CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-938**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-938

SUBMISSION DATE: 12/16/99, 2/5/99, 4/26/99, 7/9/99, 7/19/99, 7/29/99, 8/2/99

NDA TYPE: 1S

PRODUCT: MOBIC® Tablets 7.5 mg (Meloxicam)

SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877

REVIEWER: Veneeta Tandon, Ph.D.

NDA Review

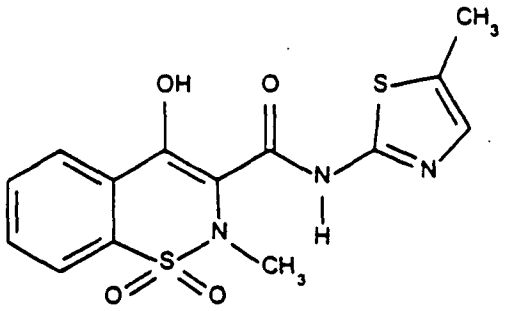
1. BACKGROUND

Pharmacological Class: Nonsteroidal anti-inflammatory drug (NSAID) belonging to the oxicam class.

Indication: For the relief of sign and symptoms of acute and chronic osteoarthritis.

Dosage and Administration: Recommended dose is 7.5 mg, with a maximum recommended daily dose of 15 mg, given orally once daily. Dose may be taken with food.

Meloxicam is chemically described as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide and has a molecular weight of 351.4. The structure and molecular formula of meloxicam is shown below.



Meloxicam is an NSAID that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models and exerts its action by preventing the biosynthesis of prostaglandins through the inhibition of cyclooxygenase synthetase.

Foreign Marketing History: Approved in over 70 countries outside U.S. for the treatment of osteoarthritis, rheumatoid arthritis and ankylosing sponylitis, available as tablets, capsules, ampules (for injection) and suppositories.

II. RECOMMENDATION

The sponsor has evaluated the pharmacokinetics of meloxicam primarily using a capsule dosage form and has conducted one bioequivalence study linking the capsule dosage form to the to-be-marketed meloxicam tablets along with clinical trials. The reviewer recommends approval of the application from a pharmacokinetics standpoint. The labeling review is deferred at this time.

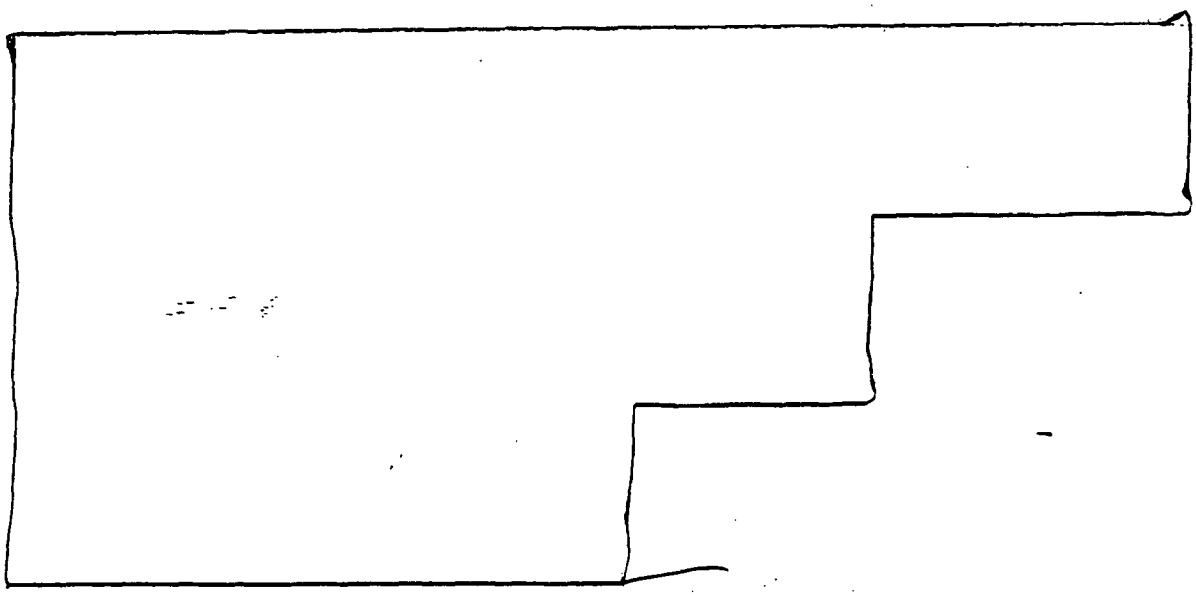
TABLE OF CONTENTS

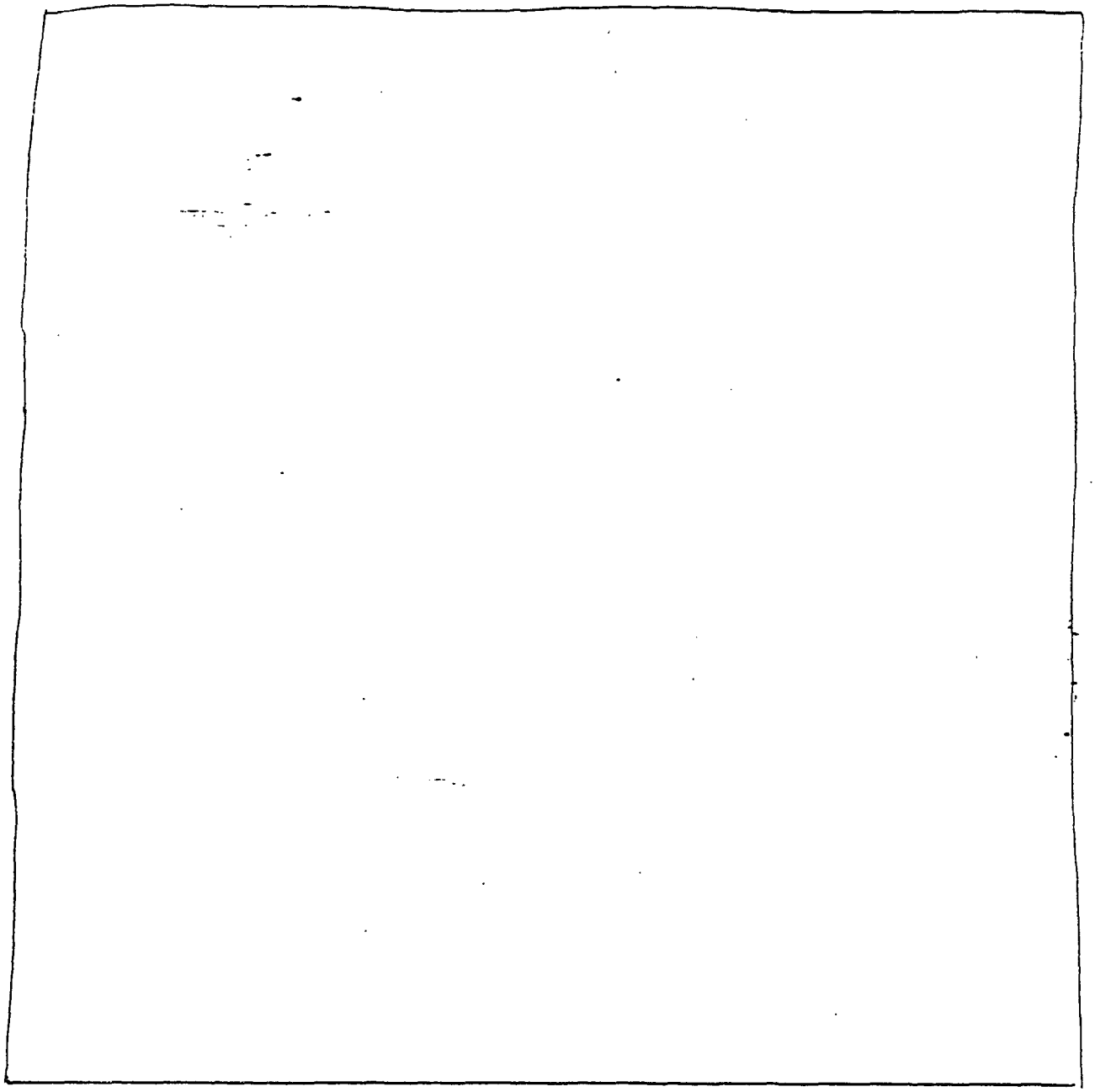
III. FORMULATION

The qualitative and quantitative composition of MOBIC® tablets, 7.5 mg is shown in the following table:

Component	Mg/tablet
Meloxicam, USP	7.5
Sodium citrate dihydrate, NF	
Lactose monohydrate, NF	
Microcrystalline cellulose, NF	
Povidone, USP	
Colloidal silicon dioxide, NF	
Crospovidone, NF	
Magenesium stearate, USP	
Total weight	180

IV. ANALYTICAL VALIDATION





Reviewer's Comment

Individual analytical study reports have been reviewed along with each study and are acceptable.

V. REVIEW OVERVIEW

The sponsor has submitted 48 in vivo pharmacokinetic studies along with 11 in-vitro studies. Out of these, 32 in vivo and 11 in-vitro studies have been reviewed in full length and important conclusive observations from the other studies have been documented in this review.

These reports have not been reviewed as the dosage form and the doses are not relevant to the to-be-marketed meloxicam formulation and doses. However, relevant information pertaining to dose proportionality has been obtained from some of the studies. The organization of the studies is given in the 'Table of Contents' on page 2, which will facilitate the reader to get an overview of the different studies submitted in support of the clinical pharmacology and biopharmaceutics of meloxicam. The conclusions and comments have been provided at the end of each section. The overall conclusions from the "Pharmacokinetics section" of the NDA are provided at the end of this review.

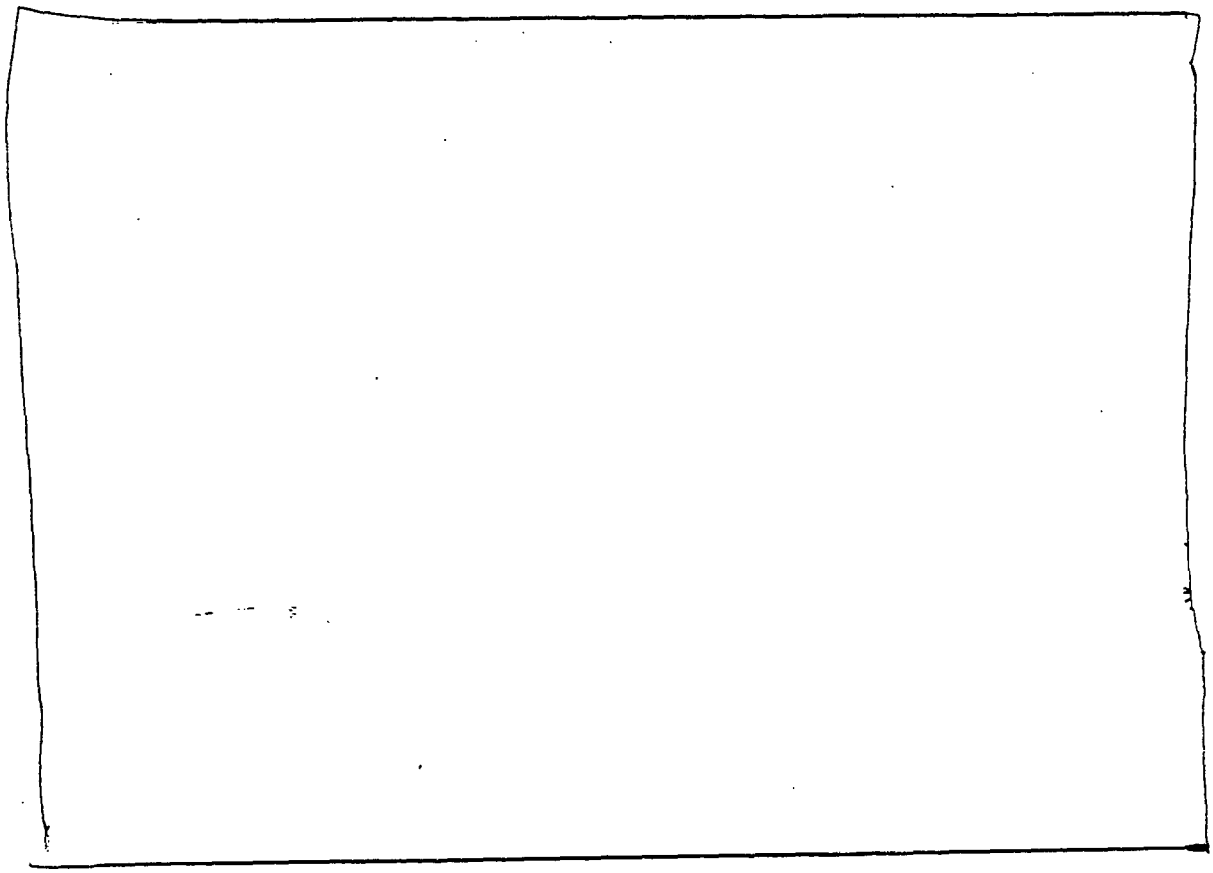
Additional eight drug interaction studies have been reviewed by Dr. Dan Wang and are provided in a separate review.

