CENTER FOR DRUG EVALUATION AND RESEARCH

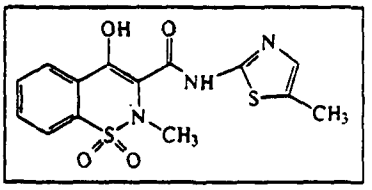
APPLICATION NUMBER: **20-938**

PHARMACOLOGY REVIEW(S)

DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMOLOGIC DRUG PRODUCTS
PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA	**20-938**
DRUG:	**Mobic™ (Meloxicam)**
CODE NAME:	**UH AC 62XX**
SPONSOR:	Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd. Ridgefield, CT 06877
SUBMISSION DATE:	December 15, 1998
TYPE OF SUBMISSION:	Original [505 (b) (1)]
DATE COMPLETED:	September 17, 1999
REVIEWER:	W. C. Josie Yang, Ph.D.
INFORMATION TO SPONSOR:	Yes
CDER STAMP DATE:	December 16, 1998
DATE RECEIVED IN HFD-550:	December 17, 1998
DATE ASSIGNED TO REVIEWER:	January 5, 1999
USER FEE GOAL DATE:	February 9, 2000
DRUG CATEGORY:	NSAID
FORMULA:	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide; $C_{14}H_{13}N_3O_4S_2$; MW=351.4; pKa=1.1 and 4.2.

Ingredients	Quantities (mg/tablet)	Function
Meloxicam, USP	7.5	Active Ingredient
Na Citrate Dihydrate, NF		
Lactose Monohydrate, NF		
Microcrystalline Cellulose, NF		
Povidone, USP		
Colloidal Silicon Dioxide, NF		
Croscarmellose, NF		
Mg Stearate, USP		
Total	180.0	



CAS Nº:	71125-38-7
INDICATION:	Signs and Symptoms of OA
DOSAGE FORM:	Oral Tablet, 7.5 mg.
RELATED DRUG/INDs/NDAs/DMFs:	

1. PHARMACOLOGY

1.1. OVERVIEW

Meloxicam (UH-AC 62 XX) is a nonsteroidal anti-inflammatory drug (NSAID) of the enolic acid (oxicam) class. Meloxicam has been developed for the treatment of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other rheumatic indications.

1.2. GENERAL PHARMACOLOGY AND PHARMACODYNAMICS

1.2.1. MECHANISM OF ACTION

The following table presents summarized results from a series of *in vitro* and *in vivo* studies related to the mechanism of action of UH-AC 62 XX.

Species/Model	Route	Parameters Measured	Results
Effects on PGE_2 Production			
Mice Zymosan Peritonitis in Mice (PGE_2)	Oral	PGE_2-content of peritoneal exudate	ID_{50} (mg/kg) UH-AC 62 XX 1.36 Piroxicam 2.62 Diclofenac >16.0 Naproxen 22.86
Rat Carrageenin-Induced Pleurisy (PGE_2)	Oral	PGE_2-content of the pleural exudate	ID_{50} (mg/kg) UH-AC 62 XX 0.65 Piroxicam 0.85 Tenoxicam 1.24 Diclofenac 5.06 Naproxen 14.17 Acetylsalicylic acid >400.00
Rat Cotton Pellet Assay	Oral	PGE_2 in exudate 9 hr after administration of a single dose	ID_{50} = 0.88 mg/kg
Rat Cotton Pellet Assay	Topical	PGE_2 in exudate 8 hr after administration	ID_{50} = 0.94 mg/kg
Rabbit Platelet Poor Plasma PAF Antagonism	*In vitro*	Effect on PAF-induced platelet agglutination	No inhibition at dose of. $1x10^{-6}$ to $1x10^{-4}$ M
Human Synovial Tissue Explants	*In vitro*	Inhibition of prostaglandin biosynthesis	Inhibited at ≥ 0.05 μM
Effects on Cartilage, Macrophages or PMNs			
Human Chondrocytes Explants	*In vitro*	prostaglandin biosynthesis	≥0.5 μg/ml: ↓
Human Articular Chondrocytes			≤5 μg/ml: ↔
Human or Porcine Articular Cartilage	*In vitro*	Synthesis or degradation of proteoglycans	≤100 μM: ↔
Human Synovial Tissue		PGE_2 and IL-1 production	≥0.05 μM: ↓ PGE_2 production by >50% ≤4 μM: ↔ on IL-1 production
PMA or Group A Streptococci Stimulated Human PMNs		Respiratory burst	0.5 μg/ml: ↓ >50%.
TNF, fMLP and PMA Stimulated Human PMNs		Intracellular oxyradical formation	↓ at 50 μM
LPS Stimulated Murine Macrophage Cells (J774)	*In vitro*	Inducible nitric oxide synthase (NOS)	≤ 10 μg/ml: ↔
LPS Stimulated Mouse Macrophage (RAW 264-7) cell line	*In vitro*	Inducible nitric oxide synthase (NOS)	$1x10^{-6}$ to $1x10^{-5}$ M: ↔
Human Umbilical Vein Endothelial Cells (HUVEC)	*In vitro*	Constitutive NOS	≤ 3×10^{-5} M: ↔
Cultured THP-1 cells	*In vitro*	IL-1β and IL-8 production	≤ 30 μM: ↔

Species/Model	Route	Parameters Measured	Results
***In Vitro* Differential Inhibition of COX-1 and COX-2**			
Cyclooxygenase from Bull Seminal Vesicles and Bovine Brain	*In vitro*	Inhibition of PG biosynthesis	EC_{50} (M) Bull Seminal Vesicles / Bovine Brain UH-AC 62 XX: 5.5×10^{-6} / 1.8×10^{-4} Sudoxicam: 7.0×10^{-6} / 1.6×10^{-4} Piroxicam: 2.0×10^{-5} / 5.1×10^{-4} Indomethacin: 3.3×10^{-7} / 1.9×10^{-7} Aminopyrine: 2.4×10^{-3} / 4.3×10^{-3}
Guinea Pig Cultivated Peritoneal Macrophages	*In vitro*	LPS-stimulated PGE generation	IC_{50} (mg/ml) During induction / Post Induction / Ratio UH-AC 62 XX: 1.91×10^{-9} / 4.47×10^{-8} / 23.0 Piroxicam: 1.75×10^{-7} / 1.68×10^{-7} / 1.0 Tenoxicam: 3.22×10^{-7} / 6.81×10^{-7} / 2.1 Tenidap: 4.78×10^{-5} / 1.04×10^{-4} / 5.4 Diclofenac: 1.91×10^{-9} / 3.47×10^{-8} / 5.5 Indomethacin: 6.36×10^{-9} / 1.00×10^{-6} / 0.2
Sheep Placenta Cyclooxygenase	*In vitro*	Inhibition of COX-2	IC_{50} (M) UH-AC 62 XX: 6.03×10^{-4} Piroxicam: 7.48×10^{-5} Tenoxicam: 8.89×10^{-5} Diclofenac: 7.33×10^{-7} Indomethacin: 1.50×10^{-5} Flurbiprofen: 9.93×10^{-7}
Bovine Aortic Endothelial Cells (COX-1) and LPS Stimulated Murine Macrophages (COX-2)	*In vitro*	Inhibition of intracellular COX-1 and COX-2	IC_{50} (μg/ml) COX-1 / COX-2 / COX-2/-1 Ratio UH-AC 62 XX: 0.075 / 0.06 / 0.8 Piroxicam: 0.0008 / 0.2 / 250 Acetylsalicylic acid: 0.3 / 50 / 167 Indomethacin: 0.01 / 0.6 / 67 UH-V 8 XX: 0.0015 / 0.2 / 133
hCOX-1 and hCOX-2 in Transfected COS A.2 Cells, Insect Cells And African Green Monkey Kidney Cells	*In vitro*	Inhibition of intracellular recombinant hCOX-1 & hCOX-2	IC_{50} (μmol/l) - Whole Cell Assay COX-1 / COX-2 UH-AC 62 XX: 2.24 / 0.16 Piroxicam: 2.03 / 0.98 Ibuprofen: 2.26 / 15.72 Naproxen: 0.33 / 7.08 Nimesulide: 1.61 / 0.36 Diclofenac: 0.0026 / 0.001 Indomethacin: 0.019 / 0.030 Acetylsalicylic acid: 4.70 / 16.03 IC_{50} (μmol/l) - Microsomal Assay COX-1 / COX-2 UH-AC 62 XX: 36.6 / 0.49 Ibuprofen: 13.88 / ~80 Naproxen: 2.7 / ~50 Nimesulide: ~50 / 9.4 6-MNA: ≥100 / NA Diclofenac: 0.059 / 0.031 Indomethacin: 0.10 / 0.35
Human Whole Blood Assay	*In vitro*	Relative selectivity for inhibition of COX-1 and COX-2	IC_{50} (μM) COX-1 / COX-2 / COX-2/-1 Ratio UH-AC 62 XX: 3.27 / 0.25 / 0.08 UH-V 8 XX: 0.79 / 0.43 / 0.54 Indomethacin: 0.17 / 0.14 / 0.82 SC-58125: 17.84 / 0.48 / 0.03
Human Whole Blood	*In vitro*	Evaluate the selectivity of NSAIDs for COX-1 & COX-2 activity	UH-AC 62 XX was 10x more selective for COX-2 than ibuprofen, naproxen or indomethacin

1.2.2. PHARMACODYNAMIC EFFECTS RELATING TO THE PROPOSED INDICATIONS

The effects of UH-AC 62 XX on anti-inflammatory, analgesic, anti-pyretic and uricosuric effects were evaluated in various animal models. The following table presents a summary of the pharmacodynamic effects relating to the proposed indication.

Model	Species	Route	Parameters Measured	Findings		
Anti-inflammatory Effects						
Kaolin-Induced Hind Paw Edema	Rat	Oral	Edema following administration of a single dose prior to kaolin		ED_{35} (mg/kg)	
				UH-AC 62 XX	7.0	
				Piroxicam	2.9	
				Sudoxicam	5.1	
				Indomethacin	2.9	
				Diclofenac	4.0	
				Phenylbutazone	49.0	
				Naproxen	6.3	
				Acetylsalicylic acid	331.0	
Carrageenin-Induced Hind Paw	Rat	Oral	Edema following administration of a single dose prior to carrageenin		ED_{35} (mg/kg)	
				UH-AC 62 XX	4.2	
				Piroxicam	1.5	
				Sudoxicam	2.9	
				Indomethacin	2.8	
				Diclofenac	3.5	
				Phenylbutazone	52.0	
				Naproxen	4.5	
				Acetylsalicylic acid	216.0	
Carrageenin-Induced Hind Paw Edema	Rat	Oral	Edema at selected intervals following administration of a single dose prior to carrageenin: comparison of potency based on the AUC		Dose (mg/kg)	AUC/(mg/kg)
				UH-AC 62 XX	4.0	264.0
				Piroxicam	4.0	144.0
				Indomethacin	4.0	84.0
				Naproxen	10.0	44.0
				Diclofenac	4.0	59.0
					8.0	51.0
				Acetylsalicylic acid	100.0	1.4
					200.0	1.6
Ovalbumin-Induced Hind Paw Edema	Rat	Oral	Edema following administration of single dose prior to ovalbumin		Dose (mg/kg)	% Inhibition of Swelling
				UH-AC 62 XX	2.0	7.4
					4.0	14.3
					8.0	8.9
					16.0	4.1
				Indomethacin	2.0	0.5
					4.0	3.7
					8.0	3.5
				Hydrocortisone	20.0	23.4
					40.0	30.9
					80.0	48.2
Granuloma Pouch Assay	Rat	Oral	Exudate volume following 14-day administration		ED_{50} (mg/kg)	
				UH-AC 62 XX	0.5	
				Sudoxicam	2.2	
				Indomethacin	1.0	
				Hydrocortisone	4.2	

