen-Week Oral Toxicity Study in Rats with a Seven-Week Interim Necropsy and a Recovery Period [Vol. 1.13; B-1512]	L-748,731-000R014
TT #95-601-0	Sept. 26, 1995	B-7: L-748,731: Twenty-Seven-Week Oral Toxicity Study in Rats [Vol. 1.13; B-1651, Vol. 1.14; B-1918; and Vol. 1.15; B-2259]	L-748,731-000R014
TT #95-018-0	Sept. 24, 1995	B-8: L-748,731: Fourteen-Week Oral Range-Finding Study in Rats [Vol. 1.15; B-2400 and Vol. 1.16; B-2612]	L-748,731-000R014 L-748,731-000R015
TT #95-055-0	Jan. 18, 1996	B-11: L748,731, Ibuprofen: Exploratory fifteen-Day Cyclooxygenase Inhibition Study in Female Rats [Vol. 1.17; p. B-3018]	L-748,731-000R009
TT #95-615-0	Sept. 28, 1995	B-13: L-752,860 and L-748,731: Exploratory Sixteen-Day Oral Toxicity Study in Rats [Vol. 1.17; p. B-3102]	L-748,731-000R014 L-752.860-000R005
TT #95-045-0	Nov. 25, 1996	B-14: L-748,731: Fifty-Three-Week Oral Toxicity Study in Rats with a 27-Week Interim Necropsy: Final Report [Vol. 1.17; B-3209; Vol. 1.18 B-3420, Vol. 1.19; p, B-3765]	L-748,731-000R014
TT #96-090-0	Mar. 16, 1996	B-15: L-748,731: Fifty-Three-Week Oral Gastrointestinal Toxicity Study in Rats [Vol. 1.19; p, B-3870]	L-748,731-000R014
TT #95-075-0,-1	Apr. 29, 1996	B-19: L-748,731: Fifteen-Day Intravenous Toxicity Study in Dogs [Vol. 1.20; p. B-4477 and Vol. 1.21; p. B-4577]	L-748,731-000R014
Mouse Study			
TT #95-610-0	Oct. 27, 1995	B-16: L-748,731: Fourteen-Week Oral Range-Finding Study in Mice [Vol. 1.19; p. B-3987]	L-748,731-000R014
CARGINOGENICITY STUDIES			
Rat Study			
TT #95-076-0	Jul. 27, 1998	E-1: One-Hundred-Six-Week Oral Carcinogenicity Study in Rats [Vol. 1.35: p. E-37 and Vol. 1.36; p. E-399]	L-748,731-000R015 and L-748,731-000R027
Mouse Studies			
TT #96-603-0, -1	Jul. 23, 1998	E-3: One-Hundred-Six-Week Oral Carcinogenicity Study in Mice [Vol. 1.37: p. E-705 and Vol. 1.38; p. E-1132]	748,731-000R027
TT #96-605-0, -1	Jul. 23, 1998	E-5: One-Hundred-Four-Week Oral Carcinogenicity Study in Mice [Vol. 1.37: p. E-1464 and Vol. 1.38; p. E-1132]	748,731-000R032
TOXICOKINETIC STUDIES			
Single Dose Studies			
Mouse Study			
TT#95-617-0	Oct. 16, 1995	A-2: L-748,731: Single Dose Oral Toxicokinetic Study in Mice [Vol. 1.7; p. A-34]	L-748,731-000R14