V.1 METABOLISM STUDIES

(A) IN-VITRO METABOLISM

Hepatic metabolism of meloxicam in man and involvement of CYP-450 enzymes:

The in vitro metabolism of meloxicam has been elucidated in several in vitro studies. The key points from all these studies and their reports have been combined and recapitulated here to better understand the metabolism of meloxicam.



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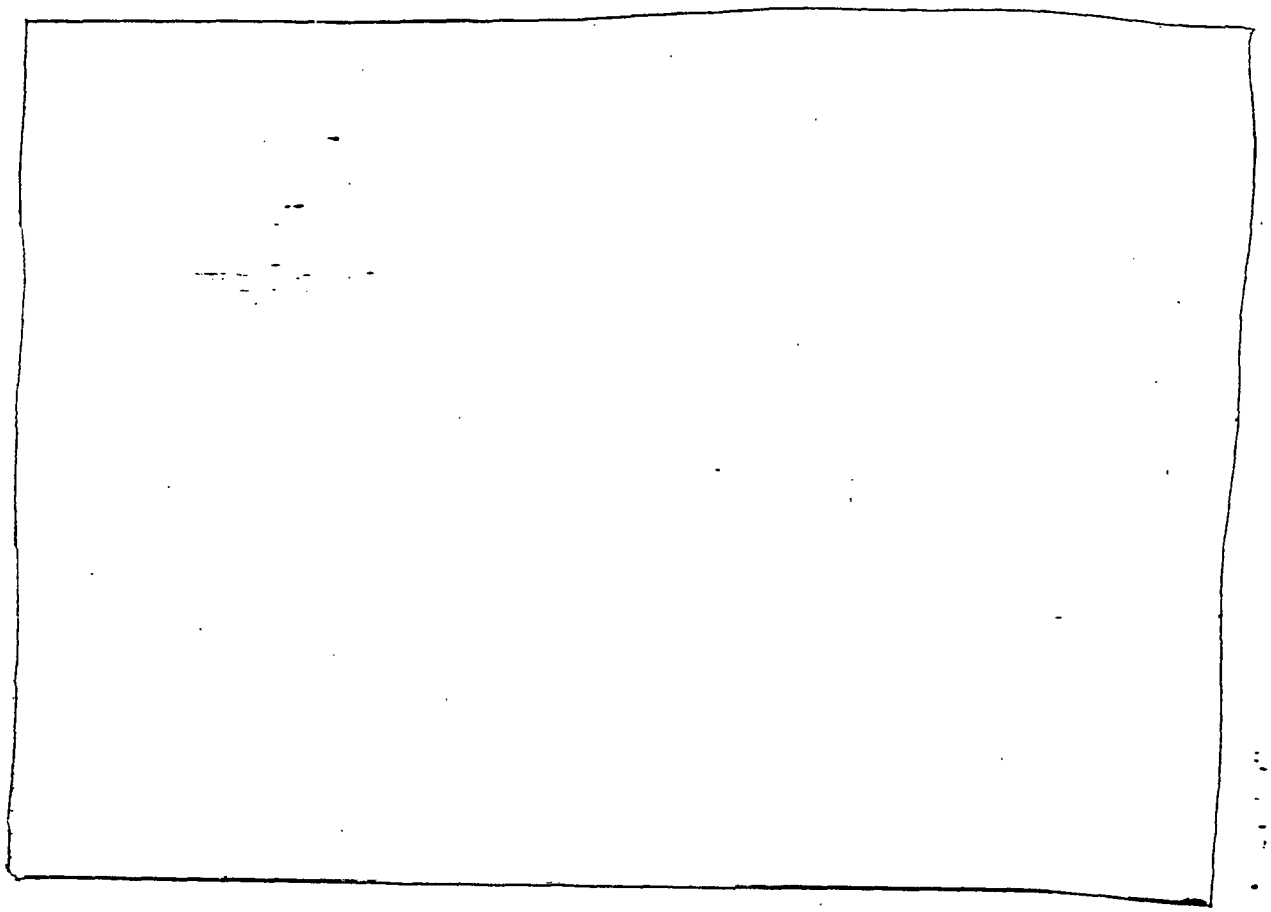

Conclusions

- There is strong evidence that CYP2C9 is involved in the biotransformation step yielding AF-UH 1SE. From another experiment it was concluded that CYP2C9 was involved in the metabolism with a Km of about 10 μM.
- The involvement of CYP3A4 cannot be ruled out. The involvement of CYP 3A4 was also shown by a Km of 475 μM in another experiment. The contribution of CYP3A4 gets more important when there is low CYP2C9 content in the liver.
- The involvement of CYP1A2 cannot be ruled out.
- Dextrometorphan, a 2D6 substrate had no influence, but quinidine (substrate for CYP3A4 and potent inhibitor of CYP2D6) activated the concentration dependent biotransformation up to 6 fold.
- There is no influence of known inducers at the rate of biotransformation of meloxicam and its metabolic pattern.
- Meloxicam has no direct effect on CYP1A, 2D6, 2E1 and 3A catalyzed activities; while it could act as a substrate or inhibitor of CYP2C.
- The other oxicams are also metabolized by CYP2C9 isoenzyme.

References:
1. Report B526: Hepatic metabolism of meloxicam in man, involvement of CYP-450 enzymes (10 experiments conducted under this report)
2. Report B460: Further investigations on hepatic metabolism, (3 experiments under this report)
3. Report B660: Metabolism of meloxicam by human liver microsomes and by recombinant CYP P450

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Amounts of meloxicam metabolites in plasma:

V.2 PROTEIN BINDING

The plasma protein binding of a substance is an important pharmacokinetic parameter because it provides information concerning the pharmacodynamic activity of a molecule, assuming that only the unbound portion of a drug produces the pharmacological effect.

The key points regarding protein binding of meloxicam are outlined below:

V.3 ABSORPTION

(A) BIOAVAILABILITY (ABSOLUTE AND GENERAL PHARMACOKINETICS)

In Healthy Subjects

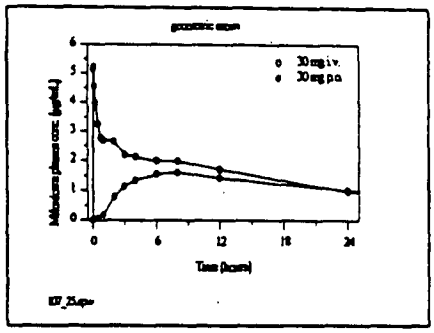
(i) Single Dose Studies

Study # 107.025: Absolute Bioavailability of meloxicam. Comparative pharmacokinetics of 30 mg orally and 30 mg IV as bolus injection in healthy volunteers.

The absolute bioavailability was determined following single 30 mg doses of meloxicam administered orally and by IV bolus injection in 12 healthy male volunteers. The detail of the study design is provided in the Appendix on page 6. The single dose was administered after an overnight fast and the subjects remained fasted for 2 hours post dose. Blood samples were collected 96 hours post dosing. The mean plasma concentration profile and pharmacokinetic parameters are provided below.

		30 mg IV bolus injection			30 mg oral capsule		
parameter	units	mean	%CV	median	mean	%CV	median
C_{MAX}	[µg/mL]	--	--	--	1.72	18.8	1.68
t_{MAX}	[h]	--	--	--	8.7	24.8	8.0
λ_Z	[h^{-1}]	0.0378	33.7	0.0327	0.0373	42.6	0.0340
$t_{½}$	[h]	20.0	28.2	21.3	22.0	39.6	20.4
$AUC_{0\text{-}TLQC}$	[µg·/mL]	72.4	30.0	72.2	62.3	26.7	64.3
$AUC_{0\text{-}\infty}$	[µg·h/mL]	76.9	30.7	77.5	67.5	29.3	67.8
MRT_{TOT}	[h]	27.0	29.1	28.2	34.2	36.3	32.2
Cl or Cl/f	[mL/min]	7.15	32.9	6.50	8.15	35.4	7.39
Vd or Vd/f	[L]	11.4	13.5	11.8	14.0	25.6	12.9
Vd_{ss}	[L]	10.7	13.0	10.8	--	--	--
f	--	--	--	--	0.892	17.4	0.909

The $AUC_{0-\infty}$ values after oral and IV bolus dosing indicated an absolute bioavailability of 89%. The t_{max} after oral administration was 8.7 hour with a slow and prolonged elimination ($t_{1/2}$ 22 h after oral route). In some cases a second meloxicam concentration peak occurred at 12-14 hours. The drug exhibited a plasma concentration profile with a pronounced plateau, probably due to the prolonged absorption. This slow absorption and elimination suggested that the use of once/day treatment could be adequate for meloxicam with relatively small peak-to-trough fluctuations. The mean residence time was 34.2 hours. The mean Vdss was 10.7 L, which approximates the extracellular fluid volume. The other pharmacokinetic parameters can be seen in the table above.



Conclusions

- The absolute bioavailability of meloxicam after a 30 mg oral dose (capsules) is 89%.
- Meloxicam has prolonged absorption and elimination with a t_{max} of ~9 hours and the half-life of 20-22 hours.
- Vdss is 10 L.

Absolute bioavailability was assessed with various dosage forms and dosage strengths. All the pharmocokinetic studies have been conducted using the capsule dosage form. A few of these studies are briefly summarized here mainly for the purpose of comparison between the studies or to assess absolute bioavailability using historical data.

Study 107.056: Pharmacokinetics and tolerability of 15 mg meloxicam as a single IM injection compared with 15 mg as a slow IV bolus injection in healthy volunteers.

A similar study was done with a lower dose of meloxicam (15 mg) to determine the absolute bioavailability after an IM dose in 12 healthy male volunteers. Blood samples were collected up to 96 hours post dosing. The IM and IV bolus doses were equivalent with respect to $AUC_{0-\infty}$ with an absolute bioavailability of 100%. The observed C_{max} (1.62 µg/ml) after IM injection was similar to that following a single oral dose (1.72 µg/ml) at twice the potency, or 30 mg (study 107.025).

Study 107.171: Absolute bioavailability and tolerability of 7.5 mg meloxicam as a single IM injection or IV infusion in healthy subjects (a crossover study).

This study is similar in design to the previous studies. The sponsor has used data for the 7.5 mg single dose of IV infusion and compared it to the historical data from another study (Study no. 107.116) to estimate the absolute bioavailability of 7.5 mg capsules. Study 107.116 is a multiple dose study. The following table shows the pharmacokinetic parameters of 7.5 mg IV infusion and 7.5 mg capsules from the two studies.

parameter	units	7.5 mg intravenous (reference) single dose			7.5 mg capsule (historical test) multiple dose		
		mean	gmean	%gCV	mean	gmean	%gCV
$C_{MAX,SS}$	[µg/mL]	1.21	1.20	14.7	1.03	0.996	27.0
AUC_{SS}	[µg·h/mL]	18.4*	18.2	14.1	17.6	16.9	30.4
$C_{MAX,SS}$ / AUC_{SS}	[1/h]	-	-	-	0.0594	0.0592	8.7
$t_{MAX,SS}$	[h]	0.53	0.52	0.54	6	5**	4-14 §
$C_{PRE,SS}$	[µg/mL]	-	-	-	0.595	0.550	42.2
$C_{MIN,SS}$	[µg/mL]	-	-	-	0.492	0.457	40.7
C_{av}	[µg/mL]	-	-	-	0.734	0.702	30.4
λ_z	[h^{-1}]	0.0389	0.0385	16.3	0.0328	0.0319	26.2
$t_{1/2}$	[h]	18.2	18.0	16.3	22.5	21.8	26.2
MRT_{TOT}	[h]	24.9	24.5	17.7	36.8	35.8	24.7
Cl/f	[mL/min]	6.93	6.86	14.1	7.73	7.42	30.4
Vd/f	[mL/min]	10.7	10.7	6.9	14.2	14.0	17.3

* AUC0-∞ **median § range

A historical comparison between this study and data from the steady state study (107.116) suggests an absolute bioavailability of 93%.

(ii) *Other Single Dose Studies*

Study 107.062: Bioequivalence of the 15 mg suppository in comparison with the 15 mg capsule of meloxicam as a single administration in healthy volunteers.