Model	Species	Route	Parameters Measured	Findings
Carrageenin-Induced Pleurisy	Rat	Oral	Pleural exudate characteristics and leukocyte migration following a single oral dose administration	Exudate: Dose (mg/kg), Volume (ml); Number of Cells: Cells x10⁶, PMNs x10⁶, MN x10⁶ UH-AC 62 XX: 4.0 / 3.34 / 117.2 / 71.5 / 42.5; 8.0 / 2.98 / 104.7 / 66.5 / 36.2 Piroxicam: 4.0 / 5.20 / 146.4 / 88.2 / 55.1; 8.0 / 4.41 / 140.7 / 85.1 / 48.7; 16.0 / 4.25 / 117.5 / 68.2 / 43.0 Indomethacin: 3.0 / 4.41 / 175.8 / 101.5 / 71.2; 6.0 / 4.82 / 156.3 / 96.7 / 57.0; 12.0 / 4.28 / 156.6 / 96.6 / 55.7 Dexamethasone: 0.1 / 2.30 / 103.9 / 64.8 / 36.7; 0.3 / 1.43 / 83.1 / 53.3 / 28.3
Adjuvant Arthritis	Rat	Oral	Paw swelling following administration of repeated doses	ED_{50} = 0.28mg/kg
Adjuvant Arthritis	Rat	Oral	Body weight, right and left foot volume after administration for 5 days	0.1, 0.25, 0.5 mg/kg: ↓ foot volume significantly
Adjuvant Arthritis	Rat	Oral	Bone and cartilage destruction in hind paws, splenic weight, ESR, and serum protein concentration following repeated administration	ED_{50} (mg/kg): UH-AC 62 XX / Piroxicam / Diclofenac Bone/Cartilage: 0.30 / 1.20 / >1.6 Spleen: 0.16 / 0.40 / >1.6 ESR: 0.20 / 0.62 / >1.6 Albumin: 0.32 / 0.99 / >1.6 A/G Ratio: 0.26 / 0.59 / >1.6
Analgesic Effects				
Thermally-Induced Pain (Hot Plate Test)	Mouse	Oral	Pain threshold following administration of a single dose	ED_{50} (mg/kg): UH-AC 62 XX: >40 Sudoxicam: >100 Indomethacin: >8 Naproxen: >200 Aminopyrine: 280
Mechanically-Induced Pain (Tail-Clamp Test)	Mouse	Oral	Anti-nociceptive effect following administration of a single dose	ED_{50} (mg/kg): UH-AC 62 XX: >40 Sudoxicam: >100 Indomethacin: >20 Naproxen: >200 Aminopyrine: 225
Inflammatory Pain in the Hind Paw (Randall-Selitto Assay)	Rat	Oral	Pain threshold following administration of a single dose and pain threshold at selected intervals following administration of a single dose	ED_{50} (mg/kg) at Selected Interval: 45 min / 90 min UH-AC 62 XX: 7.72 / 6.71 Sudoxicam: 8.11 / 9.23 Piroxicam: 7.05 / 6.35 Diclofenac: 1.93 / 0.85 Indomethacin: 2.50 / 3.06 Phenylbutazone: 61.60 / 41.9 Acetylsalicylic acid: 248.0 / 174.0 Aminopyrine: 80.20 / 80.0

Model	Species	Route	Parameters Measured	Findings	
Anti-pyretic Effects					
Effect on Body Temperature	Rat	Oral	Change in body temperature following administration of a single dose		ED_{50} (mg/kg)
				UH-AC 62 XX	>16.0
				Sudoxicam	>40.0
				Phenylbutazone	242.0
				Paracetamol	19.1
Effect on Yeast Induced Pyrexia	Rat	Oral	Antipyretic effect following administration of a single dose		ED-1°C (mg/kg)
				UH-AC 62 XX	9.0
				Sudoxicam	>32.0
				Piroxicam	4.8
				Phenylbutazone	44.1
				Indomethacin	15.9
				Diclofenac	1.9
				Naproxen	8.2
				Ketoprofen	7.4
Uricosuric Effects					
Oxonic Acid Pretreatment	Rat	Oral	Measurement of effect on uric acid excretion after treatment with oxonic acid		ED_{50} (mg/kg)
				UH-AC 62 XX	5.55
				Piroxicam	3.77
				Phenylbutazone	41.30
				Indomethacin	8.09

1.2.3. REFERENCES

1. U80-0053 Pharmacological expose on UH-AC 62 XX. (Vol. 2.006, p 1)
2. U94-2152 Pharmacological effect of UH-AC 62 XX. (Vol. 2.006, p 135)
3. U88-0743 Inhibition of carrageenan edema of rat hindpaw by meloxicam and other NSAIDs. Comparison of potency on the base of the AUCs of single oral doses. (Vol. 2.006, p 154)
4. U88-0742 Effect of meloxicam, piroxicam, indomethacin and dexamethasone on leukocyte migration and exudate formation in carrageenan induced pleurisy in the rat (Vol. 2.006, p 167)
5. U88-0836 The effects of UH-AC 62 XX, piroxicam and diclofenac on bone and cartilage destruction increase in spleen weight, increase in ESR and changes in serum protein composition in adjuvant arthritis rats. (Vol. 2.006, p. 176)
6. P96-0077 Meloxicam: a potent inhibitor of adjuvant arthritis in the Lewis rat. (Vol. 2.006, p 197)
7. U90-0430 UH-AC 62 XX- Piroxicam: Comparison of the duration of action of an oral single dose in rat. (Vol. 2.006, p 205)
8. R96-0185 Goodman Gilman A, Rall TW, Nies AS (Eds.). Goodman and Gilman's.The Pharmacological Basis of Therapeutics. 8th Edition, Pergamon Press: New York, 1990. (Vol. 2.006, p 212)
9. U92-0362 Meloxicam: Comparison of in vitro and in vivo activity. (Vol. 2.006, p 216)
10. P96-0843 Meloxicam: influence on arachidonic acid metabolism, part II. In vivo findings. (Vol. 2.006, p 232)
11. U92-0255 Effect of PGE2 content on subcutaneous implantation after epicutaneous and systemic administration. (Vol. 2.006, p 242)
12. U92-0730 General Pharmacology - Supplementary Findings. (Vol. 2.006, p 259)
13. U94-2163 Pharmacological properties of meloxicam in comparison with reference anti-inflammatory drugs. (Vol. 2.006, p 307)

14. P96-0844 Meloxicam: influence on arachidonic acid metabolism, part I. In vitro findings. (Vol. 2.006, p 370)
15. U95-2033 Meloxicam: Influence on arachidonic acid metabolism. Supplementary data. (Vol. 2.007, p 1)
16. U94-2195 The effects of meloxicam, UH-V 8 XX and piroxicam on cyclooxygenase 1 and cyclooxygenase 2 activity. (Vol. 2.007, p 53)
17. P96-2652 Selective inhibition of human cyclo-oxygenase-2 by meloxicam. (Vol. 2.007, p 65)
18. U97-2039 The effect of UH-V 8 XX as compared to UH-AC 62 XX (meloxicam) in inhibiting COX-1 and COX-2 in a human whole blood assay, as compared to indomethacin and SC 58125. (Vol. 2.007, p 76)
19. P96-10887 Differential inhibition of the cyclooxygenase activity of prostaglandin endoperoxide synthase isozymes in vitro and ex vivo in man. (Vol. 2.007, p 103)
20. P98-4103 Differential inhibition of human prostaglandin endoperoxide synthase-1 and -2 by nonsteroidal anti-inflammatory drugs. (Vol. 2.007, p 105)
21. U93-0418 Pharmacokinetics of 7.5 mg meloxicam (UH-AC 62 XX) capsules after single and multiple administration p.o. over 7 days in healthy young male and female volunteers (107.078). (Vol. 2.007, p 114)
22. U90-0296 Pharmacokinetic monitoring of the dose finding study IP-No. 107.30 (107.030). (Vol. 2.007, p 343)
23. U98-0038 A 6-week, randomized, double-blind, cross-over study to evaluate the effects of meloxicam 7.5 mg and 15 mg on the cyclooxygenase activity of human blood prostaglandin endoperoxide synthases versus placebo in healthy volunteers. (Vol. 2.007, p 369)
24. U97-2059 Open randomized cross-over study on the effect of meloxicam capsules 7.5 mg/day for 6 days on the prostanoid synthesis of healthy female volunteers, compared to indomethacin capsules 75 mg/day (P97-3366, 107.150). (Vol. 2.008, p 1)
25. U94-0394 Effects of meloxicam 0.5, 1 and 5 μg compared to ASA and control when added during 12 days to human articular chondrocytes cultivated in clusters. (Vol. 2.009, p 1)
26. U95-2043 The effects of meloxicam on nitric oxide synthase activity using intact cells. (Vol. 2.009, p 28)
27. U94-2211 Meloxicam (UH-AC 62 XX): in vitro study on nitric oxide synthase activities: summary of the results obtained by CEREP (Celaster Etudes Recherche et Production). (Vol. 2.009, p 37)
28. U90-0556 Meloxicam (UH-AC 62 XX) tested for inhibition of interleukin release from LPS-stimulated THP-1 cells. (Vol. 2.009, p 48)

1.3. SAFETY PHARMACOLOGY PHARMACODYNAMIC INTERACTIONS

Reports related to safety pharmacology were summarized in the following table.

Species/ Model	Route	Type of Study	Findings
Neuropharmacological Effects			
Mouse	Oral (SD)	Sensory function and reflexes	≤ 25 mg/kg: ↔
		Locomotor activity	≤50 mg/kg: ↔
		Barbiturate sleeping time	≤100 mg/kg: ↔
		Muscle relaxation	≤32 mg/kg: ↔
		Pentetrazol-induced shock	≤50 mg/kg: ↔
		Electric shock	≤50 mg/kg: ↔
		Anticonvulsant effect of phenobarbitone in maximal electroshock	12.5 mg/kg: No interaction
Cardiovascular Effects			
Rat - Conscious Normotensive	Oral (SD)	Systolic blood pressure : 20, 40, and 80 mg/kg	≥20 mg/kg: a slight ↑ in SBP that was not statistically significant
Cat - Anesthetized	IV (SD)	Mean arterial pressure, heart rate, and respiratory min. vol.	≥ 0.1 mg/kg: Statistically significant effect on MABP, HR, and Resp. Min. Vol
Cat - Anesthetized	IV Infusion (SD)	Blood pressure, blood flow, heart rate, respiratory minute volume, and ECG	cumulative dose of 4.0 mg/kg: ↔
Cat - Anesthetized	ID (SD)	MAP, heart rate, and respiratory minute volume: 50, 100, 200 mg/kg	↔
Dog- Conscious Normotensive	Oral (SD)	Mean arterial pressure: 2, 4, and 8 mg/kg	≥2 mg/kg: Slight but not statistically significant ↑
Dog - Anesthetized	IV (SD)	MAP, heart rate, and respiratory minute vol.	1.0 mg/kg: ↑ respiratory minute volume
Rabbit Aorta	*In vitro*	Noradrenaline-induced and spontaneous vesocontractions	≤ $3.0x10^{-4}$ mol/l: ↔
Guinea Pig - Heart	*In vitro*	Influence on coronary flow, left ventricular pressure, heart rate, and cardiac contractility	$1x10^{-5}$M: minor effects
Gastrointestinal Effects			
Rat - Stomach Ulcers	Oral (SD)	Measurement of the ulcerogenic activity: 10, 25, 50 mg/kg	UD_{50} = 15.8 mg/kg
Rat - Stomach Ulcers	Oral (SD)	Measurement of the ulcerogenic activity: 1.25, 2.5, 5.0, 10.0, 20.0 mg/kg	UD_{50} = 5.92 (3.65-10.77) mg/kg
Rat	Oral	Incidence of gastric ulcers following administration once daily for 3-day	UD_{50} = 2.31 mg/kg
Rat - GI Erosions and Adjuvant Arthritis	Oral	Determined safety ratio using GI erosion ED_{50} and adjuvant arthritis ID_{50}	Safety Ratio = 20
Rat - Anesthetized	ID (SD)	Gastric acid secretion	ED_{50} = 13.9 mg/kg
Rat - Pylorus Ligated	ID (SD)	Gastric acid and PGE_2 content of gastric secretion	ID_{50} for PGE2 - 8.99 mg/kg ED_{50} for Gastric Acid - 3.43 mg/kg
Rat - Force-Fed	Oral (SD)	Gastric emptying	ED_{50} = >32.0 mg/kg
Rat - Charcoal-Fed	Oral (SD)	Gastrointestinal transit	≤ 32 mg/kg: ↔
Genito-Urinary Effects			
Rat - H_2O and Electrolyte Loaded	Oral	H_2O, Na^+, K^+ and creatinine excretion following administration of a single dose	≤ 8 mg/kg: ↔
Rat - H_2O Loaded	Oral	Excretion of PGE_2 in urine and pleural exudate	ID_{50}: Urine PGE_2, 1.85 mg/kg; Pleural PGE_2, 0.65 mg/kg.
Bronchial/Pulmonary Effects			
Guinea Pig	IV & ID (SD)	Bradykinin-Induced Bronchospasm - Bronchodilator effect	ED_{50}: ID, 1.13 mg/kg; IV, 0.028 mg/kg
Guinea Pig	IV (SD)	PAF-Induced Bronchospasm - Bronchodilator effect	ID_{50} = 148 μg/kg
Autonomic Nervous System and Smooth Muscle Effects			
Uterus of rat in estrus	*In vitro*	Serotonin and bradykinin induced Contractions	≤$1.0x10^{-5}$ g/ml: ↔
Guinea Pig Ileum	*In vitro*	carbachol-, histamine-, $BaCl_2$-, PGE_2-, and angiotension II, induced contractions	≤$1.0x10^{-5}$ g/ml: ↔
		LTD_4-induced contractions	≤$1x10^{-4}$ M: ↔
Effects on Platelet and Coagulation			
Rabbit Platelets	*In vitro*	Effect on PAF-induced platelet agglutination	$1x10^{-6}$ to $1x10^{-4}$ M: ↔
Rat	Oral	Measurement of prothrombin time: UH-AC 62 XX 1, 2, 4, and 8 mg/kg qd x 2-day	↔
Rat	Oral	Measurement of prothrombin time: 1, 2, 4, and 8 mg/kg po qd x 2-day + 0.2 mg/kg phenprocoumon	≥4 mg/kg: significantly ↑ the response to phenprocoumon