Report No.	Report Date	Study Title	Test Material Lot
Rat Studies			
TT #95-027-0	Sept. 14, 1995	A-3: L-748,731: Single Dose Oral Toxicokinetic Study in Rats [Vol. 1.7; p. A-79]	L-748,731-000R009
TT #96-025-0	Nov. 26, 1997	A:-4 L-748,731: Single Dose Oral Toxicokinetic Study in Rats [Vol. 1.7; p. A-132]	L-748,731-000R027
Repeat Dose Studies			
Mouse studies			
TT #95-611-0	Oct. 27, 1995	B-17: L-748,731: Five-Week Oral Toxicokinetic Study in Mice [Vol. 1.20; p.B-4170]	L-748,731-000R014
TT #96-604-0	Jan. 9, 1997	E-4: L-748,731: Twenty-Seven-Week Oral Toxicokinetic Study in Mice [Vol. 1.38; p. E-1381]	L-748,731-000R027
TT #96-606-0	Jan. 9, 1997	E-6: L-748,731: Twenty-Seven-Week Oral Toxicokinetic Study in Mice [Vol. 1.38; p. E-1381]	L-748,731-000R032
Rat studies			
TT #95-022-0	Oct. 30, 1995	B-9: L-748,731: Sixteen-Day Oral Toxicokinetic Study in Male Rats [Vol. 1.16; p. B-2863]	L-748,731-000R015
TT #95-076-1	Nov. 12, 1996	E-2: L-748,731: Twenty-Seven-Week Oral Toxicokinetic Study in Rats [Vol. 1.36; p. E-613]	
TT # 95-022-1	Nov. 30, 1995	B-10: L-748,731: Sixteen-Day Oral Toxicokinetic Study in Female Rats [Vol. 1.16; p. B-2940]	L-748,731-000R015
TT #95-709-0 TT #95-709-1 TT #95-709-2	Oct. 13 1995	C-18: L748,731: Oral Toxicokinetic Study in Pregnant and Nonpregnant Rats [Vol. 1.29; p. C-2627]	L-748,731-000R009
TT #96-712-0	Oct. 14, 1996	C-19: L-748,731: Oral Toxicokinetic Study in Lactating Rats [Vol. 1.30; p. C-2738]	L-748,731-000R027
Rabbit studies			
TT #95-722-1,-1	Dec. 28, 1995	C-4: L-748,731: Oral Toxicokinetic Study in Pregnant and Nonpregnant Rabbits [Vol. 1.23; p. C-337]	L-748,731-000R009
PHARMACOKINETIC STUDIES			
TT #93-281-0,-2 Gene-Tox TT #93-8980	Memo Dec. 9, 1993	B-24: Exploratory Enzyme Induction Study in Rats of L-748,731, a COX-2 Inhibitor submitted by D. Patrick [Vol. 1.21; B-4935]	Not provided
-	-	G-1: Absorption, Distribution, Metabolism, and Excretion of L-748,731 in Rats and Dogs [Vol. 1.45; p. G-60]	
-	April 2, 1996	G-2: Dose-Dependence of MK-0966 Pharmacokinetics in Rats and Dogs [Vol. 1.45; p. G-152]	
-	April 1, 1996	G-3: Absorption, Distribution, Metabolism and Excretion of L-755,190 in Rats and Dogs [Vol. 1.45; G-190]	[^{14}C]L-755,190-001K001
-	March 2, 1998	G-4: Mechanistic Studies on the Metabolism of MK-0966 in the Rat. Investigations with Oxygen-18-Labeled Probes [Vol. 1.45; G-237]	[$^{18}O_2$]L-748,731-003X001 [$^{18}O_1$]L-755,190-002M001
-	Nov. 1, 1997	G-6: Biliary Excretion of MK-0966 in Rats Following Administration of [^{14}C]MK-0966 at 2 mg/kg/ I.V. or 5 mg/kg/P.O. and Identification of Two Biliary Metabolites [Vol. 1.45; p. G-330]	[^{14}C]L-748,731-002V001
-	Jan. 29, 1998	G-7: Biliary Excretion of L-755,190 in Rats Following Administration of [^{14}C]L-755,190 at 2m/kg I.V. or 5 mg/kg P.O. [Vol. 1.45; p. G-348]	[^{14}C]L-755,190-001K002 and 3
-	Nov. 11, 1997	G-8: Biliary Excretion in Dogs Following Administration of [^{14}C]L-748,731 at 2m/kg I.V. or 5 mg/kg P.O. [Vol. 1.45; p. G-362]	[^{14}C]L-748,731-002V001, 002, and 008
-	Oct. 26, 1997	G-9: The Effect of Food on the Absorption Kinetics of MK-0966 in Dogs Following Oral Administration [Vol. 1.45; p. G-377]	L-748,731-000R009
-	March 12, 1998	G-10: The Effect of Bile Flow on the Recirculation of MK-0966 and L-755,190 in Rats Following Intravenous [2mg/kg] and oral [5 mg/kg] Administration of [^{14}C]MK-0966 [Vol. 1.45; p. G-388]	[^{14}C]L-748,731-002V008