This study was reviewed to get information on the single dose pharmacokinetics of the 15 mg meloxicam capsule. The bioequivalance part the study design will not be discussed here.

This was a randomized open 2-way crossover study in 18 healthy male volunteers. The dose was administered in a fasted state followed by a breakfast two hours later. The mean pharmacokinetic parameters for the single dose 15 mg capsule is shown in the adjacent table.

parameter	units	15 mg capsule		
		mean	%CV	median
C_{MAX}	[µg/mL]	0.747	22.2	0.720
t_{MAX}	[h]	9.4	32.7	10.0
λ_z	[h^{-1}]	0.0339	23.2	0.0350
$t_{1/2}$	[h]	21.7	28.0	19.9
AUC_{0-TLQC}	[µg·h/mL]	26.87	23.0	25.24
$AUC_{0-\infty}$	[µg·h/mL]	30.95	30.1	28.96
MRT_{TOT}	[h]	34.9	24.6	32.2
Cl/f	[mL/min]	8.63	24.2	8.63
Vd/f	[L]	15.5	19.2	16.0

Study 107.174: Relative bioavailability of 7.5 mg meloxicam given as 12 mg UH-AC 62 MU (rapid release tablet) in comparison to 7.5 mg meloxicam capsule administered oral as single doses in healthy volunteers.

A meglumine salt of meloxicam (UH-AC 62 MU) was formulated as a rapid release tablet that differs from meloxicam itself just by a more rapid dissolution. The relative

bioavailability of the rapid release tablet is compared to 7.5 mg capsule. The reason for reviewing this study is that it would give more insight into the single dose pharmacokinetics of 7.5 mg meloxicam capsules. As such the rapid release tablet dosage form has no relevance to the current NDA. The to-be-marketed tablet is not a rapid release tablet, hence, evaluating the performance of a rapid release dosage form is not any relevance. This was the only single dose study with 7.5 mg capsules. Therefore, discussions regarding comparative pharmacokinetic parameters will be minimal in this section of the review. However, the plasma profiles and tabular summary of the results have been given below.

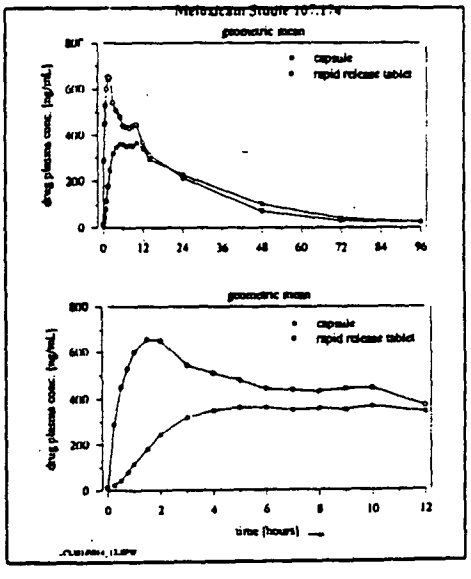
18 healthy subjects (9M and 9F) participated in this single dose crossover study with blood samples being evaluated up to 96 hours post dose. Other details of the study are provided in the Appendix on page 7. The mean pharmacokinetic parameters for the 7.5 mg rapid release tablet and the capsule dosage form is shown below.

		7.5 mg meloxicam as rapid release tablet				7.5 mg meloxicam as capsule					confidence
parameter	unit	geom. mean	gCV (%)	arithm. Mean	CV (%)	geom. mean	gCV (%)	arithm. mean	CV (%)	point estimate	interval (90 %)
C_{max}	[µg/mL]	0.81	22.6	0.83	22.8	0.42	27.3	0.44	27.9	1.91	167 - 218
t_{max} *	[h]	1.5	0.5-10	1.9	115	8.5	2-12	7.9	38.7	--	--
$AUC_{0-\infty}$	[µg·h/mL]	15.0	26.7	15.6	31.2	14.1	31.0	14.8	34.5	1.07	100 - 113
λ_z	[h^{-1}]	0.0406	32.1	0.0423	28.2	0.0355	27.9	0.0367	26.2	1.144	107 - 122
$t_{1/2}$	[h]	17.1	32.2	18.0	37.2	19.6	27.9	20.3	30.1	0.874	82.0 - 93.2
MRT_{tot}	[h]	22.8	32.0	24.0	37.8	30.5	23.5	31.3	25.8	0.746	68.9 - 80.9
Cl/f	[mL/min]	8.33	26.6	8.58	23.1	8.88	31.1	9.25	27.7	0.938	88.3 - 99.8
Vd/f	[L]	12.3	20.3	12.6	20.1	15.0	20.5	15.3	21.6	0.820	74.7 - 89.9

* median and range instead of geometric mean and gCV (%)

Historically comparing to the 7.5 mg IV data from Study 107.171, the absolute bioavailability of 7.5 mg capsules can be estimated as 78%.

Multiple peaks can be seen more prominently with the capsule and can be explained by the occurrence of (a) continued absorption of several portions of slowly dissolving drug, (b) precipitation of the drug followed by redissolution, especially because meloxicam is poorly soluble in acidic media. Hence, meloxicam could be getting precipitated in the stomach and could be redissolving after meal, (c) gastrointestinal recirculation, enterohepatic or enteroenteric.



Female subjects showed higher C_{max} than males for the rapid release tablets. However, this was not the case for capsules with female's showing a lower rate and extent of absorption than males: Data and plots attached in the Appendix on pages 8-9.

(iii) Multiple Dose Studies

The multiple dose studies summarized below are mainly relative bioavailability studies comparing different strengths of the capsule dosage form to other dosage forms (such as suspension, rapid release tablets etc). The relative bioavailability aspect of these studies is of no relevance to this application for meloxicam tablets. These studies have been reviewed only to shed some light on the 7.5 mg and 15 mg (to-be marketed dose) multiple dose pharmacokinetics of the capsule dosage form.

Study 107.172: Relative bioavailability of 15 mg meloxicam syrup (suspension) PO in comparison to 15 mg capsule PO after steady state in healthy volunteers.

This study has been reviewed to obtain multiple dose (15 mg for 7 days) pharmacokinetic information of meloxicam capsule dosage form. The drug was given in a fasted state on day 1 and serial plasma samples were obtained for up to six hours postdose. Subsequently meloxicam was given after a breakfast and complete drug plasma concentration-time profiles were determined for 72 hours after the last dose on day 7. On day 7, urine voided within 24 hours after the last drug intake was collected. The relative bioavailability of syrup and capsule dosage form is of minimal relevance to this application. Details of the study design are provided in the Appendix on page 10. This study provided some more information on the metabolism of meloxicam as well, which has been summarized in the 'in vivo metabolism' section of this review.

The pharmacokinetic parameters after multiple doses of 15 mg meloxicam are shown in the adjacent table for the capsule dosage form. Steady state was achieved by Day 5. The point estimates of concentration differed by less than 10% between Day 5 and Day 7. The time to reach steady state is in accordance with a half life of 20 hours. The plasma concentration profile after single and multiple dose of 15 mg meloxicam is attached in the Appendix on page 11.

		15 mg capsule		
parameter	units	mean	%CV	gmean
$C_{MAX,SS}$	[µg/mL]	1.98	32.7	1.88
$C_{MIN,SS}$	[µg/mL]	0.825	47.4	0.740
$t_{MAX,SS}$*	[h]	5.5	21.0	5.0*
$t_{1/2}$	[h]	19.6	28.8	18.9
AUC_{ss}	[µg·h/mL]	32.8	38.2	30.7
MRT_{TOT}	[h]	33.4	26.1	34.5
Cl/f	[mL/min]	8.68	36.6	8.13
Vd/f	[L]	13.5	20.6	13.3

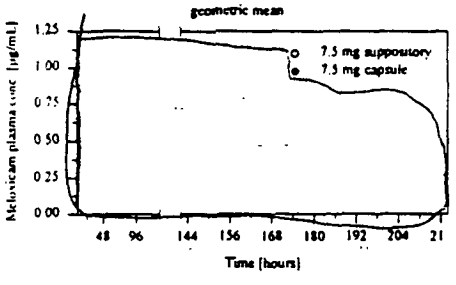
*t_{MAX} median

Study No. 107.116: Relative bioavailability of the 7.5 mg suppository in comparison with 7.5 mg meloxicam capsule at steady state in healthy volunteers

The main objective of study 107.116 was to evaluate the relative bioavailability of 7.5 mg meloxicam capsule as compared to the suppository dosage form after multiple doses for 7

days, which does not have any relevance for this application. The discussion on urinary metabolites evaluation from this study has been elaborated in the "Metabolism- In Vivo Studies" Section of this review. Only discussions on the steady state pharmacokinetics after dosing with 7.5 mg meloxicam in the capsule form is discussed here. Comparison with the suppository dosage form will not be discussed. The drug was administered within 20 minutes after a standardized breakfast in the morning with lunch 5 hours post dose. Blood samples were collected serially for 72 hours after the last dose.
The steady state geometric mean meloxicam plasma concentration profile and the pharmacokinetic parameters are shown in the table below.

Peak plasma concentrations occurred 6 hours post dose. Achievement of steady state was not formally studied. However, the individual plasma concentration-time profiles suggested that the steady state was achieved on Days 3 to 5. Geometric mean elimination half-life was 21.8 hours.



parameter	units	7.5 mg capsule		
		mean	gmean	%gCV
$C_{MAX,SS}$	[µg/mL]	1.03	0.996	27.0
AUC_{SS}	[µg·h/mL]	17.6	16.9	30.4
$C_{MAX,SS}$ / AUC_{SS}	[1/h]	0.0594	0.0592	8.7
$t_{MAX,SS}$	[h]	6	5*	4-14 §
$C_{PRE,SS}$	[µg/mL]	0.595	0.550	42.2
$C_{MIN,SS}$	[µg/mL]	0.492	0.457	40.7
C_{av}	[µg/mL]	0.734	0.702	30.4
λ_z	[h^{-1}]	0.0328	0.0319	26.2
$t_{1/2}$	[h]	22.5	21.8	26.2
MRT_{TOT}	[h]	36.8	35.8	24.7
Cl/f	[mL/min]	7.73	7.42	30.4
Vd/f	[mL/min]	14.2	14.0	17.3

In Patients

Study 107.085: Multiple-dose PK of 15 mg meloxicam capsules once daily in elderly male and female subjects with OA and RA compared to younger adult male and female patients

This study has been discussed in the section "Effect of Gender".

Study 107.090: Articular diffusion of meloxicam after single oral administration of 15 mg (capsules).

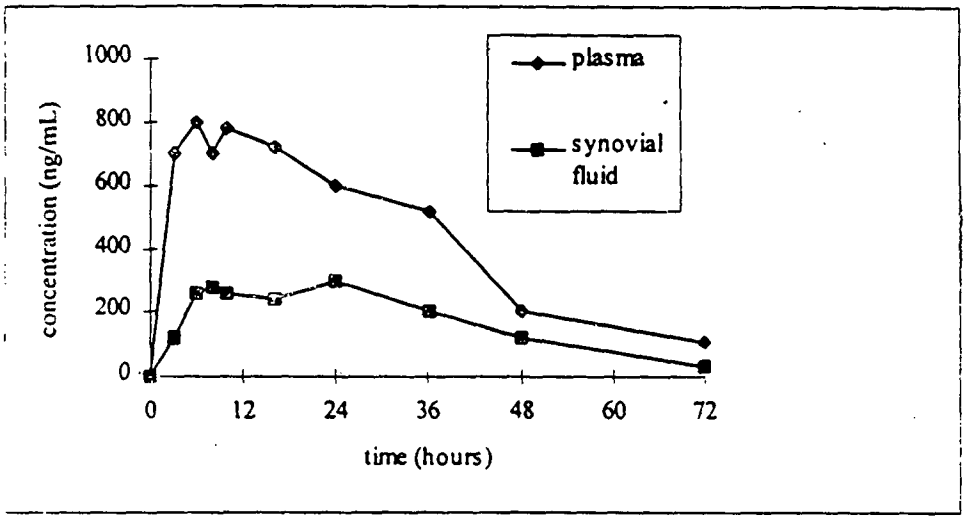
Synovial compartment is the major site of action of NSAIDs in rheumatic diseases. Hence articular distribution of meloxicam was evaluated in this single dose study and the ratio of synovial fluid to plasma concentration was determined.