Species/ Model	Route	Type of Study	Findings
Other Effects			
Guinea pig/leukocyte production of 5-HETE	*In vitro*	Inhibition of synthesis of 5-lipoxygenase	Only slight inhibition at ≤30 μM
Mice - zymosan peritonitis	Oral	PGE_2 and LTC_4 in peritoneal exudate	PGE_2 ID_{30}= 1.36 mg/kg LTC_4: 2.0 mg/kg, ↑ by ~16%
Rat - carrageenin-induced pleurisy	Oral	LTB_4 in pleural exudate	≤2.0 mg/kg: ↔
Rat	Oral (SD)	Serum concentration of TXB_2	ID_{50} = 0.47 mg/kg
Rat	Oral (SD)	Effect of paracetamol on the anti-exudative effect of UH-AC 62 XX in carrageenin-induced paw edema	ED_{30} (mg/kg) - UH-AC 62 XX: 2.95 UH-AC 62 XX + paracetamol (50 mg/kg): 1.94 UH-AC 62 XX + paracetamol (100 mg/kg): 0.93
Rat	Oral (SD)	Effect of paracetamol on the analgesic effect of UH-AC 62 XX in inflammatory pain	ED_{30} (mg/kg) at 90 min - UH-AC 62 XX: 6.53 mg/kg UH-AC 62 XX + paracetamol (50 mg/kg): 1.86 UH-AC 62 XX + paracetamol (100 mg/kg): 1.04
Rat	Oral	Effect of paracetamol on the ulcerogenic effect of UH-AC 62 XX following once daily administration for 3-day	Ulcerogenic ED_{30} (mg/kg) - UH-AC 62 XX: 2.40 UH-AC 62 XX + paracetamol (50 mg/kg): 1.11 UH-AC 62 XX + paracetamol (100 mg/kg): 0.65
Rat	Oral	Effect of pirenzepine on the ulcerogenic effect of UH-AC 62 XX following once daily administration for 3-day	Ulcerogenic ED_{30} (mg/kg) - UH-AC 62 XX: 2.55 UH-AC 62 XX + pirenzepine (200 mg/kg): 4.66
Rabbit	Oral (SD)	Effect on reduction in blood glucose levels caused by tolbutamide (40 mg/kg)	≤ 4 mg/kg: ↔
Rat	Oral (SD)	Effect on the diuretic properties of chlorthalidone	≤ 4 mg/kg: ↔
Rat	Oral	Effect on water and electrolyte excretion increased by triamterene	≤ 4 mg/kg: ↔
Rat	IV	Effect on bradycardia and hypotension in anesthetized rats caused by cumulative IV doses of propranolol	≤ 3 mg/kg: ↔
Rat	IV	Effect of UH-AC 62 XX on hypotensive and bradycardic effects of cumulative IV doses of clonidine in anesthetized SH-rats	≤ 3 mg/kg: ↔

SD = Single Dose

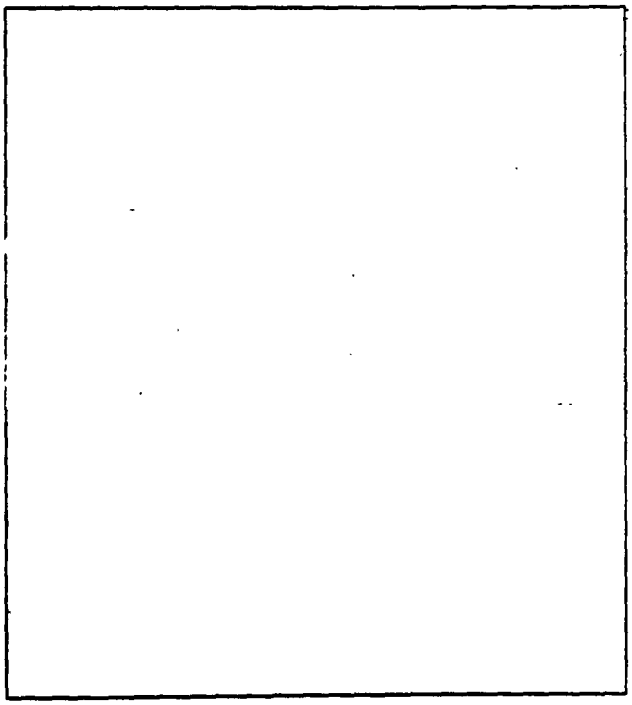
1.3.1. REFERENCES

1. U80-0053 Pharmacological expose on UH-AC 62 XX. (Vol. 2.006, p 1)
2. U94-2152 Pharmacological effect of UH-AC 62 XX. (Vol. 2.006, p 135)
3. P96-0843 Meloxicam: influence on arachidonic acid metabolism, part H. In vivo findings. (Vol. 2.006, p 232)
4. U92-0730 General Pharmacology - Supplementary Findings. (Vol. 2.006, p 259)
5. U95-2033 Meloxicam: Influence on arachidonic acid metabolism. Supplementary data. (Vol. 2.007, p 1)
6. U92-0512 Effect of UH-AC 62 XX on reflexes in mice. (Vol. 2.009, p 56)
7. U92-0557 Lack of intrinsic vasoconstrictor and norepinephrine-antagonistic effect of UH-AC 62 XX in isolated aortic rings of rabbits. (Vol. 2.009, p 62)
8. U92-0511 Effects of UH-AC 62 XX on cardiac function in guinea pig Langendorff hearts. (Vol. 2.009, p 71)
9. U95-0277 Ulcerogenic effect of meloxicam in rat stomach. (Vol. 2.009, p 80)

10. P95-3896 Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favorable gastrointestinal tolerance. (Vol. 2.009, p 92)
11. U90-0431 UH-AC 62 XX - Results of comparative study of the effect of UH-AC 62 XX and piroxicam on hydrochloric acid secretion in the rat. (Vol. 2.009, p 103)
12. U92-0368 Lack of correlation between inhibition of PG biosynthesis in the inflammation area and in the stomach. (Vol. 2.009, p 110)
13. U92-0185 Interactions of meloxicam with Phenprocoumon in the rat. (Vol. 2.009, p 130)
14. U92-0186 Influence of meloxicam on the hypoglycemic effect of Tolbutamide in the rabbit. Vol. 2.009, p 145)
15. U90-0533 Action of pirenzepine (LS 519 Cl) against the ulcerogenic effects of various nonsteroidal anti-inflammatory drugs in the rat stomach. (Vol. 2.009, p 159)
16. U92-0214 Interactions of meloxicam with Chlorthalidone in the rat. (Vol. 2.009, p 165)
17. U93-2049 Interaction of meloxicam with triamteren in the rat. (Vol. 2.009, p 184)
18. U94-2002 Drug interaction studies with meloxicam: is there an influence of meloxicam, 3 mg/kg IV, on the bradycardic and hypotensive effects of propranolol, 10, 30, and 100 μg/kg IV, in the anaesthetized rat. (Vol. 2.009, p 194)
19. U94-2003 Drug interaction studies with meloxicam: is there an influence of meloxicam, 3 mg/kg IV, on the antihypertensive effects of clonidine, 0.3, 1, 3, and 10 μg/kg IV, in anaesthetized SH rats. (Vol. 2.009, p 215)

1.4. PHARMACODYNAMIC EFFECTS OF THE METABOLITES OF UH-AC 62 XX

Three principal metabolites of UH-AC 62 XX were identified in rats and humans. These metabolites, M_1, M_2 and M_3 as shown in the right figure, were rapidly excreted in urine. A glycolyl metabolite, designated as BIBO 8032 NA, was found in urine (but not plasma) of humans at ~4.3% of an oral dose. A minor metabolite, UH-AC 101, the acylthiourea, was also detected in both human and rat urine. A series of *in vivo* and *in vitro* studies were performed to assess the pharmacodynamic effects of these metabolites and results were summarized in the following table.



Species - Model	Route	Parameter Measured	Results
Rat - Kaolin-Induced Hind Paw Edema	Oral	Measurement of edema following administration of a single dose prior to edema induction	ID_{50} (mg/kg) - UH-AC 62 XX, 3.36; M_1, >200; M_2, >200; M_3, >200.
Rat - Carrageenin Induced-Hind Paw Edema	Oral	Measurement of edema following administration of a single dose prior to edema induction	ED_{33} (mg/kg) - UH-AC 62 XX, 3.6; BIBO 8032 NA*, >100
Rat - Inflammatory Pain of the Hind Paw after Yeast Injection	Oral	Measurement of pain threshold 3 hr post yeast injection and 90 min after a single dose	ED_{33} (mg/kg) - UH-AC 62 XX: 3.63; BIBO 8032 NA: >100
Bull Seminal Vesicles Cyclooxygenase Preparation	*In vitro*	Inhibition of PG biosynthesis	ID_{50} (μmol/l) - UH-AC 62 XX, 5.5; M_1, >200; M_2, >200; M_3,>200

* LD_{50}>294 mg/kg)

1.4.1. REFERENCES

1. U92-0187 Biological activity of the main metabolites of meloxicam. (Vol. 2.009, p 232)
2. U94-2092 Anti-inflammatory and analgesic activity of BIBO 8032 NA, a metabolite of meloxicam. (Vol. 2.009, p 306)
3. U89-0194 Pharmacokinetics of ^{14}C labeled UH-AC 62 XX (meloxicam) in man (IP-No. 107.27). (Vol. 2.009, p 248)

2. TOXICOLOGY

2.1. ACUTE (SINGLE-DOSE) TOXICITY STUDIES

2.1.1. SINGLE DOSE STUDIES WITH UH-AC 62 XX AND ITS METABOLITES

2.1.1.1. U80-0053 Pharmacological expose on UH-AC 62 XX. (Vol. 2.006, p 127) (Non-GLP)

Acute Toxicity in the Mouse

Animal: Chbb (SPF) mice, weighing 20-25 g, 5/sex/dose
Compound:
Dose and Route:
Dose Volume:
Study Designs: Groups of mice were given a single dose of UH-AC 62 XX by gavage or intra-peritoneal injection. The animals were observed for 14 days. The LD_{50} was calculated with the method described

Results: The LD_{50} for UH-AC 62 XX in mice are shown in the following table.