Report No.	Report Date	Study Title	Test Material Lot
-	Dec. 16, 1997	G-11: The Effect of Bile Flow on the Recirculation of MK-0966 and L-755,190 in Rats Following Intravenous [2mg/kg] and oral [5 mg/kg] Administration of [^{14}C]L-755,190 [Vol. 1.45; p. G-388]	[^{14}C]L-755,190-001K001, 002, and 003
-	July 14, 1995	G-12: Tissue Distribution of Radioactivity Following a Single Intravenous Dose of [^{14}C]L-748,731 in Male Rats [Vol. 1.46; p. G-462	Not provided
-	Oct. 15, 1997	G-14: Distribution of MK-0966 and Its Metabolite L-755,190 in the Gastrointestinal Tract of the Rat One Hour After Oral Doses of [^{14}C]MK-0966 or [^{14}C]L-755,190 [Vol. 1.46; p. G-570]	[^{14}C]L-748,731-002V002 [^{14}C]L-755,190-001K001
-	Oct. 19, 1997	G-15: Distribution of MK-0966 and Its Metabolite L-55,190 in the Gastrointestinal Tract of the Rat 1, 4, and 6 Hours After Oral Doses of [^{14}C]MK-0966 or [^{14}C]L-755,190 at 5 mg/kg [Vol. 1.46; p. G-582]	[^{14}C]L-748,731-002V007 [^{14}C]L-755,190-001K002
-	Dec. 15, 1997	G-17: An In Vitro Plasma Protein Binding Displacement Interaction Study With [^{14}C]MK-0966 and [^{14}C]Salicylic Acid [Vol. 1.46; G-604]	[^{14}C]L-748,731-002V008
-	Nov. 5, 1997	G-20: Isolation and Identification of L-755,190 and Its ~~Glucuronide~~ Conjugate in the Urine of Rats Dosed Intravenously with [^{14}C]MK-0966 at 2 mg/kg [Vol. 1.46; G-622]	[^{14}C]L-748,731-002V002
-	Dec. 2, 1997	G-21: Metabolite Profiles of Urine From Mice and Rats Following Oral Administration of [^{14}C]MK-0966 at 100 mg/kg [Vol. 1.46; p. G-638]	[^{14}C]L-748,731-002V007
-	Dec. 6, 1997	G-22: Identification of the 3',4'-Dihydrodiol and 4'-Phenol Sulfate Metabolites of MK-0966 in Urine of Rats Dosed Orally with MK-0966 (100 mg/kg) [Vol. 1.46; p. G-652]	L-748,731-000R009
-	Nov. 12, 1997	G-23: Isolation and Identification of *trans*-Dihydro-MK-0966 Lactone, a Metabolite of MK-0966, From Unite of Dogs Following Intravenous Administration of [^{14}C]MK-0966 at 2 mg/kg. [Vol. 1.46: p. G-655]	[^{14}C]L-748,731-002V008
-	Dec. 2, 1997	G-26: Metabolite Profiles of Plasma and Urine From Mice Following Oral Administration of [^{14}C]MK-0966 at 5 mg/kg/ and of Plasma from Rats After Intravenous (2mg/kg/) or Oral (5 mg/kg) Administration of [^{14}C]MK-0966 [Vol. 1.46; p. G-761]	[^{14}C]L-748,731-002V002
-	Oct. 12, 1997	G-27: In Situ Metabolism of [^{14}C]L-755,190, a Metabolite of MK-0966, in the Rat Isolated Intestinal Segment Model [Vol. 1.46; p. G-773]	[^{14}C]L-755,190-001K001
-	Nov. 4, 1997	G-28: Identification of L-755,190 as the Major Metabolite of MK-0966 in Incubations with Liver Microsomal Preparations From Phenobarbital-Pretreated Rats [Vol. 1.46; p. G-806]	[^{14}C]L-748,731-002V001
-	Feb. 4, 1998	G-29: The Metabolism of MK-0966 by Liver Subcellular Fractions From Human, Monkey, Dog and Rat [Vol. 1.46; p. G-816]	L-748,731-000R009
-	Nov. 4, 1997	G-30: Reductive Metabolism of MK-0966 by Human Liver Cytosol [Vol. 1.46; p. G-827]	L-748,731-000R009
-	Oct. 10, 1997	G-31: The Cytochrome P-450 Mediated Oxidation of MK-0966 to L-755,190 by Human Liver Microsomes [Vol. 1.46; p. G-851]	L-748,731-000R009
-	Feb. 2, 1998	G-32; Non-Cytochrome P-450-Mediated Oxidation of MK-0966 to L-755,190 by Hepatic Subcellular Fractions [Vol. 1.46; p. G-870]	L-748,731-000R009
-	Nov. 21, 1997	G-33: Kinetics of the In Vitro Metabolism of MK-0966 by Human Liver S9 and Cytosolic Fractions [Vol. 1.46; p. G-881]	L-748,731-000R009 L-755,190-000H007
-	Oct. 13, 1997	G-34: Effects of Cimetidine and Ketoconazole on the In Vitro Metabolism of MK-0966 by Human Liver Microsomes, S9 Fractions and Cytosol [Vol. 1.46; G-901]	L-748,731-000R009