46 patients (24M, 22F) suffering from knee effusion requiring a diagnostic or therapeutic knee puncture were enrolled in the study. 28 of them suffered from osteoarthritis, 8 from rheumatoid arthritis, 4 from spondylarthopathy and 6 from other rheumatological diseases. Synovial fluid and venous blood were sampled at 1, 3, 6, 8, 10, 16, 24, 36, 48 or 72 hours after the meloxicam dose intake. From each patient only one pair of plasma

and synovial fluid samples were taken at a given time point. Protein binding of meloxicam was determined by equilibrium dialysis.

Results

The mean plasma concentration profiles in the plasma and synovial fluid are shown below. Individual concentrations showing the variability is attached in the Appendix on pages 13-14.



The meloxicam plasma and synovial fluid concentrations at different time points after a single dose is attached in the Appendix on page 12. Results showed that absorption started one hour after dose. The distribution from plasma to synovial fluid took some time, which was indicated by a synovial/plasma ratio, and was not at steady state at earlier time points. A constant ratio was achieved at about 6 hours and was maintained till 48 hours. There was an outlier (very high) at the 72 hour post dose time-point and one value BLQ. The average of the ratio at steady state was 0.392. Thus approximately 40% of the accompanying plasma concentration is achieved after about 6 hours. On average 7-9% of the plasma concentrations were found one hour post dose in synovial fluid. At three hours post dose the percentage increased to 23-24%. The individual ratios over time are shown in the Appendix on page 15.

The pharmacokinetic parameters in the plasma and synovial fluid are shown in the table below:

		Synovial fluid (test)		Plasma (reference)		Ratio
parameter	units	mean	gmean	mean	gmean	Mean
C_{MAX}	[ng/mL]	320	304	842	797	0.380
t_{MAX}	[h]	6	24	16	6	–
$t_{1/2}$	[h]	16.6	13.4	21.0	16.1	0.790
$AUC_{0-\infty}$	[ug·h/mL]	12.6	11.4	35.4	30.3	0.356
MRT_{TOT}	[h]	31.3	28.7	33.7	28.7	0.929
Cl/f	[mL/min]	19.8	21.8	7.05	8.26	2.81
Free fraction	[%]	0.969	0.868	0.390	0.339	2.49

The mean meloxicam concentrations in synovial fluid were at any time lower than in plasma. The free fraction in synovial fluid was 0.87% and 0.34%. Higher free fraction in synovial fluid may compensate for lower total meloxicam concentration in comparison to plasma.

The plasma results from this trial (in patients) was compared to that obtained from studies in healthy volunteers. The comparative PK parameters are shown in the table below.

		Trial 107.090 (test) In patients		Earlier trial (reference) In healthy	
parameter	units	mean	gmean	mean	gmean
C_{MAX}	[ng/mL]	842	797	933	916
t_{MAX}	[h]	16	6	6	5.7
$t_{1/2}$	[h]	21.0	16.1	19.3	27.7
$AUC_{0-\infty}$	[ug·h/mL]	35.4	30.3	28.8	9.01
MRT_{TOT}	[h]	33.7	28.7	31.1	30.2
Cl/f	[mL/min]	7.05	8.26	9.36	18.4

Meloxicam pharmacokinetics were similar in healthy volunteers and patients with only a slight trend towards higher AUC values and lower C_{max} values.

Conclusions

The diffusion of meloxicam in synovial fluid in patients after single administration of 15 mg meloxicam p.o. is about 40% of the corresponding concentration in plasma.

(B) EFFECT OF FOOD ON BIOAVILABILITY

The effect of food has been evaluated in two studies.

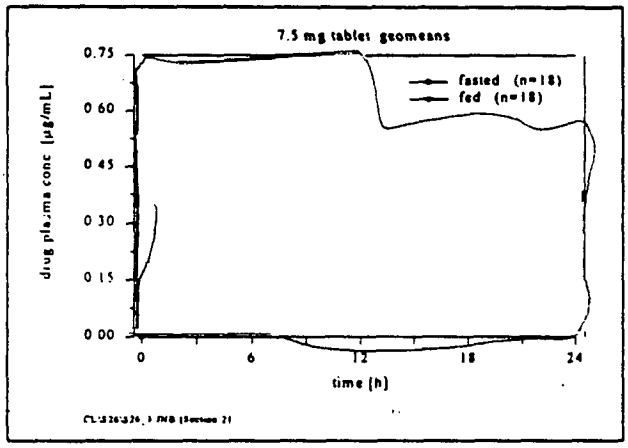
(i) *Light-fat Diet* *(according to the sponsors standards)*

Study 107.178: Influence of 40 g fat breakfast on the single oral dose pharmacokinetics of the 7.5 mg meloxicam tablet in healthy subjects

This study investigated the effect of light fat (40 g) food on the bioavailability of 7.5 mg meloxicam tablets (American type) administered orally to 9 healthy male and 9 healthy female volunteers as a single dose. Volunteers were administered single 7.5 mg tablets either following an overnight fast, remaining fasted for 4 hours post-dose, or directly after a 40 g fat (591 kcal) breakfast. The 40 g fat breakfast consisted of bread, butter, cheese and salami. Other details of the study design are outlined on page 16 of the Appendix along with the demographics on page 17.

The pharmacokinetic parameters and the plasma concentration-time profile are shown in the following table.

		7.5 mg fasted		7.5 mg + 40 g fat			
parameter	units	a.mean	%CV	a.mean	%CV	Point Estimate	90% CI
C_{max}	[µg·h/mL]	0.714	24.5	0.685	16.2	0.974	90.1-105
t_{max}	[h]	5.1	54.1	7.3	43.1	-	-
λ_z	[h^{-1}]	0:0302	24.7	0.0308	24.4	-	-
$t_{1/2}$	[h]	24.0	23.6	23.7	23.6	0.989	92.6-106
AUC_{0-24}	[µg·h/mL]	10.8	18.2	10.5	14.4	-	-
$AUC_{0-\infty}$	[µg·h/mL]	22.9	25.7	22.6	22.7	0.989	93-105
MRT_{TOT}	[h]	35.2	22.1	35.4	20.8	1.01	94.8-107
Cl/f	[mL/min]	5.81	25.9	5.85	24.8	1.01	95.1-107
Vd/f	[L]	11.6	18.5	11.5	12.9	1.00	93.4-107



The table indicates very similar similar results for both treatments fed and fasted with trend to a later t_{max}. This trend was caused by the fact that the second peak (10-11h) was higher in more subjects after fed treatment (7 of 18) in comparison with fasted treatment (3 of 18). The CL values were slightly lower and the $t_{1/2}$ higher than trials with capsules. This could be due to difference in bioavailability due to tablet dosage form.

Tables for gender differences in the fed and fasted conditions are attached in the Appendix on page 18. Females in general showed higher C_{max} (19% under fed conditions and 34% under fasted conditions) and $AUC_{0-\infty}$ (9-10% in either treatment condition), with a slightly faster absorption and a smaller volume of distribution under fasted conditions. The elimination half-life was 10% shorter in females, which is expected for a constant intrinsic clearance and a smaller volume of distribution. This trial had lower body weight of female subjects (66 vs 83 kg) and could be the reason for higher drug concentrations. The effect of gender has been evaluated in other studies too and will be discussed in subsequent sections.

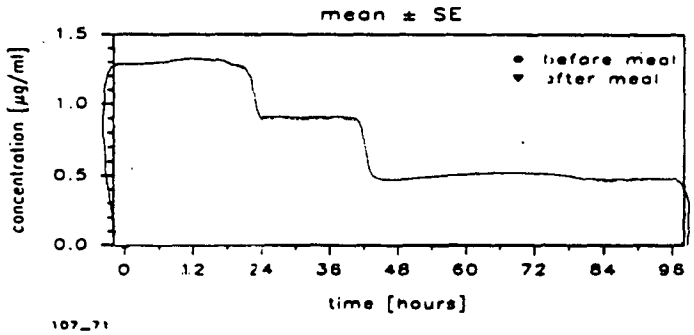
(ii) High-fat Diet (according to the sponsors standards)

Study 107.071: Influence of high fat (75 g) food on the on the bioavailability of 15 mg meloxicam capsules administered orally to healthy subjects.

This study was designed to investigate the effect of high fat breakfast (75 g) on the rate and extent of absorption of a single 15 mg capsule dose of meloxicam. 17 healthy male volunteers were administered single 15 mg capsules either following an overnight fast, remaining fasted for 4 hours post-dose, or directly after a high fat breakfast. Other details of study design is given in the Appendix on page 19. The high-fat (75 g) breakfast

consisted of a cup of muesli with 50 mL of cream and 60 mL of buttermilk, two slices of salami and one slice of liver sausage, a slice of cheese, three slices of wheat bread with 30 g of butter, a glass of 3.5% milk, and two cups of fruit tea. Bioequivalence was determined by comparison of C_{MAX} and $AUC_{0-\infty}$ values. Meloxicam plasma concentration profiles and pharmacokinetic parameters are shown below.

		15 mg fasted		15 mg + 75 g fat			
parameter	units	a.mean	%CV	a.mean	%CV	Point Estimate %	90% CI
C_{MAX}	[µg·h/mL]	0.928	19.6	1.14	7.9	124.3	115.7-134
t_{MAX}	[h]	8.8	35.9	6.1	28.6	68.7	56.6-86.6
λ_Z	[h^{-1}]	0.351	18.8	0.0379	18.5	-	-
$t_{1/2}$	[h]	20.6	23.6	19.1	27.5	-	-
AUC_{0-24}	[µg·h/mL]	31.1	32.9	33.0	25.4	-	-
$AUC_{0-\infty}$	[µg·h/mL]	34.1	35.6	36.0	26.6	105.6	102.6-112.5
MRT_{TOT}	[h]	26.4	15.3	25.5	19.1	96.1	90.7-101.7
Cl/f	[mL/min]	7.84	25.1	7.25	22.1	-	-
Vd/f	[L]	13.3	17.1	11.5	13.4	-	-



The extent of absorption was higher after a high fat breakfast, mean $AUC_{0-\infty}$ increased 6% vs. the fasting dose, while mean C_{MAX} values increased 22%. The increase in C_{MAX} was accompanied by an earlier t_{MAX}. Onset of absorption was delayed by food by approximately one hour despite the earlier t_{MAX}. The coefficient of absorption decreased significantly after food. However, the extent of this change did not exceed the predefined confidence limits for log-transformed C_{MAX} (0.70 - 1.43) or $AUC_{0-\infty}$ (0.8 - 1.25) values. The individual subject data is attached in the Appendix on pages 20-21.

Reviewer's Comment

Conclusions

Since both treatments are bioequivalent regarding AUC and C_{MAX}, no relevant food effect is assumed for the treatment in combination after a high fat breakfast.

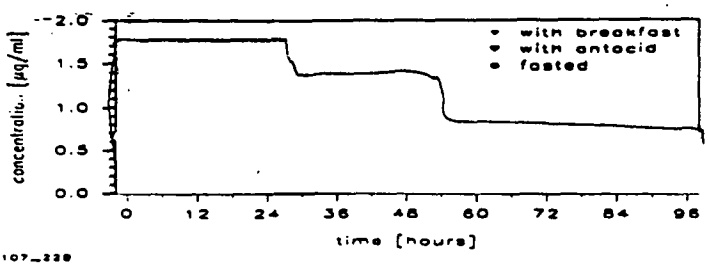
(C) EFFECT OF ANTACID ON THE BIOAVAILABILITY

Study 107.022: Effect of food and antacid (Maalox® 70) on pharmacokinetics following single oral administration of 30 mg meloxicam capsules to healthy subjects.

This randomized, three-way crossover study in six healthy male volunteers tested the influence of a continental breakfast (54 g fat) or the concomitant intake of an antacid on meloxicam single-dose pharmacokinetics. Volunteers received single 30 mg doses of meloxicam in capsules either fasting with breakfast 2 hours later, 20 minutes after a continental breakfast, or together with 600 mg $Mg(OH)_2$/900 mg $Al(OH)_3$ (Maalox® 70) with breakfast two hours later. Maalox® was given for another 3 times in the day and was continued for a total of 4 days. The breakfast consisted of one roll (with smoked ham and cheese), one boiled egg and one container of yogurt. The ingestion of the antacid was continued through Day 4 with four doses each day.