Route	LD_{50} (mg/kg)
po	470 (394-562)
ip	391 (338-423)

Acute Toxicity in the Rat

Animal: Chbb (SPF) rats, weighing 130 g, 5/sex/dose
Compound:
Dose and Route:
Dose Volume:
Study Designs: Groups of rats were given a single dose of UH-AC 62 XX by gavage or intra-peritoneal injection. The animals were observed for 14 days. The LD_{50} was calculated with the method described

Results: The LD_{50} values for UH-AC 62 XX in rats are shown in the following table.

Route	LD_{50} (mg/kg)
po	83.5 (63.0-110.6)
ip	48.0 (44.5-51.7)

Acute Toxicity in the Rabbit

Animal: Chbb rabbits, weighing 2.2 kg, 5/sex/dose
Compound:
Dose and Route:
Dose Volume:
Study Designs: Groups of rabbits were given a single dose of UH-AC 62 XX by gavage. The animals were observed for 14 days. The LD_{50} was calculated with the method described

Results: The LD_{50} value in rabbits following oral administration of UH-AC 62 XX was 320 (286-359) mg/kg.

2.1.1.2. U89-0219 Oral and intravenous acute toxicity studies with meloxicam (UH-AC 62 XX) in rat. 29 March 1989. (Vol. 2.009, p 315)

Study Nº: E 8818
Report Nº: U89-0219
Study Aims: To determine acute toxicity of meloxicam in rats by oral gavage or iv injection.
Compound:
Dose and Route:
Vehicle (iv only):

Animal: Sprague-Dawley rats, 7-8 weeks old, weighing 284-344 g for-♂, 203-254 g for ♀, 5/sex/group

Dose (mg/kg)	Route	Nº of Rats		Dose (mg/kg)	Route	Nº of Rats	
		♂	♀			♂	♀
50	po	-	5	0	iv	5	5
70.7		5	5	20		-	5
100		5	5	30		5	5
141.4		5	5	45		5	5
200		5	-	67		5	5
				100		5	-

Study Site:
Study Date: 12/5-21/1988
GLP/QAC Compliance: Yes (Japanese)
Observation Period : 14 days

Results:

- Clinical Signs and Mortality -
  oral: A total of 8 deaths occurred (♂: 1 @ 200 mg/kg on Day 5; ♀: 3 @ 100 on Days 6 and 8, and 4 @ 141.4 mg/kg on Days 5, 7, 9, and 11). Major observed clinical signs in ♂ @ ≥70.7 mg/kg and ♀ @ ≥50 mg/kg were anemia, reddish nasal discharge, black feces, and emaciated.
  iv: Decreased motor activity, black feces, reddish nasal discharge, diarrhea, and anemia were major clinical signs observed in ♂ @ ≥30 mg/kg and ♀ @ 20 mg/kg. A total of 9 deaths occurred (♂: 2 @ 100 mg/kg on Days 4 & 7; ♀: 1 @ 30 on Day 3, 4 @ 45 on Days 3, 4, & 6, and 2 @ 67 mg/kg on Days 6 & 7). The calculated LD_{50} values were:

Route	LD_{50} (mg/kg)	
	♂	♀
po	>200	98.4 (72-134.5)
iv	>100	51.7 (31.4-85.2)

- Body Weights - Body weight loss was observed from Days 2 up to Day 7 post dosing.
- Necropsy - GI perforations with peritonitis and hemascites were major gross findings in the rats that died during study. For terminal sacrified animals, macroscopic lesions including nodules in the pyloric stomach, ileum walls, adhesion between small intestinal loops were idetified.

2.1.1.3. U88-0048 Determination of the ALD_{50} of UH-AC 62 XX in the rat following intravenous administration. 29 March 1989. (Vol. 2.009, p 339)

Study Nº: 86N
Report Nº: U88-0048
Study Aims: To determine acute toxicity of UH-AC 62 XX in rats by iv administration.
Compound: [redacted]
Dose and Route: [redacted]
Animal: Chbb (SPF) rats, ~7-8 weeks of age, weighing 147-158 g, 2-3/sex/group
Study Site: [redacted]
Study Date: 10/29/1987 - 11/19/1987
GLP/QAC Compliance: Yes (OECD)
Observation Period: 14 days

Results: Rats @ 200 mg/kg died within 6 hr with signs of lethargy, lying on the side or abdomen, and cyanotic and thoracic respiration with marked inspiratory lateral movement of lower ribs. Lethargic and slow thoracic respiration with marked inspiratory lateral movement of lower ribs were also observed in animals @ 125 and 160 mg/kg right after receiving UH-AC 62 XX injection solution. Anemia, pilo-erection, chromodacryorrhea, and emaciation were also noted on Day 2 and onwards. Marked weight losses were noted in ♂ @ 160 mg/kg and ♀ @ 125 and 160 mg/kg. The following table showed mortality of each group during the course of study. The approximate LD_{50} (ALD_{50}) values were 160-200 mg/kg and 125-160 mg/kg for ♂ and ♀ rats, respectively. No necropsy was performed on rats @ 200 mg/kg. Lesions of perforated gastric ulcers with peritonitis were identified in animals at 125 and 160 mg/kg.

Dose (mg/kg)	Nº of Animals		Deaths											
			6 hr		24 hr		48 hr		7 days		14 days		Total	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
125	2	2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2	1/2	0/2	1/2
160	3	3	0/3	0/3	0/3	1/3	0/3	0/2	0/3	0/2	0/3	1/2	0/3	2/3
200	3	3	3/3	3/3	-	-	-	-	-	-	-	-	3/3	3/3

2.1.1.4. U79-0051 Study to determine the approximate LD_{50} of the substance UH-AC-62 XX in the pig after oral administration. 09 October 1979. (Vol. 2.009, p 351)

Report Nº: U79-0051
Study Aims: To determined acute oral toxicity of UH-AC-62 XX in pigs.
Compound:
Dose and Route:
Vehicle Control:
Animal: miniature pigs, 5-6 months old, weighing 9.3-19.0 kg.
Study Site:
Study Date: Not stated.
GLP/QAC Compliance: Not stated.
Observation period : 14 days
Study Design: This was a dose-escalation study with a 2-week wash out period between dosing.

Group	Nº of Pigs	Dose (mg/kg)		
1	1/sex	50	400	3200
2	1/sex	100	800	
3	1/sex	200	1600	

Results:

- Cinical Observations and Mortality -

Dose (mg/kg)	Clinical Observations
50	Normal
100	♂: Vomiting (several times on Day 2), diarrhea, ↓ food consumption; ♀: Normal.
200	↓ Food intake
400	Vomiting (several times on Days 2 & 3), loose stool
800	Vomiting (several times on Days 1 & 2)
1600	♂: Vomiting (several times 5-6 hr post-dosing), lethargy, ↓ food intake; ♀: Lethargy and died (Day 7/8).
3200	Vomiting (several times 2-5 hr post-dosing), lethargy, ↓ food intake

- Necropsy - The following table presents major macroscopic findings identified in each animal at necropsy.

Dose (mg/kg)	Gross Findings			
800	♂	Erosion in the glandular stomach	♀	Pyloric ulcer
1600	♂	Pyloric ulcer and erosions	♀	Anemic, pyloric ulcer, blood-tinged GI contents; Liver: small focal yellowish discoloration in the visceral ligaments
3200	♂	Pyloric ulcer/perforation with peritonitis	♀	Pyloric ulcer

2.1.1.5. U89-0635 Approximate acute toxicity (ALD_{50}) with UH-AC 62 XX in minipigs after oral administration. 02 October 1989. (Vol. 2.009, p 359)

Study Nº: 710
Report Nº: U89-0635
Study Aims: To determine acute oral toxicity of UH-AC 62 XX in minipigs.
Compound:
Dose and Route:
Animal: miniature pigs, 1-2 years old, weighing 11.3-15.6 kg, 1/sex/group

Study Site: [redacted]
Study Date: 7/17-31/1989
GLP/QAC Compliance: Yes (OECD)
Observation Period: 14 days
Study Design: Animals (1/sex/group) were grouped and given a single oral dose of UH-AC 62 XX as shown in the following table.

Group	Compound	Dose (mg/kg)	Nº of Animal
1	[redacted]	800	1/sex
2		1600	1/sex
3		3200	1/sex

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Body Weights - Days 0, 4, 8, 12, and 15.
- Food Consumption - 1x/day.
- Necropsy and Pathology - Day 14. The following tissues were taken at the time of necropsy and preserved in [redacted] Histological evaluations were performed on the stomach, kidneys, heart and liver.

Heart and Atrioventricular Valve	Adrenals		Jejunum	Skeletal Muscle (Biceps)
Aorta	Urinary Bladder		Ileum	Bone/Marrow (Sternum, Femur)
Lung	Pituitary		Colon	Skin
Trachea	Thyroid		Cecum	Testes/Ovary
Liver	Pancreas		Rectum	Epididymis
Gallbladder	Glandula Mandibularis		Cerebrum	Prostate/Uterus
Spleen	Tongue	Esophagus	Cerebellum	Mammary Gland
Lymph Nodes (Jejunalis, Popliteus, Cervicalis)			Spinal Marrow (Neck, Thorax, Lumbar Region)	
Kidneys	Stomach (Cardia, Fundus, Pylorus)		Nervus Ischiadicus	Thymus
Lesions	Duodenum		Eyes with Optic Nerve	Seminal Vesicle

Results:

- Clinical Signs and Mortality - Repeated vomiting was observed in pigs @ ≥1600 mg/kg. There were two deaths (1♂ @ 1600 mg/kg and 1♀ @ 3200 mg/kg at 24 hr post dose).
- Body Weights and Food Consumption - Decreased food consumption was noted in the surviving ♂ @ 3200 mg/kg. No remarkable changes in the body weight were noted.
- Necropsy and Pathology - Sanguineous pulmonary edema, hyperemia of the gastric mucosa, and hemorrhagic infiltration in the subendo- and epicardial region of the right heart ventricle were noted in the pigs that died during the study. A cyst of 5 mm was observed in the kidney of ♀ @ 800 and 1600 mg/kg. The surviving ♂ @ 3200 mg/kg had gastric ulcers (3 mm→6 cm) and perforated gastric wall.
- Histopathology - Terminal congestions in lung, liver and gastric mucosa and an acute pulmonary edema were identified in two animals that died during the study. One of these two pigs had hemorrhagic myocardial necroses in the myocardial sections. Ulcers in the stomach of surviving ♂ @ 3200 mg/kg proved to be older ulcers with a marked granular tissue.

2.1.1.6. U91-0618 Approximate acute toxicity (ALD_{50}) of UH-AC 62 XX by intravenous administration in micro-pigs. 19 June 1991. (Vol. 2.010, p 104)

Study Nº: 60 Q
Report Nº: U91-0618
Study Aims: To determine acute toxicity of UH-AC 62 XX in micro-pigs by iv injection.
Compound: [redacted]

Vehicle Control:

Dose and Route:

Animal: Micro-pigs ~2 years of age, weighing 17.6-28.5 kg for ♂ and 17.3-23.0 kg for ♀, 1/sex/group

Study Site:

Dosing Date: 4/29/1991

GLP/QAC Compliance: Not stated.

Observation Period: 14 days

Study Design: Groups of 1/sex pigs were given placebo, 50, 100 or 200 mg/kg of UH-AC 62 XX by intravenous injection. Pigs were monitored for signs of toxicity for 2 weeks.

Results: No deaths occurred in the pigs @ ≤100 mg/kg. Both pigs @ 200 mg/kg died within 3 hr post dosing with clinical signs of slight ataxia, dyspnea, lateral positioning and somnolence prior to death. Repeated vomiting was observed in pigs @ 100 mg/kg during 1st 2 hr post injection. Blood congestion of the liver and kidneys and subendocardial extravasates in the left ventricle were identified during necropsy.

2.1.2. *SINGLE DOSE STUDY WITH DECOMPOSED UH-AC 62 XX*

2.1.2.1. U90-0509 Investigation of the acute toxicity of stressed UH-AC 62 XX solution (decomposition 4.65%) by intravenous administration to rats. 08 August 1990. (Vol. 2.010, p 29)

Study N°: 12 Q

Report N°: U90-0509

Study Aims: To determine the acute toxicity of decomposed UH-AC 62 XX solution by iv injection.