Report No.	Report Date	Study Title	Test Material Lot
-	Sept. 22, 1997	G-35: Evaluation of MK-0966 as an Inhibitor of Human Liver Microsomal Cytochrome P-450 Activity [Vol. 1.46; p. G-913]	L-748,731-000R009
TT # 93-283-0, -5 Gene Tox TT #93-8988	Dec. 10, 1993 Memo	Q-2: Exploratory Enzyme Induction Study in Rats of L-748,731, a COX-2 Inhibitor [Vol. 1.49; p. Q-57]	Not provided
TT #94-253-0, -2 GeneTox TT #94-8905	Nov. 14, 1994	Q-4: Exploratory Enzyme Induction Study in Rats of L-748,731, a Cox 2 Inhibitor [Vol. 1.49; Q-70]	Not provided
TT #93-283 -0,-5	Jan. 30, 1995 Memo	Q-12: Western and Northern Blots from Exploratory Enzyme Induction Study in Mice [Vol. 1.51; p. Q-1009]	Not provided
TT #93-281-0, -2	Jan. 30, 1995 Memo	Q-14: Western and Northern Blots from Exploratory Enzyme Induction Study in Rats [Vol. 1.51; p. Q-1009]	Not provided
TT #98-049-0	July 17, 1998	Q-6: MK-0966: Sixteen-Day Oral Toxicokinetic Study Dogs [Vol. 1.49; Q-129]	L-748,731-000R069
TT #93-281-0, -2	Nov. 22, 1994 Memo	Q-13: Characterization of P-450 Activities in Microsomal Samples Using Testosterone Hydroxylation Assay	Not provided
DMPK Report No. 97015	April 1, 1997 Memorandum	C-139: CNS Penetration of MK-966 [L-748,731] in the Rat [Vol. 1.3]	L-748,731-000R002
GENOTOXICITY STUDIES			
***In Vitro* Studies**			
TT #94-8024 TT #91-8026	Aug. 12, 1994	D-1: L-748,731: Microbial Mutagenesis Assay [Vol. 1.32; p. D-39]	L-748,731-000R009
TT #94-8209 TT #94-8220 TT #94-8221	Aug. 16, 1994	D-2: L-748,731: *In Vitro* Alkaline Elution/Rat Hepatocyte Assay [Vol. 1.32; D-103]	L-748,731-000R009
TT #94-8626 TT #94-8627	Aug. 1, 1994	D-5: L-748,731: Assay for Chromosomal Aberrations *In Vitro*, in Chinese Hamster Ovary Cells [Vol. 1.32; D-257]	L-748,731-000R009
TT #96-9604	May 29, 1996	D-6: L-748,731: Assay for Chromosomal Aberrations *In Vitro*, in Chinese Hamster Ovary Cells [Vol. 1.32; D-327]	L-748,731-000R009
TT #95-8510 TT #95-8506 TT #95-8501 TT #95-8503	Aug. 9, 1996	D-8: L-748,731: V-79 Mammalian Cell Mutagenesis Assay [Vol. 1.33; p. D-484]	L-748,731-000R009
***In Vivo* Studies**			
TT #94-8222	Sept. 20, 1994	D-3: L-748,731: In Vivo Alkaline Elution/Rat Liver DNA Damage Assay in Male Rats [Vol. 1.32; D-171]	L-748,731-000R009
TT #94-8223	Sept. 16, 1994	D-4: L-748,731: In Vivo Alkaline Elution/Rat Liver DNA Damage Assay in Female Rats [Vol. 1.32; D-214]	L-748,731-000R009
TT #96-8614 TT #96-8624	Dec. 9, 1996	D-7: MK-0966: Assay for Chromosomal Aberrations *In Vivo*, in Mouse Bone Marrow [Vol. 1.33; D-403]	L-748,731-000R027
REPRODUCTIVE TOXICOLOGY STUDIES			
Rabbit Studies			
TT #94-737-6	Jan. 4, 1995	C-1: L-748731: Oral Range-Finding Study in Non-Pregnant Rabbits [Vol. 1.23; p. C-142]	L-748,731-000R009
TT# 94-737-5	Feb. 24, 1995	C-2: L-748731: Oral Range-Finding Study in Pregnant Rabbits [Vol. 1.23; p. C-183]	L-748,731-000R009
TT #95-704-0	July 18, 1995	C-3: L-748,731: Oral Developmental Toxicity Study in Rabbits [Vol. 1.23; p. C-269]	L-748,731-000R009
Rat Studies			
TT #94-733-5	Feb. 15, 1995	C-5: L-748731: Oral Range-Finding Reproduction Study in Rats [Vol. 1.24; p. C-396]	L-748,731-000R009
TT #94-733-0	April 19, 1995	C-6: L-748,731: Oral Developmental Toxicity Study in Rats [Vol. 1.24; p. C-597 and Vol. 1.25; p. C-806]	L-748,731-000R009
TT #95-705-0	June 30, 1995	C-7: L-748,731: Oral Fertility Study in Female Rats [Vol. 1.25; p. 860]	L-748,731-000R009
TT #92-721-0	Mar 8, 1996	C-8: L-748,731: Oral Fertility Study in Female Rats with a Recovery Period [Vol. 1.25; p. 860]	L-748,731-000R009