Mean pharmacokinetic parameters and plasma concentration-time profile are shown below.

		fasted			fed			with antacid		
parameter	units	mean	%CV	median	mean	%CV	median	mean	%CV	median
C_{MAX}	[µg/mL]	1.51	28.0	1.48	1.43	15.7	1.36	1.45	15.8	1.47
t_{MAX}	[h]	10.7	30.6	12.0	9.7	27.5	10.0	10.3	25.7	12.0
λ_z	[h^{-1}]	0.0311	34.2	0.0256	0.0290	33.3	0.0285	0.0323	44.5	0.0288
$t_{1/2}$	[h]	24.3	28.7	27.1	26.9	42.5	24.4	25.3	43.9	24.3
AUC_{0-TLQC}	[µg·h/mL]	58.8	38.9	57.3	62.5	26.9	58.1	62.5	37.0	61.9
$AUC_{0-\infty}$	[µg·h/mL]	66.5	38.3	66.3	73.0	37.2	64.1	72.1	41.5	70.6
MRT_{TOT}	[h]	37.5	26.7	40.7	42.8	37.8	39.7	40.0	38.0	40.1
Cl/f	[mL/min]	8.54	39.1	7.68	7.50	28.5	7.90	8.09	42.1	7.51
Vd/f	[L]	16.5	21.1	15.3	15.8	9.9	15.8	15.2	14.6	15.6
		Treatment			Point estimates			90% CI		
C_{MAX}		fed vs fasted			0.969			0.776 - 1.21		
		+ antacid vs fasted			0.980			0.750 - 1.28		
AUC		fed vs fasted			1.11			0.968 - 1.28		
		+ antacid vs fasted			1.07			1.00 - 1.15		



Concomitant food or antacid resulted in very slightly higher $AUC_{0-\infty}$ values for meloxicam (11% with food and 7% with antacid). C_{max} values differed by only 3.1% and 2% from reference treatment 'fasted'. Confidence intervals exceeded acceptance range minimally. This trial was done in only six subjects, hence, such slight differences cannot be justified. The MRT was slightly different between the fasted and fed group suggesting an alteration in the uptake of meloxicam.

Conclusions

Antacid does not affect the bioavailability of meloxicam in this formulation and also unlikely to be a problem for the US formulation.

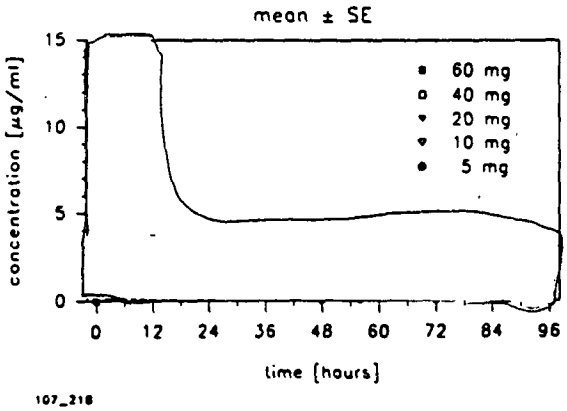
V.4 DOSE PROPORTIONALITY

Dose-proportionality of a drug is desired to ensure easy dose-adjustment. Dose proportionality in the clinical dosing range has been assessed in one study (#107.082) and in three other trials covering a higher dose range.

***Study 107.021:** Pharmacokinetics and dose proportionality following single bolus doses increasing from 5 to 60 mg in healthy volunteers.*

This was an ascending-dose tolerance study performed in six groups of 5 healthy volunteers each. Fasted volunteers received single intravenous bolus doses of placebo, 5, 10, 20, 40 to 60 mg meloxicam. Blood samples were collected predose as well as serially for 96 hours postdose. Other details of study design are provided on page 23 of the Appendix.

The mean plasma concentration profile is shown in the figure below.



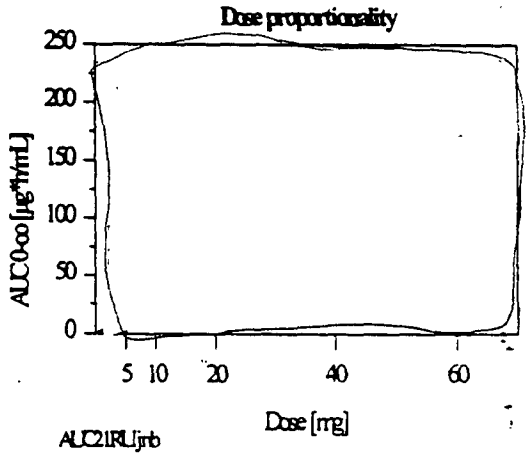
The mean pharmacokinetic parameters following IV bolus doses of 5 to 60 mg is shown in the following table.

parameter	units	meloxicam dose				
		5 mg	10 mg	20 mg	40 mg	60 mg
λ_z	(h^{-1})	0.0394 (40.9%)	0.0358 (38.8%)	0.0322 (29.9%)	0.0423 (17.2%)	0.0319 (11.6%)
$t_{1/2}$	(h)	20.4 (43.6%)	23.4 (58.0%)	22.8 (25.6%)	16.7 (15.3%)	22.0 (10.7%)
AUC_{0-TLOC}	(µg·h/mL)	8.56 (29.6%)	25.91 (63.9%)	43.22 (35.6%)	116.61 (29.8%)	161.42 (13.3%)
$AUC_{0-\infty}$	(µg·h/mL)	10.61 (32.0%)	31.36 (73.2%)	48.38 (35.1%)	119.31 (30.9%)	169.40 (14.3%)
MRT_{TOT}	(h)	28.5 (41.6%)	31.7 (62.2%)	31.1 (27.6%)	24.6 (15.1%)	29.5 (12.6%)
Cl	(mL/min)	8.63 (36.8%)	7.11 (48.1%)	7.68 (40.5%)	5.98 (27.6%)	6.00 (13.6%)
Vd	(L)	13.6 (15.2%)	11.6 (18.6%)	14.0 (12.1%)	8.38 (14.3%)	11.3 (11.5%)
Vd_{ss}	(L)	13.2 (13.1%)	10.7 (14.1%)	13.1 (8.5%)	8.54 (15.2%)	10.5 (11.4%)

Values are reported as mean (%CV).

The dose normalized AUCs values (dose-normalized to 60 mg dose level) are tabulated below.

Dose	Dose-normalized $AUC_{0-\infty}$ (µg.hr/ml)/mg		
	Mean	Min	Max
5 mg	2.12	1.21	3.02
10 mg	3.13	1.44	7.14
20 mg	2.42	1.38	3.46
40 mg	2.98	2.01	4.49
60 mg	2.82	2.40	3.41



The dose proportionality has been illustrated by a linear relationship between dose and AUC. Additionally, dose-normalized AUCs demonstrate the same as well. The results indicated that the pharmacokinetic parameters ($t_{1/2}$, V_{ss}, CL, MRT) are comparable across the dose groups. It can be seen from the figure that there were two deviations at doses 10 mg and 40 mg. These volunteers (No. 8 and 19) had either a very long half-life or a very short one. The individual pharmacokinetic parameters for all the subjects in all the dose groups are attached in the Appendix on pages 24-26. It is obvious that inter-individual variations of AUC values are relatively high. This effect could be dependent on the existence of the individual amount of entero-enteric circulation of meloxicam in man.

Study # 107.002: A Phase I clinical study to determine pharmacokinetic parameters and to ascertain the tolerability with cumulative dosing of meloxicam

This was a placebo controlled double-blind study in eight healthy male volunteers. Six volunteers received oral capsule doses once per day for 22 days on the following ascending dosage schedule—Days 1-7, 20 mg/day; Days 8-14, 50 mg/day; and Days 15-22, 100 mg/day. Two subjects received placebo doses throughout the study. Predose samples were taken on Days 1-5, 8-12, 15-18, and 22. Additional serial blood samples were taken up to 10 hours postdose on Days 1 and 8 and up to 168 hours postdose on Day 22. Other details of study design are provided on page 26 of the Appendix.

The mean pharmacokinetic parameters after multiple doses of 20 mg, 50 mg and 100 mg in six healthy volunteers are shown in the following table.

day	parameter	C_{MAX}	t_{MAX}	AUC*	$C_{PRE,SS}$	$C_{MIN,SS}$	λ_Z	$t_{1/2}$
		[µg/mL]	[h]	[µg·h/mL]	[µg/mL]	[µg/mL]	[h^{-1}]	[h]
day 1	mean	1.13	7.5	19.51	1.55	--	--	--
20 mg	SD	0.23	2.3	3.25	0.70	--	--	--
	% CV	19.9	30.1	16.7	45.2	--	--	--
	median	1.05	7.0	20.0	1.30	--	--	--
day 8	mean	3.83	6.5	69.08	4.23	--	--	--
50 mg	SD	1.42	3.5	23.02	1.64	--	--	--
	% CV	37.0	54.0	33.3	38.8	--	--	--
	median	3.60	7.0	63.16	4.64	--	--	--
day 22	mean	15.4	8.0	303	10.0	9.25	0.0222	35.5
100 mg	SD	5.6	2.2	125	5.2	4.99	0.0091	12.6
	% CV	36.6	27.4	41.3	52.1	53.9	41.0	35.6
	median	14.1	8.0	288	9.9	8.81	0.0182	38.8

* AUC is AUC (0-24h) on day 1, AUC (168-192h) on day 8 and AUC_{ss} on day 22.

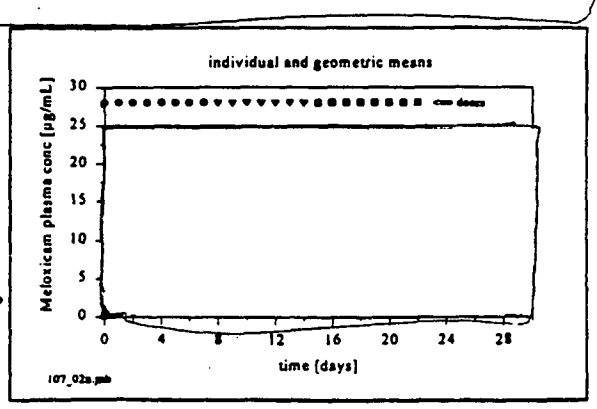
The dosing and sampling schedule of this trial has provided data for 20 mg single dose pharmacokinetics and 100 mg multiple dose pharmacokinetics of meloxicam. The plasma concentration-time profile after the first 50 mg dose was preceded by multiple 20 mg doses and therefore was not in steady state for 50 mg of meloxicam. Hence, not comparable to that for 100 mg multiple doses or the 20 mg single dose.

The pharmacokinetic parameters after a single dose of 20 mg is shown in the table above (Day 1). The sampling time was 10 hours post dose; hence, reliable estimates of elimination half life could not be obtained. The 10 hour sample was the last sample before the predose concentration on Day 2. Meloxicam predose concentrations were similar after the [redacted] and the [redacted]. Steady state appeared to be achieved after 4 days of treatment with 20 mg doses.

Plasma concentrations were not in steady state for the 50 mg doses because of the preceding multiple 20 mg doses. However, a rise in predose plasma concentrations were seen, which were constant after the [redacted]

The drug plasma concentration profile after seven once daily 100 mg meloxicam doses was used to determine multiple dose parameters as shown in the previous table. Steady state conditions were achieved after the [redacted]

Individual and geometric mean plasma meloxicam concentrations after multiple doses of 20 mg, 50 mg and 100 mg in six healthy male volunteers are shown in the adjacent figure. Mean predose concentrations were [redacted] for 20 mg, 50 mg, and 100 mg doses, respectively.



Concentrations when normalized to 1 mg were reasonably constant with a slight increasing trend and increased variability at 100 mg. The figure is attached in the Appendix on page 27. The individual subject pharmacokinetic data after 100 mg is also attached in the Appendix on page 28, which shows wide inter-subject biological variability.

Study107.001: Phase I study to determine the tolerability and pharmacokinetics of meloxicam

This study was the preliminary study and due to study design constraints the dose proportionality cannot be assessed, but is summarized here to evaluate the trend in the plasma concentration profile at the different doses.

The three healthy male volunteers received five to six ascending oral meloxicam capsule doses ranging from 5 mg to 100 mg (5, 10, 20, 50, 100 mg), given as single doses two days apart from each other with placebo dosing on the intervening days. Doses were given after a twelve-hour fast, followed by a standardized breakfast one hour after drug intake. Only plasma samples from 20 mg, 50 mg and 100 mg doses were analyzed. Plasma samples were obtained predose and serially up to 48 hours. Other details of study design are attached in Appendix on page 29.