Compound:

Dose and Route:

Animal: ♂ and ♀ Rats, Chbb (SPF), 51 days of age, weighing 156-172 g.

Group	Dose (mg/kg)	N° of Rats
1	125	3♀
2	160	3♂ & 3♀
3	200	3♂

Study Site:

Dosing Date: 3/12/1990

GLP/QAC Compliance: Yes (OECD)

Observation Period: 14 days

Study Design: Groups of rats were dosed with decomposed UH-AC 62 XX solution by iv infusion at a rate of 1.2 ml/mim. The animals were observed for 14 days for signs of toxicity and mortality. Body weight was recorded daily.

Results: The mortality incidence for each group is presented in the following table.

Dose (mg/kg)	Deaths									
	6 h		7-24 hr		Day 2-7		Day 8-14		Total	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
125	-	0/3	-	0/3	-	1/3	-	1/3	-	2/3
160	0/3	0/3	0/3	1/3	0/3	0/3	0/3	2/3	0/3	3/3
200	3/3	-	-	-	-	-	-	-	3/3	-

- Clinical Observations - Signs of lethargy and lay prone or on the side with chromodacryorrhea were noted immediately after dosing in Groups 1 and 2 animals. Chromodacryorrhea, ruffled fur and anemic were noted from Day 2 and onwards. The animals @ 200 mg/kg showed lethargic and thoracic respiration with marked inspiratory lateral movement of the lower ribs, and cyanosis immediately after dosing. These animals died ~3 hr after dosing.
- Necropsy - The animals (3 Group 3 and 1 Group 2) that died within 2 days after dosing showed abnormal gastric mucosa and had reddish black stomach contents. Blood tinged small intestinal contents were observed in two of these 4 rats. Peritonitis with duodenal perforation was seen in one ♀ that died during the study. No pathological changes were characterized in all of the surviving animals.

2.1.3. *SINGLE DOSE TOXICITY WITH UH-AC 62 XX METABOLITES IN RATS*

2.1.3.1. U96-0299 Single dose toxicity study of UH-AC 110 SE, AF-UH 1XX and DS-AC 2 NA (metabolites of UH-AC 62 XX) in rats by intravenous administration. 11 November 1996. (Vol. 2.010, p. 57)

Study Nº: K96006
Report Nº: U96-0299
Study Aims: To determine acute toxicity (approximate lethal dose) of UH-AC 62 XX metabolites, UH-AC 110 SE, AF-UH 1XX and DS-AC 2 NA, in rats by iv injection.
Compound:
Dose and Route:
Vehicle Control:

Animal: rats, ~7 weeks of age, weighing 228-267 g for ♂ and 177-210 g for ♀, 5/sex/group.

Study Site:

Study Date: 7/9/1996 - 7/23/1996

GLP/QAC Compliance: Yes

Observation Period: 14 days

Study Designs: Groups of rats were given a single iv dose of either vehicle, UH AC 110 SE, AF-UH 1XX or DS-AC 2 NA as shown in the following table. The animals were monitored for signs of toxicity and mortality.

Group	Compound	Dose (mg/kg)	Nº of Animals
1		0	5/sex
2		50	5/sex
3		70	5/sex
4		400	5/sex

Results:

- Clinical Observations and Mortality - No deaths occurred. No changes in behavior and general condition were observed in rats given UH-AC 110 SE or AF-UH 1 XX. Rats treated with DS-AC 2 NA showed tachycardia immediately after and crouching position, abdominal position, and decreased motor activities from 5→60 min after receiving the compound.
- Body Weights - No changes in the body weight gains were noted.
- Necropsy Findings - Hemorrhage in the lungs with microscopic characteristics of atelectasis was identified in a ♂ received AF-UH 1 XX and gastric mucosal hemorrhage without microscopic changes was characterized in a ♀ received DS-AC 2 NA.

2.1.3.2. U94-2131 UH-AC 62 XX (meloxicam): Single dose toxicity study (ALD50) of BIBO 8032 NA, a metabolite of UH-AC 62 XX, in rats after intravenous administration. 22 July 1994. (Vol. 2.010, p 122)

Study Nº: 46 S

Report Nº: U94-2131

Study Aims: To determine acute toxicity (ALD_{50}) of BIBO 8032 NA, a metabolite of UH-AC 62 XX, in rats by iv injection.

Compound:

Dose and Route:

Vehicle Control:

Animal: (SPF) rats, 44 days old, weighing 169-173 g for ♂ and 139-141 g for ♀, 3/sex.

Study Site:

Dosing Date: 4/27/1994

GLP/QAC Compliance: Yes

Observation period: 14 days

Results: There were no remarkable changes in the clinical signs or behavior. No deaths occurred. The body weight gains were not affected. No gross pathological changes were observed during necropsy.

2.2. REPEATED DOSE TOXICITY STUDIES

2.2.1. MOUSE STUDIES

2.2.1.1. U88-0002 13 week toxicity study of UH-AC 62 XX in NMRI-mice by administration in the diet. 18 August 1987. (Vol. 2.010, p 144)

U93-0473 Toxicokinetic monitoring at the end of a 13 week toxicity study of UH-AC 62 XX in mice at doses of 8.0, 17.5 and 35.0 mg/kg by administration in the diet (study Nº 3806/86). 05 April 1993. (Vol. 2.010, p 348)

Report Nº: U88-0002 and U93-0473 (PK)
Study Aims: To determine subchronic toxicity of UH-AC 62 XX in mice via diet admix.
Compound:
Dose and Route:
Animal: (SPF) mice, 26-29 days old, weighing 14.9-16.8 g. 10-20/sex/group.
Study Site:
Study Date: 2/13/97 (1st dosing date) - 5/15/1987
GLP/QAC Compliance: Yes
Study Design: Mice were randomly assigned to 4 dose groups as shown in the following table.

Group	Dose (mg/kg)	Actual Dose (mg/kg) ♂	Actual Dose (mg/kg) ♀	Route	Dosing Duration	Nº of Mice
1	0	0	0	Oral via Diet Admix	13-week	20/sex*
2	8.0	7.65 ± 0.53	7.69 ± 0.43			10/sex
3	17.5	16.69 ± 0.94	16.91 ± 1.36			10/sex
4	35	33.05 ± 2.07	34.11 ±2.13			20/sex*

* 10/sex/group were designated for clinical laboratory study and blood was drawn at Weeks -1, 6, and 12.

- Clinical Signs and Mortality - 1x/day.
- Food Consumption and Body Weights - 1x/week.
- Clinical Pathology - Weeks -1, 6 and 12. The following parameters were analyzed:

Hematology			
RBC	WBC and Differential	Reticulocytes	Hb
Thromboplastin	Blood Clotting Time	Platelets	Ht
Clinical Chemistry			
ALT (SGPT)	Alkaline Phosphatase (ALP)	Blood Urea	Glucose
Na	K	Ca	Cl
AST (SGOT)	Total Protein	Total Bilirubin	Total Cholesterol
Creatinine	Lactate Dehydrogenase (LDH)		

- Ophthalmology (Ophthalmoscope & Slit Lamp) - Week 13 before terminal sacrifice on all UH-AC 62XX treated mice.
- Necropsy - Week 13. The following organs from each group (10/sex) were preserved in 10% buffered formalin and those tissues with asterisk sign (*) were examined histopathologically.

Adrenals	Ileum*	Lungs and Bronchi	Heart	Liver	Kidneys*
Colon*	Jejunum*	Rectum*	Duodenum*	Stomach*	

- PK/TK - Week 13. Blood samples were obtained from each group (10/sex/group) prior to sacrifice. Plasma UH-AC 62XX levels were determined by an HPLC assay. The limit of quantitation [redacted]

Results:

- Clinical Signs and Mortality - There were no remarkable clinical signs attributable to the treatment. A total of 8 deaths occurred:
  - 1♀ @ 0 mg/kg;
  - 2♂+1♀ @ 35.0 mg/kg with macroscopic findings of dark-red discolored lungs and reddened dilated small intestine;
  - 1♂+3♀ @ 35.0 mg/kg that were assigned to clinical pathology study as results of blood drawing error.
- Food/H_2O Consumption and Body Weights - Food consumption and H_2O intake were not affected by the treatment. Lower mean body weights were noted for ♂ @ 8.0 mg/kg during Weeks 7-13 by 6-8%, ♂ @ 17.5 mg/kg during Weeks 1-13 by 8-14%, and high-dose ♂ during Weeks 1-13 by 6-10%.
- Clinical Pathology - High-dose ♂ had significantly lower total WBC (↓43%) and slightly higher platelet counts (↑25%) at Week 12. Increased blood clotting time was noted in both ♂ and ♀ @ 35 mg/kg (♂: 324 vs 222 sec in controls; ♀: 348 vs 280 sec in controls) at Week 12. Slightly elevated values in creatinine and alkaline phosphatase were noted in ♂ @ 35 mg/kg, but these changes were biologically insignificant.
- Ophthalmology (Ophthalmoscope & Slit Lamp) - No abnormalities were found.
- Necropsy -

  Organ Weights: Increased absolute spleen weight was observed in mice @ 17.5 (♂: 1.38x; ♀: 1.6x) and 35 mg/kg (♂: 3x; ♀: 3.4x).

  Macroscopic Examination:
  - 8.0 mg/kg/day - No treatment-caused gross lesions were observed.
  - 17.5 mg/kg - The following findings were described in the text (Vol. 2.10, p 153 and 169) of summary and results sections: 2 round tissue mass (~5 mm in diameter) at the testicles in 1♂; enlarged spleen in 1♀ and adhesions of ileum and colon in the region of appendix in another ♀. However, no gross pathological findings were stated in the Table 26 (Vol. 2.10, p 238) and summary table (Vol. 2.10, p 171-174).
  - 35 mg/kg/day - dark-red discoloration in the lungs plus dilated and reddened small intestine in 2♂+1♀ that died during the study; enlarged spleen in 2♂+1♀ with thickened gastric wall and partial adhesions to the liver in 1♂ and lumpy pancreas and partial adhesions to the liver and spleen in another ♂.

  Histopathology: Microscopic lesions with characteristics of perforated ulcer (1♂), chronic ulcer (1♂), and erosion (1♂ + 2♀) with or without peritonitis in the stomach of mice @ 35 mg/kg/day and focal ulcerative cholitis (colitis ?) in the large intestine of 1♀ @ 17.5 mg/kg were identified. In addition, 1♀ @ 35 mg/kg had marked bilateral interstitial fibrosis with mild tubular dilation in the kidney.
- PK/TK - UH-AC 62XX was readily absorbed through the diet. The mean plasma UH-AC 62XX levels are shown in the following table. High inter-individual variations were noted; the range of coefficients of variation was 29-51%. No apparent gender differences in the mean plasma UH-AC 62XX levels were identified.

Dose (mg/kg)	UH-AC 62XX Conc. (μg/ml)	
	♂	♀
8.0	0.81	0.77
17.5	1.6	1.6
35	2.0	1.9

Note:

1. **"Cholitis" was mentioned several times in this report, U88-0002 (Vol. 2.010, p. 2260, 2263, and 2401). The sponsor should provide the clarification and definition of this word.**
2. **Findings described in the result section were not in agreement with the findings listed in the tables. The following findings were described in the text (Vol. 2.10, p 153 and 169): 2 round tissue mass (~5 mm in diameter) at the testicles in 1♂; enlarged spleen in 1♀ and adhesions of ileum and colon in the region of appendix in another ♀. However, no gross pathological findings were stated in the Table 26 (Vol. 2.10, p 238) and summary table (Vol. 2.10, p 171-174).**

2.2.2. RAT STUDIES

2.2.2.1. U88-0427 Range finding study on the substance UH-AC 62 XX in rats by oral administration over a period of 4 weeks. 03 May 1988. (Vol. 2.010, p 369)

Study Nº: 11F
Report Nº: U88-0427
Study Aims: To determine the toxic threshold after repeated administration of UH-AC 62XX by oral gavage to rats for 4-week.
Compound: [redacted]
Dose and Route:
Dosing Duration: 4-week
Vehicle Control: Not Indicated.
Animal: Species and age of the rats were not stated; 5/sex/group.
Study Site: Not Stated.
Study Date: 2/14/1979 - 3/13/1979
GLP/QAC Compliance: Not Stated.
Study Design:

- Clinical Observation - Not indicated.
- Food/H_2O Intake - Not monitored.
- Body Weights - 1x/week.
- Necropsy - Week 4. Only macroscopic examination was performed.