Report No.	Report Date	Study Title	Test Material Lot
TT #95-715-0	Oct. 11, 1995	C-9: L-748,731: Oral Ovulation/Fertilization Study in Female Rats [Vol. 1. 26; p. C-1214	L-748,731-000R009
TT #95-716-0	Oct. 11, 1995	C-10: L-748,731: Oral Implantation Study in Rats [Vol. 1.26; p. C-1270]	L-748,731-000R009
TT #95-742-0	Dec. 22, 1995	C-11: L-748,731: Oral Estrous Cyclicity/Ovulation/ Fertilization Study in Female Rats [Vol. 1.26;p. C-1316]	L-748,731-000R014
TT #95-739-0	May 20, 1996	C-12: L-748,731: Oral Fertility Study in Female Rats with Gestation Days 15 and 21 Laparotomies [Vol. 1.26; p. C-1379]	L-748,731-000R009
TT #95-730-0	Jan. 22, 1996	C-13: L-748,731 Fostering/Cross-Fostering Study in Rats [Vol. 1.26; p. C-1437 and Vol. 1.27; p. C-1590]	L-748,731-000R009
TT #96-719-0	Oct. 22, 1996	C-14: L-748,731:Oral Length of Gestation and Parturition Study in Female Rats [Vol. 1.27; p. C-1682]	MK-0966-000R027
TT #96-718-0	Nov. 5, 1996	C-15: MK-0966: Oral Study in Rats to Assess Effects on Fetal Ductus Arteriosus [Vol. 1.27; p. C-1900]	L-748,731-000R027
TT #95-706-5	Jun 13, 1995	C-16: L-748,731: Oral Range-Finding Late Gestation and Lactation Study in Rats [Vol. 1.28; p. C-1937]	L-748,731-000R014
TT #95-706-0	Oct. 14, 1996	C-17: L-748,731: Oral Late Gestation and Lactation Study in Rats with Postweaning Evaluation [Vol. 1.28; p. C-2084; Vol. 1.29; p. C-2318]	L-748,731-000R009
TT #95-734-0	Jun. 6, 1996	C-20: L-748,731: Oral Fertility Study in Male Rats [Vol. 1.30; p. C-2786]	L-748,731-000R009
LOCAL TOLERANCE STUDIES			
TT #95-2701	Dec. 27, 1995	H-1: L-748,731: Exploratory Dermal Irritation Study in Rabbits [Vol. 1.47; p. H-12]	L-748,731-000R025
TT #95-4272	Oct. 26, 1995	H-2: Effect of L-748,731 in the Bovine Corneal Opacity and Permeability [BCOP] Assay [Vol. 1.47; p. H-23]	L-748,731-000R025
TT #-95-4273	Dec. 28, 1995	H-3: L-748,731: Exploratory Primary Eye Irritation Study in Rabbits [Vol. 1.47; p. H-52]	L-748,731-000R025
SPECIAL TOXICOLOGY STUDIES			
TT #95-2691	March 31, 1996	Q-1: L-748,731: Acute Oral Phototoxicity Study in Mice [Vol. 1. 49; Q-41]	L-748,731-000R009
TT #95-078-0	April 1,1996	Q-5: L-748,706; L-755,190; Ibuprofen: Exploratory 15-Day Cyclooxygenase Inhibition Study in Female Rats [Vol. 1.49; p. Q-76]	L-755,190-000H007
TT #95-056-0	March 6, 1996	Q-7: L-755,190; Five-Week Oral Toxicity Study in Rats [Vol. 1.49; p. Q-167]	L-755,190-000H007
TT #95-070-0	March 4, 1996	Q-8: L-755,190: Fifteen-Day Intravenous Toxicity Study in Rats [Vol. 1:50; p. Q-472]	L-755,190-000H007
TT #95-073-0	March 15, 1996	Q-9: L-755, 190: Sixteen-Day Intravenous Toxicity Study in Dogs [Vol. 1.50; Q-608]	L-755,190-000H007

Studies not reviewed within this submission

Report No.	Report Date	Study Title
TT # 95-022-1	Nov. 30, 1995	L-748,731: Sixteen-Day Oral Toxicokinetic Study in Female Rats [Vol. 1.16; p. B-2940]
-	Jan. 29, 1998	G-5: A Repeat Study of the Excretion of Radioactivity in the Urine and Feces of Rats Following Oral Administration of [^{14}C]MK-0966 (5mg/kg)[Vol. 1.45; p. G-322][a]
-	April 18, 1997	G-24: An Open, Oral, Single-Dose, 4-Period Study in Healthy Subjects to Investigate the Absorption, Metabolism, Excretion and Mass Balance of [^{14}C]MK-0966 in Solution (Protocol 0120 [Vol. 1.46; p. G-679]
-	Nov. 5, 1997	G-25: Isolation and Identification of Metabolites in Urine of a Human Subject Following Oral Administration of MK-0966 at 250 mg [Vol. 1.46; p. G-750]
-	May 14, 1998	F-30: Ancillary Pharmacology: Effects of Celecoxib, a Cyclooxygenase II[COX-2] Inhibitor, on Renal Function and Electrolyte Excretion in Conscious Dogs [Vol. 1.43; F-518][b]
TT #94-045-0	Feb. 8, 1995	B-20: L-748,706: Fourteen-Week Oral Toxicity Study in Dogs [Vol. 1.21; B-4645]