Results showed that meloxicam concentrations were always detectable at the time of the next dose (i.e. 48 hours). Pharmacokinetic evaluation indicated a prolonged absorption with multiple peaks. Elimination half-life values were 20.4, 20.5 and 43 hours for the 20, 50 and 100 mg doses, respectively. C_{max} and AUC values were not comparable due to the design of this study. The individual pharmacokinetic parameters are shown in the following table. The concentration-time profiles are attached in the Appendix on page 30.

dose	vol.	C_{MAX} [µg/mL]	t_{MAX} [h]	λ_Z [h^{-1}]	$t_{½}$ [h]	$AUC_{(0-48)}$ [µg·h/mL]
20 mg	1	1.87	10	0.0292	23.8	59.97
	2	0.603	10	0.0398	17.4	17.48*
	3	0.724	8	0.0345	20.1	19.47*
	mean	1.07	9	0.0345	20.4	32.31
	median	0.724	10	0.0345	20.1	19.47
50 mg	1	2.23	10	0.0212	32.7	82.83
	2	2.46	6	0.0496	14.0	59.92
	3	1.62	10	0.0472	14.7	46.13
	mean	2.10	9	0.0393	20.5	62.96
	median	2.23	10	0.0472	14.7	59.92
100 mg**	1	10.4*	6	0.0146	47.3	203.34*
	2	3.23	6	0.0138	50.3	65.34
	3	4.30	10	0.0221	31.4	90.00
	mean	5.98	7	0.0168	43.0	119.56
	median	4.30	6	0.0146	47.3	90.00

* AUC(0.5 - 48h)

** 100 mg dose group AUC was 0-24h unless otherwise indicated.

Study 107.082: Determination of the relative bioavailability of 7.5 mg meloxicam tablets q.d. compared with 7.5 mg meloxicam capsules and dose proportionality between 7.5 mg and 15 mg meloxicam capsules q.d. after oral administration over 7 days to healthy volunteers.

Study 107.82 was primarily designed to evaluate the relative bioavailability (bioequivalence) of 7.5 tablet in comparison to 7.5 mg capsules. A third arm of 15 mg capsules was added to this study to evaluate dose proportionality in a crossover trial. Only the dose proportionality part the study results will be discussed here. The remaining details of the study will be discussed in the "Bioequivalence" section of the review.

Briefly, this was an open, randomized, multiple dose, three-way crossover study in 18 healthy volunteers. Pharmacokinetic parameters were obtained after the 7th day of dosing. All pharmacokinetic parameters were adjusted to a 15 mg dose, to allow easy comparison of data. The adjustment to 15 mg dose was chosen by the sponsor, since this dose was the most often studied meloxicam dose in pharmacokinetic trials.

Pharmacokinetics parameters were tested for dose proportionality by means of the bioequivalence approach. Dose proportionality was considered to be demonstrated if the shortest 90% confidence intervals for the ratio test versus reference were located in the range of 0.80 to 1.25. The following table shows the dose normalized mean values along with the confidence intervals for the pharmacokinetic parameters.

Parameter	Product	Mean	Point estimator [%]	90% Confidence Interval
AUC_{SS}	7.5 mg capsule (A)	27.8	A vs. C 0.935	0.845-1.04
	7.5 mg tablet (B)	30.7	B vs. C 1.04	0.937-1.15
	15 mg capsules (C)	30.00	-	-
$C_{MAX,SS}$	7.5 mg capsule	1.76	0.918	0.828-1.02
	7.5 mg tablet	2.11	1.10	0.994-1.22
	15 mg capsules	1.92	-	-
$C_{MIN,SS}$	7.5 mg capsule	0.662	0.885	0.787-0.995
	7.5 mg tablet	0.739	0.978	0.870-1.10
	15 mg capsules	0.748	-	-
$C_{PRE,SS}$	7.5 mg capsule	0.757	0.856	0.752-0.975
	7.5 mg tablet	0.840	0.938	0.824-1.07
	15 mg capsules	0.899	-	-

The 7.5 mg tablets when dose normalized to 15 mg were within the acceptance criteria for all the parameters. The values for the 7.5 mg capsules were slightly lower (11.5% for $C_{MIN,SS}$ and 14.5% for $C_{PRE,SS}$, exceeding the acceptance limit by 2.4% ($C_{MIN,SS}$) and 4.8% ($C_{PRE,SS}$). The figures showing the dose normalized parameters are attached in the Appendix on pages 84-87.

Conclusions

Data from different studies were pooled together for a comparative analysis. Intravenous

doses were dose-proportional in the tested range of 5 mg to 60 mg. Capsules were dose proportional in the range of 7.5 mg to 30 mg after single doses and in the tested dose range of 7.5 mg to 15 mg once a day after multiple doses. Additional tables from dose normalized data from various studies are given in the "Gender Effect" section of the review on pages 33-34.

V.5 SPECIAL POPULATIONS

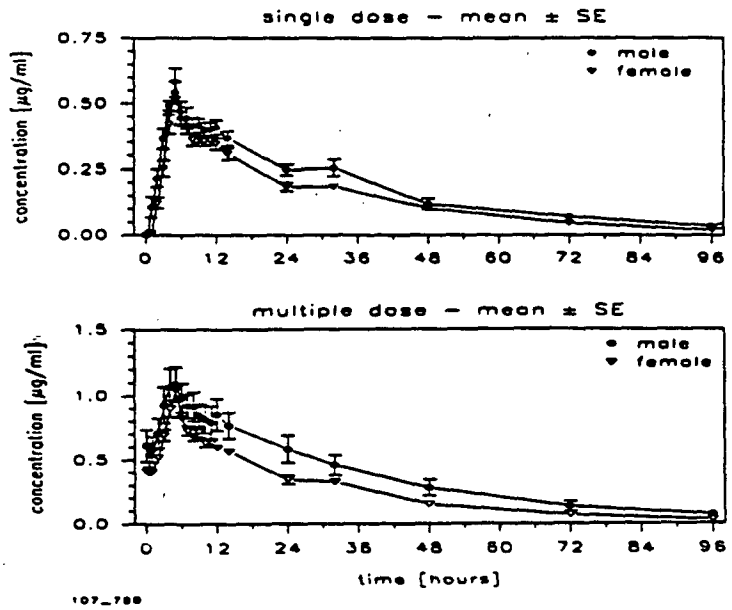
(A) GENDER EFFECT

The effect of gender has been studied in one study. Comparitive analysis has been performed across various studies and summary tables have been provided.

Study 107.078: Pharmacokinetics of 7.5 mg meloxicam capsules after single and multiple administration p.o. over 7 days in healthy young male and female volunteers.

This study was a nonblinded, sequential single- and multiple-dose study in nonfasted (drug given in the morning within 30 minutes after breakfast) healthy volunteers to compare the effect of gender on the single- and multiple-dose pharmacokinetics of meloxicam. Six male and six female volunteers each received 7.5 mg meloxicam in a capsule formulation as a single dose. After a washout period of 4 days, on Day 5, each subject received a 7.5 mg capsule daily for seven days. Blood samples were collected predose and serially for 96 hours postdose after the single dose, predose on Days 5 to 11 as well as for 96 hours after the last dose on Day 11. Other details of study design are given on page 31 of the Appendix.

The mean plasma concentration profiles and the mean pharmacokinetic parameters after the single and multiple dose of 7.5 mg meloxicam capsules are given below.



Pharmacokinetic parameters after Single dose of 7.5 mg capsule

parameter	units	males			females		
		mean	%CV	median	mean	%CV	median
C_{MAX}	[µg/mL]	0.566	17.3	0.559	0.580	23.4	0.623
t_{MAX}	[h]	5.2	19.0	5.0	5.0	0.0	5.0
λ_Z	[h^{-1}]	0.0307	20.7	0.0300	0.0364	16.3	0.0353
$t_{1/2}$	[h]	23.4	21.8	23.2	19.5	15.5	19.8
MRT_{TOT}	[h]	35.1	20.1	34.6	31.3	11.2	31.1
AUC_{0-TLOC}	[µg·h/mL]	16.79	22.9	17.71	13.31	12.3	13.81
$AUC_{0-\infty}$	[µg·h/mL]	18.04	26.3	18.85	13.85	12.5	14.44
Cl/f	[mL/min]	7.39	28.7	6.70	9.16	13.6	8.66
Vd/f	[L]	14.3	9.2	14.0	15.3	15.5	14.9

Pharmacokinetic parameters after multiple doses of 7.5 mg capsules

parameter	units	males			females		
		mean	%CV	median	mean	%CV	median
$C_{MAX,SS}$	[µg/mL]	1.10	31.2	1.01	1.08	6.3	1.05
$C_{MIN,SS}$	[µg/mL]	0.519	44.3	0.482	0.339	21.4	0.338
$C_{PRE,SS}$	[µg/mL]	0.612	50.6	0.605	0.412	12.4	0.432
$t_{MAX,SS}$	[h]	4.8	15.6	5.0	4.8	8.4	5.0
λ_Z	[h^{-1}]	0.0337	21.3	0.0344	0.0395	17.1	0.0375
$t_{1/2}$	[h]	21.4	22.5	20.2	17.9	15.7	18.5
MRT_{TOT}	[h]	34.9	18.9	32.3	29.5	12.6	30.9
AUC_{SS}	[µg·h/mL]	18.73	33.9	18.02	14.02	8.4	14.36
Cl/f	[mL/min]	7.33	32.7	6.94	8.97	8.7	8.72
Vd/f	[L]	12.8	12.8	12.4	14.0	19.2	14.2

After Single dose

After a single dose of 7.5 mg meloxicam capsule it can be seen that the $AUC_{0-\infty}$ was 24% lower for the females. The total median CL was 29% higher, resulting in a 16% lower mean $t_{1/2}$ in females. The C_{max} was 11% higher in the females. There was no appreciable difference in the T_{max} values. Apparently, the males showed a much higher variability than females for most pharmacokinetic parameters than females, except for Vd.

At steady state

After multiple doses, the AUC_{ss} was 25% lower for the females. The mean total CL was 22% higher for females and the half-life was 9% lower in the females. There was no appreciable difference in C_{max} or T_{max}, but the $C_{min\ ss}$ was 35% lower for the females, which resulted in a 63% higher % PTF for females than for males. The Vd was 9% higher in the females. Once again, the males showed a much higher variability than females for most pharmacokinetic parameters than females, except for Vd.

The study results also suggested linearity of pharmacokinetics regardless of gender. Clearance values were not appreciably different after multiple doses and the ratio of $AUC_{0-\infty}/AUC_{ss}$ was 96% or higher for both genders, suggesting constant absorption conditions and linear pharmacokinetics for 7.5 mg doses.

The following accumulation ratios were calculated and the values are tabulated in the following table.

A. ratio	definition	males			females		
		mean	%CV	median	mean	%CV	median
R1	$AUC_{ss}/\tau/AUC_{0\text{-}24h}$	2.33	23.8	2.01	2.03	10.7	2.08
R2	$C_{min\,ss}/C_{24h}$	2.04	29.7	1.87	1.87	19.7	1.96
R3*	$AUC_{ss}/\tau/AUC_{0-\infty h}$	1.03	18.1	1.00	1.02	6.6	1.03

*to test linearity in accumulation ratios

R1 and R2 show that drug exposure per day is about twice as high as after a single dose of meloxicam. R3 of 1 indicated a linearity of meloxicam pharmacokinetics after single and multiple doses.
The pharmacokinetic parameters for the individual subjects are attached in the Appendix on pages 32-35.

Inter-study comparison of gender effect:

The pharmacokinetic parameters from different studies have been compared in the following table. The studies have been discussed elsewhere in the review. The pharmacokinetic parameters are dose normalized to a 15 mg dose. Young healthy male volunteers exhibited higher C_{max} (median +34%) and AUC_{ss} (median +22%) and consequently lower total clearance values (-29%) as shown in the following table.

	Trail no	107.78, females			107.81, females			107.74, males		
	N	6			16			24		
		mean	%CV	median	mean	%CV	median	mean	%CV	median
C_{maxss}	[µg/mL]	2.15	6.3	2.10	1.60	31.1	1.49	2.32	30.2	2.25
AUC_{ss}	[µg·h/mL]	28.04	8.4	28.72	27.18	30.6	26.26	36.17	34.5	33.82
$t_{1/2}$	[h]	17.9	15.7	18.5	22.4	32.9	21.1	22.2	39.7	20.1
Vd/f	[L]	8.97	8.7	8.72	10.2	35.5	9.52	7.57	28.5	7.40

Conclusions

- Young females have 22-24% lower AUC_{ss} values as compared to young males.
- Young females have 22-29% higher CL values as compared to young males.
- These differences could be due to weight differences between males and females.
- Differences in C_{max} could not be clearly defined due to sample size differences between studies, although cross study comparisons showed a 34% higher C_{max} in young males between the largest male and female trials.

Summary tables from the data pooled together from different studies after single and multiple oral doses in males and females are tabulated in the following tables. The "N" given in the following tables indicate the number of subjects pooled from different studies.