Results:

- Mortality - Dose-dependent mortality was observed. The incidence of cumulative death for each group is presented in the following table.

Group	Dose (mg/kg)	Week 1		Week 2		Week 3		Week 5	
		♂	♀	♂	♀	♂	♀	♂	♀
0	0	0	0	0	0	0	0	0	0
1	2	0	0	0	0	0	0	0	0
2	5	0	0	0	0	0	0	0	0
3	10	0	0	0	1	0	1	0	1
4	20	2	3	2	5	2	5	2	5
5	30	5	5	5	5	5	5	5	5
6	40	5	5	5	5	5	5	5	5
7	50	5	5	5	5	5	5	5	5

- Body Weights - **No data were submitted.**
- Macroscopic Findings - GI ulcers/perforations with peritonitis were major pathological lesions observed in all dead and 3 surviving (2 @ 10 mg/kg and 1 @ 20 mg/kg) rats.

2.2.2.2. U81-0061 Subacute toxicity study on the substance UH-AC 62 XX with oral administration to rats for 3 months. 24 July 1981. (Vol. 2.011, p 1)

U82-0077 Comparison of blood levels and excretion in non-pretreated and subacutely pretreated rats. 10 July 1982. (Vol. 2.012, p 302)

Study Nº: 9.G/80 and ADME 24/82 (PK)
Report Nº: U81-0061 and U82-0077 (PK)
Study Aims: To determine the toxicity of UH-AC 62 XX in rats by oral administration for 13 weeks with a 6-week recovery phase.
Compound:
Dose and Route:
Vehicle Control:
Animal: ♂ & ♀ rats, (SPF), 12-13 weeks of age, weighing 170-190 g, 12-24/sex/group.
Study Site:
Dosing Date: 4/28/1980 - 7/27/1980
Study Date: 4/8/1980 - 9/9/1980
GLP/QAC Compliance: Yes
Study Design: Rats were assigned to four different groups and given either vehicle or UH-AC 62 XX for 13 weeks by gavage as shown in the following table. Twelve/sex from Groups 0 and 3 were allowed to have a 6-week recovery period. Additional 20♂ were allotted to Group 2 as PK animals and were given 3.5 mg/kg UH-AC 62 XX for 13 weeks followed by a single dose of [^{14}C]UH-AC 62 XX. A single dose of 3.5 mg/kg [^{14}C]UH-AC 62 XX was given to another group of 20♂ to serve as controls for PK study.

Group	Compound	Dose (mg/kg)	Nº of Animals	
			Toxicology	PK[b]
0	Vehicle Control	0	24/sex[a]	-
1		1.0	12/sex	-
2		3.5	12/sex	20♂
3		10	24/sex[a]	-

[a] 12/sex were allowed to have a 6-week recovery period.

The following parameters were monitored.

- Clinical Signs and Mortality - 1x/day.
- Food Consumption, H_2O Intake, and Body Weights - 1x/week.
- Blood Pressure and Heart Rate Measurements - Weeks -1, 2, 7, and 13 (Pre-R, 2 and 4 hr post-dose, 5/sex from Groups 0, 2, and 3).
- Clinical Pathology - Hematology: Weeks -2, 2, 7, 13 and 19 (recovery animals, 12/sex from Groups 0 and 3); Urinalysis: Weeks 2/3, 12/13, and 18. The following parameters were analyzed:

Hematology			
RBC	WBC and Differential	Reticulocyte	Hb
MCH	MCHC	MCV	
TT (Thromboplastin Time)	PTT (Partial Thromboplastin Time)	Platelets	Ht
Serum Chemistry			
ALT (SGPT)	Alkaline Phosphatase (ALP)	BUN	Glucose
Sodium	Potassium	Calcium	Chloride
AST (SGOT)	Total Protein	Total Bilirubin	Total Cholesterol
Creatinine	Lactate Dehydrogenase (LDH)	Total Glycerol	Inorganic Phosphate
Urinalysis			
RBC	Protein	Glucose	Ketone
Urobilinogen	Bilirubin	Urine Volume	Urine Sediment

- Necropsy - Week 13. The following organs from each group were preserved in [redacted] and examined microscopically. Tissues/organs with asterisk (*) were weighed. Bone marrow smears were prepared from each animals, but only smears from 5/sex animals in Groups 0 & 3 were evaluated.

Heart*	Lung*	Liver*	Kidneys*,1	Thymus*	Spleen*	Gonads*,1
Adrenals*	Pituitary*	Thyroid with Parathyroids*		Brain* (Cerebrum & Cerebellum)		Prostate*
Parotid Gland	Stomach	Duodenum	Jejunum	Colon	Pancreas	Lymph Node
Aorta	Skeletal Muscle(femoris)		Sublingual Gland	Submandibular Gland		Trachea
External Lacrimal Gland		Peripheral Nerve (Sciatic)[1]		Eye with Optic Nerve[1]		Lesions

* Tissues/Organs were weighed; [1] Tissues/Organs were fixed in Bouin's fluid.

- PK/TK - Week 13. Blood (at 15, 30 and 60 min and 1, 2, 3, 5, 7, 9, 24, 32, 48, 72, and 72 hr post dosing), urine (0-4, 4-24, 24-48, 48-72, and 72-96 hr) and fecal (0-24, 24-48, 48-72, and 72-96 hr) samples from 3.5 mg/kg and PK control (single dose) groups were analyzed for radioactivity. The metabolic pattern in plasma was determined by thin-layer chromatography (TLC).

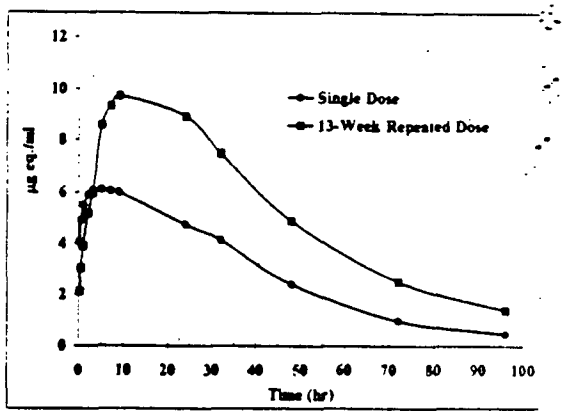
Results:

- Clinical Signs and Mortality - A total of 30 deaths occurred (1♂ @ 3.5 mg/kg as the result of gavage error; 11♂ & 18♀ @ 10 mg/kg due to GI toxicity - perforated GI ulcers with peritonitis). Dark feces, tender abdominal walls, and pale appearance were noted in the Group 3 animals.
- Food Consumption, H_2O Intake, and Body Weights - No treatment-related changes in food consumption and mean body weight. However, a significant increase in H_2O intake was noted in Group 3 (♂: ↑ ~35%; ♀: ↑74%).
- Blood Pressure and Heart Rate Measurements - There were some minor and physiologically insignificant changes in blood pressure and heart rate during the course of study.
- Clinical Pathology - The changes seen in the hematology and serum chemisty parameters were secondary reponse to treatment-induced GI ulcerations/perforations. These significant alterations observed in the high-dose group (10 mg/kg/day) included:
  - ↑ Total WBC Count - ♂: ↑1.5-1.8x, Weeks 2, 7, & 12; ♀: ↑3.1-3.4x, Weeks 2, 7, & 12;
  - ↑ Absolute Segmented Neutrophil Count - ♂: ↑6.1-8.6x Weeks 2, 7, & 12; ♀: ↑13.6-14.6x, Weeks 2, 7, & 12 and ↑3.0x, Week 19-recovery phase;
  - ↑ Absolute Lymphocyte Count - ♂: ↑1.4x, Week 2; ♀: ↑1.5-1.9x, Weeks 2, 7, & 12;
  - ↓ RBC - ♂: ↓21%, Week 12; ♀: ↓27-33%, Weeks 2, 7, & 12;
  - ↓ Ht - ♂: ↓12-17%, Weeks 7 & 12; ♀: ↓23-25%, Weeks 2, 7, & 12;
  - ↓ Hb - ♂: ↓20%, Week 12; ♀: ↓28-32%, Weeks 2, 7, & 12;
  - ↓ MCHC - ♂: 8-11%, Weeks 2, 7, & 12;
  - ↑ MCV - ♂: ↑6%, Week 12; ♀: ↑6-16%, Weeks 2, 7, & 12;
  - ↑ Reticulocyte - ♂: ↑2.2-3.9x, Weeks 2, 7, & 12; ♀: ↑5.4-6.8x, Weeks 2, 7, & 12 and ↑2.7x, Week 19-recovery phase;
  - ↓ Platelet - ♀:↓ 13-19%, Weeks 2, 7, & 12;

- ↓ Total Protein - ♀: ↓21-23%, Weeks 2, 7, & 12;
- ↓ Albumin - ♂: ↓16-30% Weeks 2, 7, & 12; ♀: ↓40-50%, Weeks 2, 7, & 12; and
- ↓ A/G ratios - ♂: ↓11-32% Weeks 2, 7, & 12; ♀: ↓40-50%, Weeks 2, 7, & 12.

Females @ 3.5 mg/kg also had ↑ absolute segmented PMN counts by 2.9-5.3x of controls at Weeks 2, 7, and 12. Reduced urine volume was noted in ♂ of Groups 1 (↓47 & 41% at Weeks 2/3 and 12/13, respectively), 2 (↓14 & 21% at Weeks 2/3 and 12/13, respectively), and 3 (↓25 & 40% at Weeks 2/3 and 12/13, respectively) and ♀ of Groups 2 (↓22% at Week 12/13) and 3 (↓30 and 33%, at Weeks 2/3 and 12/13, respectively).

- Bone Marrow Smear Evaluation - Significant decreases in segmented neutrophil (↓16%) and total granulocyte (↓11%) were noted in Group 3 ♂ and reduced RBC (↓25%), segmented neutrophil (↓56%), and plasma cell (↓68%) with increased lymphoreticulocyte (↑15%) were observed in Group 3 ♀.
- Necropsy - The major gross and microscopic changes were limited to the GI and kidneys. Microscopic lesions were mainly peptic pyloric ulcers in Group 2 (9/12♂ and 11/12♀) and pyloric and/or duodenal perforation with peritonitis in Group 3 (11/12♂ and 12/12♀; recovery animals: 9/12♂ and 8/12♀) and swelling in epithelial cells of proximal renal tubule sections with brownish lysosmal residual bodies (6/12♂ and 5/10♀; 1 recovery ♀) and pyelonephritis/pyelitis (1♂ and 1 recovery ♂) in Group 3.
- PK/TK - Blood radioactivity levels following an oral dose of 3.5 mg/kg [^{14}C]UH-AC 62 XX to rats that had not previously treated or received UH-AC 62 XX for 13-week are depicted in the right figure. Higher blood concentrations (μg eq/ml radioactive dose) were noted in rats that had been treated with UH-AC 62 XX for 13-week. **The metabolic pattern in the plasma determined by the TLC method was not interpretable as the results presented in the current submission were ambigous and illegible.** The mean (± SE) % cummulative (0-96 hr) radioactivity excreted in urine and feces for single or repeated dose groups were as followings.



	% Radioactivity	
	Single Dose	Repeated Dose
Urine	71.5 ± 2.3	65.5 ± 4.3
Feces	20.3 ± 1.2	25.8 ± 2.5
Total	91.9 ± 2.9	91.4 ± 3.5

Note: In U81-0061 and U82-0077 (PK), the submission did not state whether single dose control group in the PK report was dosed at the same time as repeated dose group. The sponsor is encouraged to derive PK parameters based on the presented information. The date of animals sacrificed at moribund state or unscheduled deaths in the Toxicology Study Groups, was not reported. The method used to determine radioactivity in the blood was not addressed. No detailed information on metabolic pattern in the plasma was presented. Over all the study reports (toxicology and PK) were in very poor quality.