Report No.	Report Date	Study Title
TT #95-069-0	Feb. 26, 1996	B-12: L-748,731: Exploratory Fifteen-Day Cyclooxygenase Inhibition Study in Female Rats. [Vol. 1.17; B-3066]
TT #95-735-5	April 1, 1996	C-22: Aspirin and Indomethacin: Exploratory Oral Study in Rats to Assess Effects on Fetal Ductus Arteriosus [Vol. 1.30; p. C-2857]
TT #97-082-0	Dec. 23, 1997	Q-10: L-791,398: Exploratory Single-Dose Oral Toxicokinetic Study in Dogs [Vol. 1.51; Q-828]
TT #97-098-0	Dec. 19, 1997	Q-11: L-791,398: Exploratory 16-Day Oral Toxicity Study in Rats [Vol. 1.51; Q-863]
TT #94-253-0, -2	Jan. 30, 1995	Q-15: Western Blots from Exploratory Enzyme Induction Study in Rats of L-748,731[c]

[a]Results of this study are discussed in review of study entitled "Absorption, Distribution, Metabolism, and Excretion of L-748,731 in Rats and Dogs"
[b]Sponsor's conclusion – Oral celecoxib at 10 mg/kg decreased urine output and Na excretion in 4/5 conscious female dogs, but did not significantly alter GFR, effective renal plasma flow, or filtration fraction.
[c]Results of this study are discussed in conjunction with review of Study TT #93-281-0,-2; Western and Northern Blots from Exploratory Enzyme Induction Study in Rats.

Disclaimer (Use of sponsor's material): Sponsor submitted information was utilized in the preparation of this review.

Introduction/Drug History: Cyclooxygenase [COX] or prostaglandin H_2 synthase catalyzes the conversion of arachidonic acid to prostaglandin H_2 [PGH_2]. Subsequently, PGH2 serves as the substrate for a number of enzymes involved in the generation of eicosanoids [e.g. PGE_2, PGD_2, $PGF_{2\alpha}$, PGI2, and thromboxane A_2]. The determinant for which end product is formed is, in part, dependent on the specific enzymes present within a given cell type. The eicosanoids play a regulatory role in a number of physiological and pathophysiological processes including renal function, immune function, inflammation, pain, female reproduction, blood vessel tone, and integrative function in the brain.

Two isoforms of the COX enzyme have been identified. Overall, the two isoforms demonstrate a number of structural and biochemical similarities. However, there are several dissimilarities that help explain the apparent functional differences. COX-1 and COX-2 are products of separate genes with 63% sequence homology. COX-2 is able to utilize a larger number of fatty acid substrates than COX-1. However, one of the major differences between these isoforms is in their regulation and expression. COX-1 is constitutively expressed in most normal tissues and appears to be involved in regulation of homeostatic or "housekeeping" functions. COX-2, however, is primarily an inducible enzyme with constitutive expression in a limited number of tissues including the brain, pancreas, and kidney. COX-2 expression is upregulated in response to a number of bioactive endogenous and exogenous molecules such as cytokines [e.g. interleukin-1 and tumor necrosis factor$_\alpha$] and lipopolysaccharide. The role of COX-2 in both physiological and disease states has not been fully delineated. However, it is generally accepted that COX-2 activity is associated with the inflammatory response and neutrotransmission involved in the pain response.

The "COX-2 hypothesis" suggests that inhibition of the activity of this isoform will reduce inflammation and ameliorate pain secondary to a number of processes without the adverse effects [e.g. gastrointestinal ulceration, renal toxicity] of non-specific COX inhibition. This is the basis for the development of rofecoxib, a selective COX-2 inhibitor, for the treatment of inflammation associated with osteoarthritis and acute pain.

1. Pharmacology:

The following studies were submitted in a report entitled "Pharmacological studies of L-748,731" [Vol. 1.42; p. F-227] and were compiled at the Merck Frost Centre for Therapeutic Research in Quebec, Canada. The initial Pharmacology/Toxicology Reviewer, Dr. Will Coulter, reviewed the majority of these studies. Additional comments by the current Pharmacology/Toxicology are in italics.

1.1 PHARMACOLOGICAL STUDIES OF L-748,731 – *In Vitro Studies*

1.1.1 *IN VITRO* STUDIES OF L-748,731

1) Effects of L-748,731 in Whole Cell Cyclooxygenase Assays [Vol. 1.42; p. F-241]:

The results of the effects of indomethacin and L-748,731 on PGE_2 synthesis by human histiocytic lymphoma U-937 cells (express only COX-1) and by human osteosarcoma 143 cells (express only COX-2) in response to 10 μM arachidonic acid are indicated in the following table [p. F-245].