Summary of pharmacokinetic parameters after single capsule dose of meloxicam to young healthy male volunteers.

parameter	units	N	mean	SD	%CV	gmean	min	max
NC_{MAX}	[µg/mL]	187	0.897	0.233	25.9	0.87	0.385	1.70
t_{MAX}	[h]	*106	*9.08	*3.28	*36.0	*10.0	*2.00	*24.0
		§81	§6.20	§2.47	§39.8	§6.00	§2.00	§12.0
$t_{1/2}$	[h]	187	21.6	7.64	35.3	20.6	10.1	66.0
NAUC	[µg.h/mL]	187	33.5	12.7	37.8	31.7	17.6	106
MRT_{TOT}	[h]	187	34.3	11.1	32.3	32.9	16.8	97.8
CL/f	[mL/min]	187	8.27	2.44	29.5	7.88	2.35	14.2
Vz/f	[L]	187	14.4	3.51	24.3	14.1	7.84	27.4
age	[y]	187	38	10	27	36	21	64
weight	[kg]	179	78.2	8.16	10.4	77.8	55.0	101
height	[cm]	179	178	5	3	178	163	190

Study: 107.174/87/78/71/66/62/64/51/52/55/31/32/25/22/18 (male, young, < 65 years)
Dose capsule, single dose
Normalized to a 15 mg dose
* - fasted, § - fed

Summary of pharmacokinetic parameters after a single capsule dose of meloxicam to young healthy female volunteers.

parameter	units	N	mean	SD	%CV	gmean	min	max
NC_{MAX}	[µg/mL]	19	0.952	0.269	28.3	0.916	0.524	1.43
t_{MAX}	[h]	*13	*8.15	*3.02	*31.7	*9.00	*5.00	*12.0
		§6	§5.00	§5.00	§0.00	§5.00	§5.00	§5.00
$t_{1/2}$	[h]	19	21.1	7.09	33.6	20.2	12.2	45.8
NAUC	[µg.h/mL]	19	32.0	13.7	42.9	29.9	18.8	71.2
MRT_{TOT}	[h]	19	33.1	10.1	30.5	32.0	19.1	69.7
CL/f	[mL/min]	19	8.81	2.64	30.0	8.36	3.51	13.3
Vz/f	[L]	19	15.0	3.25	21.7	14.6	7.13	21.0
age	[y]	19	40	10	25	39	29	61
weight	[kg]	19	65.2	8.65	13.3	64.6	45.3	81.0
height	[cm]	19	167	7	4	167	155	180

Study: 107.174/78/51 (female, young, < 65 years)
Dose: capsule, single dose
Normalized to a 15 mg dose
*- fasted, § - fed

Summary of pharmacokinetic parameters after multiple dosages of meloxicam capsules in healthy male volunteers.

parameter	units	N	mean	SD	%CV	gmean	min	max
$NC_{MAX,ss}$	[µg/mL]	152	2.07	0.712	34.4	1.97	0.759	5.95
$NC_{PRE,ss}$	[µg/mL]	152	1.08	0.544	50.2	0.958	0.0680	3.37
$NC_{MIN,ss}$	[µg/mL]	152	0.917	0.47	51.2	0.811	0.0520	2.97
$t_{MAX,ss}$	[h]	152	5.64	1.74	30.7	5.00	4.00	17.0
$t_{1/2}$	[h]	152	21.5	10.3	47.8	19.8	6.15	86.7
NAUCss	[µg.h/mL]	152	34.4	13.6	39.6	32.2	13.2	100
MRT_{TOT}	[h]	146	34.5	16.0	46.3	32.4	17.3	169
CL/f	[mL/min]	152	8.25	3.00	36.4	7.74	2.49	18.9
Vz/f	[L]	152	14.0	4.67	33.4	13.2	3.66	30.8
PTF	[%]	152	86.5	25.4	29.4	82.7	24.7	184
age	[y]	152	35	9	26	34	18	63
weight	[kg]	152	76.8	10.1	13.2	76.2	56.0	111
height	[cm]	148	178	6	4	178	163	192

Study: 107.172/116/87/85/82/78/74/68/64/02 (male, young, < 65 years)
Doses: capsule, multiple dose
Normalized to a 15 mg dose

Summary of pharmacokinetic parameters after multiple dosages of meloxicam capsules in healthy female volunteers.

parameter	units	N	mean	SD	%CV	gmean	min	max
$NC_{MAX,ss}$	[µg/mL]	35	2.17	0.836	38.5	2.02	0.859	4.14
$NC_{PRE,ss}$	[µg/mL]	35	0.997	0.569	57.1	0.868	0 274	3.05
$NC_{MIN,ss}$	[µg/mL]	35	0.896	0.546	61.0	0.779	0.274	3.05
$t_{MAX,ss}$	[h]	35	4.80	1.16	24.1	5.00	2.00	8.00
$t_{1/2}$	[h]	35	20.4	6.55	32.1	19.5	10.5	41.0
NAUCss	[µg.h/mL]	35	35.4	16.3	46.1	32.4	13.1	81.9
MRT_{TOT}	[h]	35	32.5	9.61	29.6	31.4	21.5	62.9
CL/f	[mL/min]	35	8.39	3.44	41.0	7.73	3.05	19.1
Vz/f	[L]	35	14.5	6.76	46.7	13.1	3.46	36.8
PTF	[%]	35	92.7	27.4	29.6	88.4	32.1	155
age	[y]	35	33	10	31	32	19	64
weight	[kg]	35	65.1	10.8	16.5	64.3	52.0	100
height	[cm]	28	168	7	4	168	154	180

Study: 107.78/68/81/85 (female, young, < 65 years)
Dose: capsule, multiple dose
Normalized to a 15 mg dose

Reviewer's comment

When comparing parameters across studies, the trial design should be kept in mind. Study 107.078 comprised of more blood sampling points than the Study number 107.081. Hence, differences the AUC and CL can be defined more directly from the different studies and show consistent results than the C_{max} across different studies. Different doses were also used in these trials. Similar results were obtained on pooling the data as well.

(B) EFFECT OF AGE

Initially study 107.038 (single dose) and Study 107.039 (multiple dose) studies were conducted to evaluate the effect of age and gender. The sponsor also conducted a review of the clinical trials (107.014/030/036/040/041/042/043/044) to assess the effect of age. Study 107.085 was conducted later to verify the effect of age. Since this study is of primary importance, it has been summarized first in the subsection. The other studies are given as supportive studies.

Study 107.085: Multiple-dose PK of 15 mg meloxicam capsules once daily in elderly male and female subjects with OA and RA compared to younger adult male and female patients

In this multiple dose trial, young and elderly patients of either gender suffering from rheumatoid arthritis or osteoarthritis were included. The patients were administered meloxicam 15 mg orally once daily for a total of 14 days. Steady state plasma levels were determined on Days 11 to 13 and a pharmacokinetic profile was performed after the last administration of meloxicam on Day 14 to Day 17. The younger subjects aged ≤ 55 and the elderly subjects aged ≥ 65. Details of study design are given on page 36 of the Appendix.

The mean pharmacokinetic parameters in the young and elderly subjects are tabulated in the following tables.

Males:

		younger males n = 6			elderly males n = 5		
parameter	units	mean	%CV	gmean	mean	%CV	gmean
$C_{MAX,SS}$	[µg/mL]	2.08	51.0	1.90	2.33	59.0	2.01
$C_{PRE,SS}$	[µg/mL]	0.937	64.4	0.782	1.207	70.8	0.945
$C_{MIN,SS}$	[µg/mL]	0.823	71.7	0.674	1.049	78.1	0.786
$t_{MAX,SS}$	[h]	6.7	27.9	6.0*	4.6	11.9	5.0*
λ_Z	[h^{-1}]	0.0513	50.3	0.0466	0.0363	37.0	0.0345
$t_{1/2}$	[h]	16.2	40.9	14.9	21.0	33.5	20.1
AUC_{SS}	[µg·h/mL]	34.8	58.9	30.7	38.9	68.7	31.6
MRT_{TOT}	[h]	31.7	45.3	29.2	33.3	32.6	31.9
Cl/f	[mL/min]	9.02	45.8	8.13	9.91	75.9	7.92
Vd/f	[L]	10.8	24.5	10.5	14.7	41.5	13.7

* median

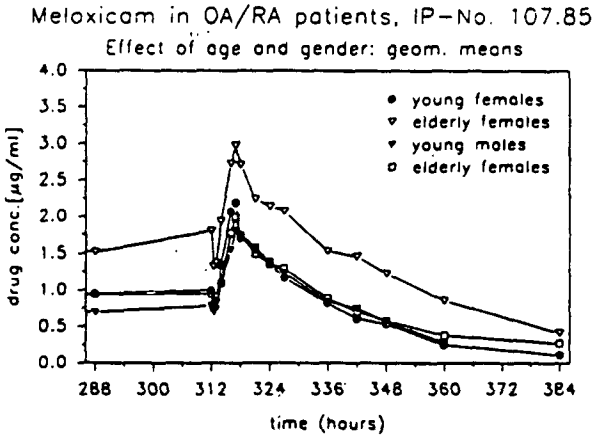
Females:

parameter	units	younger females n = 6 mean	%CV	gmean	elderly females n = 8 mean	%CV	gmean
$C_{MAX,SS}$	[µg/mL]	2.25	25.3	2.19	3.21	23.9	3.13
$C_{PRE,SS}$	[µg/mL]	1.011	19.1	0.994	1.845	24.4	1.799
$C_{MIN,SS}$	[µg/mL]	0.731	21.4	0.716	1.338	23.6	1.303
$t_{MAX,SS}$	[h]	5.0	0.0	5.0 *	5.6	26.8	5.0 *
λ_z	[h^{-1}]	0.0431	7.2	0.0430	0.0307	23.5	0.0298
$t_{1/2}$	[h]	16.1	7.1	16.1	24.2	33.6	23.3
AUC_{ss}	[µg·h/mL]	32.1	20.9	31.5	51.3	22.0	50.2
MRT_{TOT}	[h]	25.4	13.1	25.2	42.2	32.6	40.5
Cl/f	[mL/min]	8.08	21.3	7.93	5.09	22.4	4.98
Vd/f	[L]	11.3	20.8	11.1	10.4	29.5	10.1

* median

The pharmacokinetic parameters were similar to those obtained in healthy volunteers in previous studies. No statistical differences were detected between elderly and younger males for AUC_{ss} and $C_{max\ ss}$. AUC_{ss} and $C_{max\ ss}$ values were statistically significantly higher (59% and 43%) in elderly females compared with younger females.

The plasma concentration-time profile showing the effect of age and gender is shown in the following figure.



The differences in AUC_{ss} and $C_{max\ ss}$ are reflected in a lower meloxicam clearance for elderly females. Weight adjustment to 0.2 mg/kg dose did not change the results relevantly. Differences were much smaller for younger and older males ($C_{max\ ss}$ 6% and AUC_{ss} 3%) and were not significantly different in the young and older men. The significant differences have been written in bold in the following tables.

		AUCss (μg.h/ml)			WAUCss (μg.h/ml)		
		g. mean	g.mean ratio	p-value	g mean	g.mean ratio	p-value
Age (all patients)	Younger vs. Elderly	31.1 42.0	1.35	0.1164	29.9 39.8	1.33	0.1005
Sex (all patients)	Males vs Females	31.1 41.1	1.32	0.1494	32.5 36.4	1.12	0.5345
Male patients	Younger vs. Elderly	30.7 31.6	1.03	0.9461	30.5 35.2	1.15	0.7094
Female patients	Younger vs. Elderly	31.5 50.2	1.59	**0.0018**	29.2 42.9	1.47	**0.0049**

		Cmaxss (μg/ml)			WCmaxss (μg/ml)		
		g. mean	g.mean ratio	p-value	g. mean	g.mean ratio	p-value
Age (all pateints)	Younger vs. Elderly	2.04 2.64	1.29	0.1349	1.96 2.50	1.28	0.1054
Sex (all pateints)	Males vs Females	1.95 2.68	1.38	0.0613	2.04 2.38	1.16	0.3228
Male patients	Younger vs. Elderly	1.90 2.01	1.06	0.8681	1.89 2.24	1.19	0.5842
Female patients	Younger vs. Elderly	2.19 3.13	1.43	**0.0228**	2.03 2.67	1.32	**0.0502**

Body weight adjustment to a 0.2 mg/kg dose decreased the difference between males and females AUC_{ss} from 32% to 12% and $C_{max\ ss}$ from 38% to 16%. The 43% increase in $C_{max\ ss}$ in elderly female was statistically significant. An adjustment for body weight decreased the difference in young and elderly female from 43% to 32%, which was at the borderline of statistical significance. The weight-adjusted parameters are also shown in the tables above. Therefore, inspite of the weight adjustment, the young and elderly female showed a statistically significant difference in both AUC_{ss} and $C_{max\ ss}$, which was not seen in the case of young and elderly male subjects. Overall the gender difference in AUC_{ss} and $C_{max\ ss}$ was not statistically significant, but a clear effect on age was seen in case of females only. The different age groups of elderly males and females enrolled in the study could explain some of these differences. The elderly males age ranged from 65-69 years with mean of 67 years, where as the females age ranged from 68-80 years, with a mean of 74 years. As both body composition and metabolic states change with age, these differences could also contribute to the differences seen.