2.2.2.3. U93-0609 Repeated dose toxicity study with meloxicam (UH-AC 62 XX) in rats dosed orally by gavage for 3 months. 16 October 1991. (Vol. 2.018, p 28)

Study N^{a}: E8907

Report Nº: U93-0609
Study Aims: To determine the toxicity of UH-AC 62 XX in rats by oral administration for 3 months with a 6-week recovery phase.
Compound:
Dose and Route:
Dosing Duration: 3-mon with a 6-week recovery phase
Vehicle Control:
Animal: Sprague-Dawley rats, 7 weeks old, weighing 212-284 g for ♂ and 162-212 g for ♀, 15-25/sex/group.
Study Site:
Study Date: 1/9/1990 - 6/9/1990
GLP/QAC Compliance: Yes
Study Design: Rats were assigned to four different groups and given either vehicle or UH-AC 62 XX for 3 months by gavage as shown in following table. Ten/sex from Groups 0 and 3 were allowed to have a 6-week recovery period. The doses selected were based on the results from a 13-week pilot study conducted during 7/4-10/4/1989 showing that deaths occurred at a dose of 10 mg/kg but not at doses of 3.5 or 7 mg/kg.

Group	Compound	Dose (mg/kg)	Nº of Animals Toxicology
0	Vehicle Control	0	25/sex*
1		1.0	15/sex
2		2.5	15/sex
3		7	25/sex*

* 10/sex were allowed to have a 6-week recovery period.

The following parameters were monitored.

- Clinical Observations and Mortality - 2x/day.
- Body Weights - 1x/day and 1x/week during recovery phase.
- Food and H_2O Consumption - 1x/week.
- Ophthalmology (Fundus Photography and Pupillary Reflexes) - Pre-R and Weeks 5, 13, and 19 (Recovery Phase) (5/sex/group).
- Clinical Pathology - Hematology and Chemistry: Weeks 6, 13, and 19; Urinalysis: Weeks 5, 13, and 19; Fecal Occult Blood: Weeks 13 and 19. The following parameters were analyzed.

HEMATOLOGY		CLINICAL CHEMISTRY		URINALYSIS	
RBC	MCV	GOT (AST)	Cholesterol	Volume	Urobilinogen
WBC	MCH	GPT (ALT)	Triglycerides	Specific Gravity	Na and K
Platelets	MCHC	Alkaline Phosphatase	Total Bilirubin	pH	Chloride
Hemoglobin (Hb)		Total Protein	Creatinine	Protein	Creatinine
Hematocrit (Ht)		Albumin	Calcium	Glucose	Bilirubin
Reticulocytes		A/G Ratio	Potassium and Sodium	Ketone	
Prothrombin time (PT)		Glucose	Chloride	Blood	
Leukogram (Differential)		Urea nitrogen	Protein Fractions	Sediment Examination	

- Necropsy - Week 19. The following organs from each group were preserved in and examined microscopically. Tissues/organs with asterisk (*) were weighed.

Heart*	Lungs*	Liver*	Kidneys*	Spleen*	Thymus*		Brain*
Adrenals*	Pituitary*	Thyroids with Parathyroids*		Gonads*	Epididymides*		Prostate*
Salivary Glands (Submaxillary Sublingual and Parotid Glands)*				Stomach	Duodenum		Jejunum
Ileum	Cecum	Colon	Seminal Vesicle	Pancreas	Bladder	Esophagus	Sternum	Trachea
Uterus	Vagina	Mandibular Lymph Node	Aorta	Sciatic Nerve	Skeletal Muscle (Quadriceps Femoris)		
Skin	Mammary Glands	Femur with Bone Marrow	Tongue	Spinal Cord	Femur-Tibia Junction		Lesions
Eye Balls with Optic Nerves[1]		Eyelid[1]	Harderian Glands[1]				

* Tissues/Organs were weighed; [1] Tissues were fixed in Davidson's fluid.

Slides from the above tissues/organs except the tongue, vagina, spinal cord, and sternum were examined microscopically.

Results:

- Clinical Observations and Mortality - There were 10 deaths (1♂ each @ 0, 2.5 and 7 mg/kg; 7♀ @ 7 mg/kg). The cause of death for control and Group 2 ♂ was unknown. The death of Group 3 ♂ was due to dosing error. All 7♀ @ 7 mg/kg died as a result of treatment-related GI toxicity with clinical signs of anemia, black feces, emaciation and hypothermia.
- Body Weights, Food and H_2O Consumption - Slightly lower (↓5-7%) mean body weights were noted in ♀ @ 7 mg/kg during Weeks 3→19. High dose ♂ had a slight increase in H_2O (↑10-14%) intake during Weeks 10-13.
- Ophthalmology (Fundus Photography and Pupillary Reflexes) - No treatment-related effects were noted.
- Clinical Pathology - Treatment-related findings in hematology and serum chemistry are summarized in the following table. These alterations were secondary response to GI injury. Positive results of occult fecal blood tests were seen in 1♀ @ 2.5 and 1♂ + 7♀ @ 7 mg/kg at week 13 analysis. No positive occult blood tests were identified at Week 19 (recovery phase).

Dose		RBC		Hb		Ht		Total Protein		Albumin		Triglyceride	
mg/kg		Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13
1	♂											↓19%	↓28%
	♀												
2.5	♂											↓29%	↓33%
	♀												
7	♂								↓7%		↓9%	↓23%	↓38%
	♀	↓12%		↓11%		↓10%		↓15%	↓16%	↓19%	↓21%		

Dose		WBC		Seg. PMN		Lymphocyte		Monocyte		Reticulocyte		Platelet	
mg/kg		Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13	Wk 6	Wk 13
1	♂												
	♀				↑71%		↓7%	↑64%		↑23%	↑14%		
2.5	♂	↑22%											
	♀				↑53%		↓7%	↑136%		↑8%	↑21%		
7	♂	↑21%	↑28%	↑35%	↑81%		↑23%						
	♀	↑61%	↑65%	↑336%	↑509%	↑35%	↑31%	↑263%	↑10%	↑192%	↑121%	↑28%	↑42%

- Necropsy -

Organ Weights: A summary of major significant findings is presented in the following table.

Dose mg/kg		Terminal Sacrifice (Week 13)						Recovery Sacrifice (Week 19)					
		Kidney		Spleen		Thyroid		Kidney		Spleen		Thyroid	
		Abs.	Rel.	Abs.	Rel.	Abs.	Rel.	Abs.	Rel.	Abs.	Rel.	Abs.	Rel.
1	♂		↑6%		↑7%								
	♀	↑15%	↑18%	↑19%	↑20%								
2.5	♂	↑7%	↑14%		↑14%	↓19%	↓13%						
	♀	↑14%	↑16%	↑14%	↑15%								
7	♂	↑18%	↑21%	↑12%	↑15%					↑13%	↑13%	↓18%	↓17%
	♀	↑23%	↑31%	↑38%	↑46%			↑15%	↑22%	↑11%	↑20%		

Gross Pathology: Blood-tinted or yellowish green ascites, adhesions of abdominal organs, intestinal ulcers were observed in 7 ♀ @ 7 mg/kg that died or were sacrificed at moribund during the study. At terminal sacrifice (Week 13), treatment-caused gross lesions of ulcerous scar in the stomach (one each ♂ @ 1 and 2.5 mg/kg, 1♀ @ 7 mg/kg) and cecum (1♂ @ 7 mg/kg) and erosion in the stomach (1♂ @ 7 mg/kg) were characterized.

Histopathology: Major microscopic findings at terminal sacrifice (Weeks 13 and 19) were

- stomach - ulcer, 1♂ @ 7 mg/kg; necrosis, 1♂ @ 7 mg/kg.
- jejunum & ileum - ulcer, 1♀ @ 7 mg/kg.
- cecum - ulcer, 3♂ + 1♀ @ 7 mg/kg.
- kidney - papillary edema, 1♂ + 2♀ @ 2.5 and 4♂ + 2♀ + 1 recovery ♀ @ 7 mg/kg; pyelonephritis/chronic prulent nephritis (murine nephritis caused by bacterial infection), 1♀ @ 1 mg/kg, 3♂ + 1♀ + 1 recovery ♀ @ 7 mg/kg; papillary necrosis, 2♀ + 1 recovery ♀ @ 7 mg/kg; infarct, 1♂ @ 2.5 mg/kg and 1 recovery ♂ @ 7 mg/kg.

2.2.2.4. U85-0347 Chronic toxicity study of the substance UH-AC 62 XX in rats following oral administration over a period of 26 weeks. 08 February 1985. (Vol. 2.013-2.014)

Study Nº: 67 K
Report Nº: U85-0347
Study Aims: To determine chronic toxicity of UH-AC 62 XX following oral administration for ≥6 months to rats.
Compound:
Dose and Route:
Vehicle Control:
Animal: Rats (SPF), 87 days old, weighing 200-253 g, 24/sex/group.
Study Site:
Dosing Date: 1/25/1984 - 7/24/1984
Necropsy: 8/2/1984
GLP/QAC Compliance: Yes
Study Design: Groups of 24 rats/sex were randomly assigned to 4 dose groups as shown in the following table. The doses selected were based on the findings from a 13-week oral toxicity study in which at 10 mg/kg/day UH-AC 62 XX caused deaths and at 3.5 mg/kg induced pyloric ulcerations without clinical signs.

Group	Compound	Dose (mg/kg)	Dosing Vol. (ml/kg)	Dosing Duration	Nº of Animals
0	Vehicle Control	0	2.5	26 weeks	24/sex
1	UH-AC 62 XX	1.0			24/sex
2		2.0			24/sex
3		3.5			24/sex

The following parameters were monitored.

- Clinical Signs and Mortality - 1x/day.

- Food Consumption, H_2O Intake, and Body Weights - 1x/week for Weeks 1-12 and 1x/4 weeks thereafter.
- ECG (Lead I or II) - Weeks -1, 7, 13 and 25 (Pre-R, 2 and 4 hr post-dose, 5/sex from Groups 0, 2, and 3).
- Clinical Pathology-- Hematology and Serum Chemistry: Weeks -2, 5(♂)/6(♀), 12, 19(♂)/20(♀) and 26; Urinalysis: Weeks 6, 15, 20(♂)/21(♀), and 26. The following parameters were analyzed:

Hematology					
RBC		WBC and Differential	Reticulocyte	Hb	Ht
MCH	MCHC	TT (Thromboplastin Time)	MCV	Platelets	PTT (Partial Thromboplastin Time)
Serum Chemistry					
ALT (SGPT)		Alkaline Phosphatase (ALP)	BUN		Glucose
Leucine Arylamidase (Leucine Aminopeptidase) (LAP)			Glutamate Dehydrogenase		γ-Glutamyl Transpeptidase
Sodium		Potassium	Calcium		Magnesium
AST (SGOT)		Total Protein	Total Bilirubin		Total Cholesterol
Creatinine		Chloride	Total Glycerol		Inorganic Phosphate
Urinalysis and Fecal Occult Blood					
Specific Gravity, Color		pH	Glucose		Ketone
Protein		RBC/Leukocyte	Nitrite		Urine Sediment Analysis
Urobilinogen		Bilirubin	Urine Volume		Fecal Occult Blood

- Ophthalmology (Ophthalmoscope & Slit Lamp) - Weeks -3, 11, and 24.
- Necropsy - Week 26. The following organs from each group were preserved in [redacted] and examined microscopically (except femur and sternum). Tissues/organs with asterisk (*) were weighed. Bone marrow smears were prepared from each animals, but only smears from 5/sex animals in Groups 0 & 3 were evaluated.