	IC_{50} (nM)	
	U-937 Cells (COX-1)	Osteosarcoma Cells (COX-2)
Indomethacin	10 (n=3)*	20 (n=4)
L-748,731	>50,000 (n=4)	26 ± 10 (n=5) <10 (n=1)

* Tests were done in triplicate at 3-6 concentrations, with n equal to the number of times the compound was tested.

In this assay, L-748,731 was approximately 1000X more potent as an inhibitor of COX-2 compared to COX-1.

2) Effects of L-748,731 in Human and Dog Kidney Microsomal Cyclooxygenase Assays [Vol. 1.42; p. F-246]

The effects of indomethacin and L-748,731 on PGE_2 synthesis by human, dog, and rat kidney microsomal preparations in response to arachidonate are shown below [p. F-249].

	IC_{50} (μM)		
	Human	Dog	Rat
Indomethacin	0.30 (n=8)*	0.25 (n=2)	0.32 (n=3)
L-748,731	14 (n=4)	> 30 (n=2)	> 30 (n=3)

* Tests were done in duplicate at 4-9 concentrations, with n equal the number of times the drugs were tested.

IC_{50} values were higher in rats and dogs than in humans. A maximum inhibition of approximately 70-90% was observed in the human microsomal preparations. However, it appears from the information presented that there was minimal to no inhibition seen in dog or rats at the highest concentrations used.

3) Effects of L-748,731 on Cyclooxygenase Activity of U-937 Cell Microsomes [Vol. 1.42; p. F-249]

When the cyclooxygenase assay was carried out with U-937 cell microsomes, which express COX-1 selectively, and 0.1 μM arachidonic acid, L-748,731 inhibited the production of PGE_2 ($IC_{50} \approx$ 7 μM), but was less potent than indomethacin ($IC_{50} \approx 30$ nM). These results are in fair agreement with the results above in 1 using 10 μM arachidonic acid.

4) Studies of Kinetic Mechanism of COX Inhibition by L-748,731 [Vol. 1.42; p. F-251]

The results of kinetic mechanism studies of L-748,731 on the purified and microsomal recombinant hCOX-1 and hCOX-2 indicated a two step mechanism *["a rapidly reversible binding of enzyme followed by a slow isomerization to a tightly bound inhibited complex [which is]...only very slowly reversible"]* was involved in microsomal hCOX-2 inhibition, with a K_i = 6 nM. On the other hand, a weak and rapid*ly* reversible inhibition of hCOX-1 ($IC_{50} \approx 15$ μM) was determined.

5) Effect of L-748,731 or Indomethacin on Human Platelet Aggregation [Vol. 1.42; p. F-268]:

No effect was seen at 10 μM on the rate of collagen, ADP, or U-46619 (a thromboxane mimetic) induced aggregation of human gel-filtered platelets. The nonspecific cyclooxygenase inhibitor, indomethacin, at 10 μM inhibited the rate of platelet aggregation by 28% in the presence of collagen activation, but not in the presence of ADP or U-46619. Collagen induced aggregation was said to proceed by a cyclooxygenase dependent pathway. *The level of inhibition with indomethacin was low. It would have provided additional insight if a dose response for both compounds had been conducted.*

6) Effect of L-748,731 in Lipopolysaccharide (LPS)-Induced Human Whole Blood PGE_2 and Serum TXB_2 Assays [Vol. 1.42; p. F-270]

Since normal human blood does not contain COX-2, L-748,731 would not show an effect on PGE_2 production. However, COX-2 was induced after incubation with LPS. A concentration dependent inhibition of PGE_2 synthesis was then seen in human whole blood with L-748,731 (IC_{50} = 0.59 μM) or with indomethacin (IC_{50} = 0.50 μM).

Platelets contain large amounts of COX-1 and are activated during blood clotting. During this clotting, thromboxane A_2 (TXA_2) is generated. This was assayed by measuring its stable metabolite, TXB_2. Both indomethacin (IC_{50} = 0.16 μM) and L-748,731 (IC_{50} = 13.12 μM) produced a concentration dependent inhibition of TXB_2 *with a maximum inhibition of 90% and 64%, respectively.*

In this assay, L-748,731 is approximately 20X more selective as an inhibitor of COX-2 compared to COX-1.

7) Effect of L-748,731 on LPS Induced PGE_2 Generation by Human and Rat Mononuclear Cells [Vol. 1.42; p. F-275]:

There was no significant difference between the inhibition of LPS induced PGE_2 synthesis with L-748,731 (IC_{50} = 29 μM) or indomethacin (IC_{50} = 26 μM) in human mononuclear cells. In rat mononuclear cells the IC_{50} values were 23 nM (L-748,731) and 87 nM (indomethacin).