Heart*	Lung*	Liver*	Kidneys*,†	Thymus*	Spleen*	Gonads*,†	
Adrenals*	Pituitary*	Thyroid with Parathyroids*		Brain* (Cerebrum & Cerebellum)		Prostate*	
Parotid Gland	Esophagus	Stomach	Duodenum	Jejunum	Ileum	Colon	Mesenteric Lymph Node
Aorta	Skeletal Muscle (femoris)		Sublingual Gland	Submandibular Gland	Pancreas	Trachea	
Epididymis	Uterus	Fallopian Tube	Ovaries	Bladder	Skin	Mammary Glands	
Lacrimal Gland	Sternum, Femur	Peripheral Nerve (Sciatic)†		Eye with Optic Nerve†	Lesions	Bone Marrow	

* Tissues/Organs were weighed; † Tissues/Organs were fixed in [redacted]

Results:

- Mortality - A total of 6 deaths occurred; three were not treatment-related deaths (1♂ @ 1.0 mg/kg and 1♂+1♀ @ 2.0 mg/kg) as a result of procedure error and three were treatment-related deaths (3♀ @ 3.5 mg/kg) due to cardionephric failure.
- Clinical Signs - From Week 16, the bedding and urine of several high dose females showed blood stained. Several high dose females appeared to be anemic.
- Food/H_2O Consumption and Body Weights - No treatment-related effects on food consumption were noted. Increased H_2O intake (↑8-40%) was observed for ♀ @ 3.5 mg/kg during Weeks 8 →24. Lower mean body weight gains (↓12-18%) were observed in high-dose ♀ from Week 4 and onwards.
- Ophthalmoscopy - No treatment-related abnormalities were observed.
- ECG and Heart Rate - No anomalies were recorded.
- Hematology - There were some minor but not biological meaninful changes in hemograms. Increased leukocyte count (♂: 1.2-1.4x; ♀: 1.4-1.6x) with ↑ absolute segmented neutrophil count (♂: 2.6-3.6x; ♀: 2.2-5.9x) was identified in the high-dose group at Weeks 19 and 26 analyses.
- Clinical Chemistry - Slightly lower mean total protein (♂: ↓7%; ♀: ↓15%) with lower mean albumin (♂: ↓14%; ♀: ↓21%) values in high-dose group at Week 26. Urinalyses revealed that ♀

@ 2.0 and 3.5 mg/kg had an increased presence of blood and epithelial cells at Week 26 and Weeks 15 and 26, respectively. No positive fecal occult blood tests were obtained.

- Pathology -

Organ Weights: Slight increases in the absolute and relative spleen and kidney weights were observed in UH-AC 62-XX treated groups. Mean % changes in absolute and relative (to body weight) weights of kidney and spleen observed for each group is shown in the following table.

Dose (mg/kg)	Kidney Weight				Spleen Weight			
	Absolute		Relative		Absolute		Relative	
	♂	♀	♂	♀	♂	♀	♂	♀
1.0	↑10%	↑6%	↑8%	↑7%				
2.0	↑6%	↑16%	↑8%	↑13%		↑13%		↑9%
3.5	↑10%	↑28%	↑12%	↑41%	↑21%	↑21%	↑23%	↑33%

Gross Pathology: Kidney and GI were the target organs. The incidence of major macroscopic findings for each group is listed in the following table.

Gross Findings	Control		1 mg/kg		2 mg/kg		3.5 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Enlarged Kidney		1/24					2/24	
GI Ulcer - Pylorus			1/24			3/24	10/24	3/24
Fundus						1/24		1/24
Duodenal								2/24
Liver-Fatty Degeneration				2/24			5/24	
Pyelonephritis						1/24		3/24
Fissured Skin			1/24				1/24	1/24

Microscopic Pathology: Treatment-related histopathological alterations were limited to the GI and kidney. Dose-dependent incidence of gastric ulcers was observed. The GI lesions were characterized as extensive areas of inflammation in the region of the mucosa and submucosa with or without re-epithelialization, and perforating ulcers occasionally including the subserosa. The following table lists the incidence of major identified microscopic pathological changes for each group.

Microscopic Findings	Control		1 mg/kg		2 mg/kg		3.5 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Chronic nephritis		1/24						3/24
Brown lysosomal residual body in renal tubule				3/24	2/24	4/24	10/24	14/24
Pyelonephritis/papillary necrosis						1/24		8/24
Stomach - chronic ulcer/erosion and or			1/24			2/24	11/24	14/24
Stomach - granulating/proliferative inflammation			3/24		5/24	11/24	17/24	18/24
Duodenal Ulcer								2/24

Note: The sponsor reported that 2♂ @ 1.0 mg/kg had ulceration of gastric mucosa in the summary section; however, the reviewer could only identify 1♂ in this group with pyloric ulcer. Additionally, in the pathology report stated that 1♀ (animal Nº 354) @ 3.5 mg/kg had hyperplasia of the epididymis (197 mg). The sponsor should further clarify this observation. This is the 4th amendment submission for this NDA; yet, errors are still found in the report.

2.2.2.5. U88-0093 Chronic toxicity of UH-AC 62 XX in comparison with piroxicam in rats by oral administration over a period of 12 months. (Vol. 2.019, p 1)

U93-0493 Toxicokinetic monitoring of UH-AC 62 XX in rats during a long term study (52 weeks) at daily oral doses of 0.2, 0.4 and 0.8 mg/kg in comparison with piroxicam (0.8 mg/kg) (study no. 66 M). (Vol. 2.021, p 356)

Study Nº: 67 M

Report Nº: U88-0093 and U93-0493 (PK/TK)
Study Aims: To determine chronic toxicity of UH-AC 62 XX following oral administration for 12 months to rats.
Compound:
Dose and Route:
Vehicle Control:
Reference Article:
Animal: Wistar albino rats, 6-8 weeks of age, weighing 180-200 g, 20/sex/group.
Study Site:
Dosing Date: 1/28/1986 - 1/26/1987
GLP/QAC Compliance: Yes
Study Design: Groups of 20 rats/sex were randomly assigned to 5 dose groups as shown in the following table.

Group	Compound	Dose (mg/kg)	Dosing Vol. (ml/kg)	Dosing Duration	Nº of Animals
0	Vehicle Control	0	2.5	52 weeks	20/sex
1	UH-AC 62 XX	0.2			
2		0.4			
3		0.8			
4	Piroxicam	0.8			

The following parameters were monitored.

- Clinical Signs and Mortality - 2x/day.
- Food Consumption, H_2O intake, and Body Weights - 1x/week for Weeks 1-12 and 1x/4 weeks thereafter.
- Heart Rate and ECG - Weeks -1, 17, 28 and 51 (Pre-R, 2 and 4 hr post-dose, 5/sex from Groups 0, 3, and 4).
- Clinical Pathology - Hematology and Serum Chemistry: Weeks -2, 8, 13, 26(♂)/27(♀), and 52; Urinalysis: Weeks -2(♂)/-1(♀), 7, 13, 28, and 52; Fecal Occult Blood, Weeks -2, 2, 8, 12, 25, and 51. The following parameters were analyzed:

Hematology					
RBC	WBC and Differential	Reticulocyte		Hb	Ht
MCH / MCHC	TPT (Thromboplastin Time)	MCV	Platelets	pTT (Partial Thromboplastin Time)	
Serum Chemistry					
ALT (SGPT)	Alkaline Phosphatase (ALP)	BUN	Creatinine	Chloride	
Leucine Arylamidase (Leucine Aminopeptidase) (LAP)		Total Glycerol		Potassium	
AST (SGOT)	Aldolase	Calcium	Sodium	Magnesium	
γ-Glutamyl Transpeptidase	Total Bilirubin	Total Protein		Total Cholesterol	
Choline Esterase	Glucose	Protein Fractions		Inorganic Phosphate	
Urinalysis and Fecal Occult Blood					
Specific Gravity, Color	pH	Glucose		Ketone	
Protein	Blood	Nitrite		Urine Sediment Analysis	
Urobilinogen	Bilirubin	Urine Volume		Fecal Occult Blood	

- Ophthalmology (Ophthalmoscope & Slit Lamp) - **Not determined.**
- PK/TK - Blood samples were taken at Weeks 1, 7, 13, and 52 prior to daily dosing for determination of plasma UH-AC 62 XX trough levels.
- Necropsy - Week 52/53. The following organs from each group were preserved in [redacted] and examined microscopically [except femur and tubes (?)]. Organs with asterisk (*) were weighed. Bone marrow smears (from femoral bone) were prepared from all animals, but only smears from 5/sex animals in Groups 0, 3, & 4 were evaluated.

Heart*	Lung*		Liver*		Kidneys*,1			Thymus*			Spleen*	Testes*,1	
Adrenals*	Pituitary*		Thyroid with Parathyroids*					Brain* (Cerebrum & Cerebellum)				Prostate*	
Parotid Gland	Esophagus		Stomach		Duodenum		Jejunum	Ileum		Colon	Lymph Node (Cervical & Mesenteric)		
Aorta	Skeletal Muscle (Vastus)				Sublingual Gland			Submandibular Gland			Pancreas	Trachea	
Epididymis	Uterus		Tube (?)		Ovaries*			Bladder			Skin	Mammary Glands	
Lacrimal Gland	Sternum	Femur	Peripheral Nerve (Sciatic)					Eye with Optic Nerve1			Lesions	Bone Marrow	

* Tissues/Organs were weighed; 1 Tissues/Organs were fixed in Bouin's fluid.

Results:

- General Condition and Mortality - No remarkable clinical signs were observed. There were 19 unscheduled deaths (7 @ 0, 2 @ 0.2, 3 @ 0.4, and 2 @ 0.8 mg/kg UH-AC 62 XX; 5 @ 0.8 mg/kg piroxicam). The causes of most of these deaths except two rats that died of tumors (one with a pituitary adenoma, the other with a unidentified tumor) were resulted from improper handling technique or over dose of anethesia.
- Food Consumption and Body Weights - There were no treatment-related changes.
- Heart Rate and ECG - No treatment-related effects were noted.
- Clinical Pathology - Minor changes (↑ or ↓) were observed, but the values were within normal biological ranges.
- PK/TK - Mean plasma trough levels of UH-AC 62 XX and piroxicam at Weeks 1, 7, 13, and 52 are shown in the following table. Apparent gender differences in drug metabolism were noted as ♀ had 3x higher blood trough UH-AC 62 XX levels at Week 52 than ♂ did. Repeated dosing of either UH-AC 62 XX or piroxicam caused accumulation of drug in the females.

Compound	Dose (mg/kg)	Plasma Drug Levels (μg/ml)							
		Week 1		Week 7		Week 13		Week 52	
		♂	♀	♂	♀	♂	♀	♂	♀
UH-AC 62 XX	0.2	0.71	2.7	0.78	3.0	1.1	3.0	1.2	3.7
	0.4	1.4	4.2	1.6	4.5	1.7	4.2	2.4	7.7
	0.8	2.3	6.6	3.0	8.5	4.4	9.8	3.5	12
Piroxicam	0.8	0.57	3.7	0.97	4.7	0.63	3.6	0.76	5.6

- Necropsy -

  Organ Weights: A slight increase in absolute kidney (↑12%) and liver (↑12%) weights was seen in ♂ @ 0.8 mg/kg.

  Gross Pathology: Erosions or hemorrhagic erosions in the stomach were noted in 1♀ @ 0, 1♂ @ 0.2, 1♂ @ 0.4, and 1♂+1♀ @ 0.8 mg/kg and 1♂ in the piroxicam group. A small ulcer in the stomach of 1♂ @ 0.2 and 1♂+1♀ @ 0.8 mg/kg was also characterized.

  Histopathology: No ulcerous changes were identified in those animals that had a gross ulcer lesion in the stomach. Erosions in the stomach were found in a total of 13 UH-AC 62 XX treated animals: 0 mg/kg, 3♂+1♀; 0.2 mg/kg, 1♂+2♀; 0.4 mg/kg, 2♂+2♀; and 0.8 mg/kg, 2♀. Three (1♂+2♀) piroxicam treated rats also had erosions in the stomach.

No drug-caused effects on clinical signs, mortality, body weight, food consumption, ECG, and clinical pathology parameters were observed. Although gross lesions of gastric ulcers were identified in some animals, these observations were not confirmed by microscopic examination of serial sections of the collected gross lesions. Since the incidence of microscopic gastric erosions was evenly distributed in each group, it might not be treatment-related. In addition, lesions of gastric erosions are common in aged rats. **Therefore, MTD was not achieved in the present study.**

Note:

1. **This is an oral toxicity study. However, "injection point" was included in the list of organs collected during necropsy (Vol. 2.019, p 33) for histology.**