8) Effects of L-748,731 on Arachidonic Acid (AA) Induced PGE_2 Production in LPS Stimulated Dog Blood [Vol. 1.42; p. F-280]

L-748,731 produced a dose related inhibition of PGE_2 (AA induced) in LPS stimulated dog whole blood. At 62 μM a 62% inhibition was seen (IC_{50} = 10.8 μM). Diclofenac also produced a dose related inhibition which was >90% at 3 μM (IC_{50} = 0.14 μM)

1.1.2 MISCELLANEOUS SPECIFICITY STUDIES:

1) Effect of L-748,731 on LTB_4 Biosynthesis by Isolated PMNs [Vol. 1.42; p. F-283]:

This system is a "cell-based assay" used for assessment of leukotriene biosynthesis. L-748,731 (0.31 to 25 μM) was said to have no significant effect [*0-30%*] on the inhibition of LTB_4 derived from polymorphonuclear leukocytes (PMN) that were challenged with A23187. A23187 is a divalent calcium ionophore that stimulates PMN production of LTB_4.

2) Studies of L-748,731 on 15-Lipoxygenase Activity [Vol. 1.42; p. F-285]

Minor inhibition [*0 and 18% in 2 experiments*] was said to be produced by 20 μM L-748,731 [*0.7 –20 μM*] on 15-lipoxygenase derived from human leukocytes. *The positive control resulted in 90% inhibition at 20 μM.* This enzyme oxidizes arachidonic acid to 15-HETE. The IC_{50} was >20 μM.

3) Effect of L-748,731 on TXB_2 and 12-HETE Production by Calcium Ionophore Activated Human Platelets [Vol 1.42; p. F-286]

These synthetic pathways involve the activity of 12-lipooxyegenase or COX-1 and thromboxane synthase. No significant reduction (<15%) of the release of TXB_2 and 12-HETE occurred when human platelets were activated by the calcium ionophore A23187 *in the presence of L-748,731[1, 5, and 20 μM]. The IC_{50} was >20 μM.*

4) Studies of L-748,731 on LTD_4, LTB_4, and CB_2 Receptors [Vol. 1.42; p. F-288]

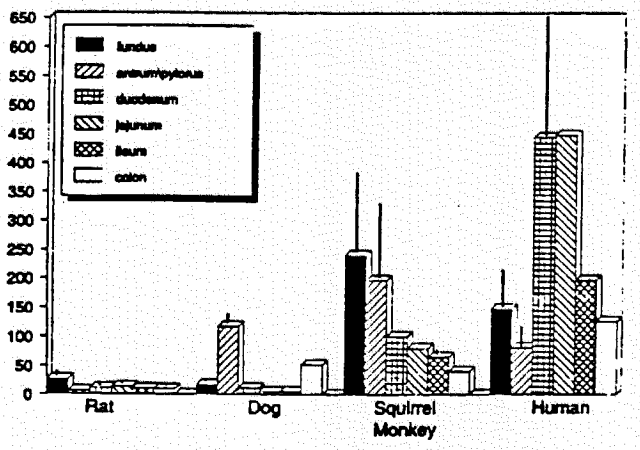
L-748,731 was inactive as a competing ligand at the LTD_4, LTB_4, and CB_2 receptors.

1.1.3 IDENTIFICATION OF COX-1 [PGHS] IN GASTROINTESTINAL TRACT

1) Expression of COX-1 in the GI Tract of Rat, Dog, Squirrel Monkey, and Human [Vol. 1.42; F-311]:

This study quantitated the levels of prostaglandin G/H synthase-1 (PGHS-1) in several species, including humans. The results are shown in the following figure (p. F-314).

Expression of PGHS-1 in the GI tract
(ng/mg microsomal protein)



There was considerable variability in the pattern of COX-1 distribution in the various species evaluated. The rank order of COX-1 levels throughout the GI tract was generally humans>monkey>dog>rat. The COX-1 levels in the stomachs of the squirrel monkey, however, were greater than that observed in humans. The Sponsor suggests that there "appear[s] to be an inverse relationship between levels of PGHS-1 protein observed and the sites within the gastrointestinal tract where ulceration is commonly observed".

1.1.4 Receptor Binding Specificity

1) Specificity of Action (Panlabs) of L-748,731 [Vol. 1.42; p. F-351]

L-748,731 was submitted to [redacted] to evaluate for any undetected receptor binding [*up to 10 μM*] and enzyme assays [up to *300 μM*] in their [redacted] Significant activity was not seen in the binding of 28 radiolabeled ligands to their respective receptors or in the inhibitory activity of 5-lipoxygenase, 15-lipoxygenase, lipid peroxidase, phospholipase A_2, and protein kinase C, calpain, and EGF tyrosine kinase enzymes.

The following studies were submitted in a report entitled "Additional In Vitro Biochemical Studies of MK-0966" [Vol. 1.42; p. F-356]] and were conducted at the Merck Frosst Centre for Therapeutic Research in Quebec, Canada. The current Pharmacology/Toxicology Reviewer reviewed the following studies. A signed QA statement was provided.