There was a trend to longer elimination half-lives in elderly group (+35%). The apparent elimination half-lives were 45% longer in elderly females. The apparent volume of distribution remained apparently constant. A slower metabolism is more likely to be the reason for lower clearance than an enhanced volume of distribution. Gender differences in metabolism was also found in preclinical trials (female rats exhibit much higher metabolism than male rats-report U93-0299, March 15, 1993). Meloxicam is bound to plasma by more than 99%. This might be the reason why renal clearance is negligible for this drug. However, the plasma protein binding of elderly females was not significantly

higher in comparison to younger females (report U93-0340, March 16, 1993) and the volume of distribution in the terminal phase was not affected indicating altered binding may not be the reason for higher AUC_{ss} values.

The clearance and volume of distribution parameters before and after weight adjustment in young and elderly males and females is also shown below.

		Younger males n=6			Elderly males, n=5			
		mean	%CV	gmean	mean	%CV	gmean	ratio
CL/f	ml/min	9.02	45.8	8.13	9.91	75.9	7.92	0.97
WCL/f	ml/min	8.85	39.3	8.20	9.16	86.4	7.11	0.87
Vz/f	l	10.8	24.5	10.5	14.7	41.5	13.7	1.31
Wvz/f	l	10.9	27.7	10.6	13.4	46.9	12.3	1.17
		Younger females n=6			Elderly females n=8			
CL/f	ml/min	8.08	21.3	7.98	5.09	22.4	4.98	0.63
WCL/f	ml/min	8.63	14.2	8.56	5.98	25.2	5.82	0.68
Vz/f	l	11.3	20.8	11.1	10.4	29.5	10.1	0.91
Wvz/f	l	12.0	12.7	11.9	12.1	26.7	11.7	0.98

A table showing the differences in other parameters and individual subject data is attached in the Appendix on pages 38-46 along with the demographic data on page 37.

The assessment of global efficacy was poorer in both elderly males and females. There was no relationship between assessment of efficacy and AUC_{ss} and $C_{max\ ss}$ values. The elderly patients rated worse tolerance than the younger ones. The scatter plots are attached in the Appendix on page 40.

A meta-analysis was performed comparing the data from this study in patients to data from previous studies in healthy subjects. AUC and $C_{max\ ss}$ data from multiple dose trials were normalized to a 15 mg dose and to a 0.2 mg/kg dose (=weight adjustment to a 15 mg and a 75 mg standard weight. The meta-analysis of $C_{max\ ss}$, AUC_{ss} and CL/f values in males and females combined from different trials is tabulated below.

		younger males (< 65 y)				elderly males (≥65 y)				gmean	t-test
parameter	units	n	mean	% CV	gmean	n	mean	% CV	gmean	ratio	p value
$C_{max\ ss}$	[µg/mL]	83	2.15	36.1	2.04	11	2.24	43.9	2.05	1.01	0.9578
$C_{max\ ss}$ *	[µg/mL]	83	2.18	33.7	2.08	11	2.31	41.9	2.12	1.02	0.8468
AUC	[µg·h/mL]	93	36.8	45.0	34.0	18	38.9	40.7	35.7	1.05	0.6296
AUC *	[µg·h/mL]	85	36.6	43.0	34.0	18	39.7	38.1	36.7	1.08	0.4429
Cl/f	[mL/min]	93	7.87	36.6	7.35	18	7.75	55.0	7.00	0.95	0.6332
Cl/f *	[mL/min]	85	7.90	37.9	7.36	18	7.56	57.6	6.81	0.92	0.4461

* weight-normalized

parameter	units	younger females (< 65 y)				elderly females (≥65 y)				gmean ratio	t-test p value
		n	mean	% CV	gmean	n	mean	% CV	gmean		
$C_{max,ss}$	[µg/mL]	35	2.17	38.5	2.02	14	3.28	23.7	3.19	1.58	**0.0002**
$C_{max,ss}$ *	[µg/mL]	35	1.86	39.4	1.73	14	2.74	29.6	2.61	1.51	**0.0010**
AUC	[µg·h/mL]	39	37.1	46.0	33.8	20	58.1	33.1	55.3	1.64	**<0.0001**
AUC *	[µg·h/mL]	39	31.4	47.6	28.7	20	47.2	34.9	44.7	1.56	**0.0005**
Cl/f	[mL/min]	39	8.08	42.4	7.41	20	4.74	31.7	4.52	0.61	**<0.0001**
Cl/f *	[mL/min]	39	9.47	39.8	8.72	20	5.91	33.9	5.59	0.64	**0.0002**

* normalized

As seen in the Tables, there was a constant increase of $C_{max\ ss}$ and AUC_{ss} values with age in females, but not in males. No significant differences between age groups were detected for males for the considered parameters. In females, moderate and statistically significant differences between age groups were found for $C_{max\ ss}$, AUC_{ss} and Cl/f. $C_{max\ ss}$ and AUC increased while clearance decreased with age. $C_{max\ ss}$ and AUC increased approximately 15-20% per 10 years of age. Clearance decreased approximately 8 - 10 % per 10 years of age in the female population. There was higher variability in males as compared to females. Figures showing the pharmacokinetic parameters after dose and body weight adjustment versus the age is attached in the Appendix on pages 41-42. Data used for historical comparisons in the meta-analysis is given on pages 47-52 of the Appendix.

Conclusions

- There were no differences in the pharmacokinetic parameters between healthy subjects and patients with osteoarthritis.
- Drug concentrations for young and elderly patients (genders combined) were similar with a trend towards higher concentrations in elderly patients
- Drug concentrations for males and females (age combined) were similar, with a trend towards higher concentrations in female patients.
- $C_{max\ ss}$ and AUC_{ss} were 43% and 59% higher for elderly females as compared to young females and a lower CL in elderly females.
- Weight adjustment did not change the results.
- Differences in pharmacokinetic parameters between young and elderly males were minor and not statistically significant and body weight adjustment did not change the results.

Study 107.039: Multiple-dose PK of 15 mg meloxicam capsules once daily in elderly male and female healthy subjects

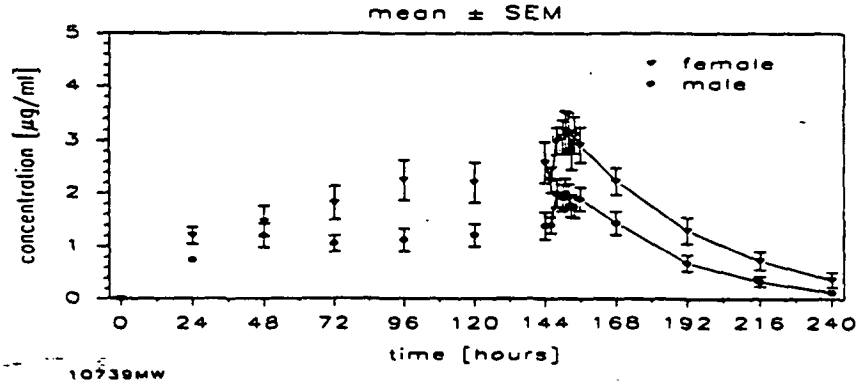
This study was performed to obtain information about steady state pharmacokinetics of meloxicam in healthy elderly volunteers. Six male and six female volunteers received daily 15 mg doses of meloxicam for seven days after a light breakfast. Blood samples were taken predose on Days 1 to 7 and serially for 96 hours postdose on Day 7. Other details of study design are presented on page 53 of the Appendix.

Elderly volunteers investigated in this study reached steady state within 4-6 days of treatment. Female elderly volunteers exhibited higher mean $C_{MAX,SS}$ (+56%) and $C_{MIN,SS}$ (+62%), $C_{PRE,SS}$ (+86%) and AUC_{SS} (+59%) values when compared to elderly male volunteers. This difference decreased after weight adjustment and was then not statistically significant (see Table below). Other mean pharmacokinetic parameter values were similar for both genders except clearance, which was lower in elderly females (-37%) and statistically significantly different, even after weight-adjustment. In contrast to the previous study, the two populations in this study were better matched for age.

		Elderly males			Elderly females			ANOVA
parameter	units	mean	%CV	median	mean	%CV	median	p-value
$C_{MAX,SS}$	[µg/mL]	2.17	29.3	2.16	3.38	25.3	3.38	**0.0191**
$C_{MIN,SS}$	[µg/mL]	1.29	36.2	1.21	2.09	28.7	2.01	**0.0272**
$C_{PRE,SS}$	[µg/mL]	1.39	45.2	1.21	2.59	37.1	2.72	**0.0282**
$t_{MAX,SS}$	[h]	7.0	42.4	7.0	7.7	29.4	7.5	0.6749
λ_z	[h^{-1}]	0.0337	10.2	0.0349	0.0284	27.8	0.0309	0.1642
$t_{1/2}$	[h]	20.8	10.8	19.9	26.8	39.2	22.5	0.1989
AUC_{SS}	[µg·h/mL]	41.21	30.5	37.33	65.44	26.2	62.87	**0.0190**
MRT_{TOT}	[h]	37.8	17.0	35.0	45.0	29.2	40.8	0.2512
Cl/f	[mL/min]	6.49	26.0	6.74	4.08	30.2	3.98	**0.0180**
Vd/f	[L]	11.5	20.7	12.3	8.92	24.5	9.03	0.0802
WNC_{MAX}	[µg/mL]	2.08	23.4	2.19	2.70	37.6	2.59	0.2073
WNC_{MIN}	[µg/mL]	1.23	27.9	1.20	1.67	41.0	1.52	0.1835
WNC_{PRE}	[µg/mL]	1.31	34.1	1.28	2.06	45.8	1.85	0.1064
WNAUC	[µg·h/mL]	39.71	25.1	42.14	52.29	38.54	46.73	0.2006
WNCl/f	[mL/min]	6.53	40.5	6.70	3.11	23.7	2.71	**0.0123**
WNVd/f	[L/kg]	0.159	26.1	0.144	0.155	27.8	0.150	0.8747

WN weight-adjusted parameter (standard wt: 75 kg)

The mean plasma concentration time profile in elderly male and female volunteers is shown below.



The lack of significant difference after weight adjustment may be due to delayed absorption in females as shown by their prolonged $t_{MAX,SS}$. The elevated $C_{MIN,SS}$ and $C_{PRE,SS}$ values in elderly females confirm the trend towards longer elimination half-life.

A historical comparison was done between the young healthy volunteers from a different study (107.074), which had a similar study design. The results are given in the following table.

parameter	units	males				females			
		107.039 elderly	107.074 young	% diff. per 10 y	p-value	107.039 elderly	107.081 young	% diff. per 10 y	p-value
$C_{MAX,SS}$	[µg/mL]	2.17	2.32	-1.7	0.628	3.38	1.60	27.1	**0.001**
$C_{MIN,SS}$	[µg/mL]	1.29	0.948	10.3	0.080	2.09	0.680	50.6	**<0.001**
$C_{PRE,SS}$	[µg/mL]	1.39	1.14	6.3	0.305	2.59	0.680	68.5	**<0.001**
AUC_{SS}	[µg·h/mL]	41.2	36.2	4.0	0.394	65.4	27.2	34.3	**<0.001**
$t_{1/2}$	[h]	19.9	22.2	-3.0	0.700	26.8	22.4	4.8	0.2853
$WNC_{MAX,SS}$	[µg/mL]	2.08	2.40	-3.8	0.323	2.70	1.33	25.1	**0.004**
$WNC_{MIN,SS}$	[µg/mL]	1.23	0.977	7.4	0.177	1.67	0.568	47.3	**0.001**
$WNC_{PRE,SS}$	[µg/mL]	1.31	1.18	3.1	0.575	2.06	0.568	64.1	**<0.001**
$WNAUC_{SS}$	[µg·h/mL]	39.7	37.3	1.8	0.673	52.3	22.7	31.8	**0.001**

The pharmacokinetic parameters were constant for young and elderly males. In elderly females the pharmacokinetic parameters ($C_{MAX,SS}$, $C_{MIN,SS}$, $C_{PRE,SS}$, AUC_{SS}) were significantly higher (see p-values). Taken together, these changes indicate higher drug levels in elderly females for equal doses, but a reduced peak-trough fluctuation, since the relative change for $C_{MAX,SS}$ was smaller than for $C_{MIN,SS}$. These differences decreased only slightly after weight normalization. Elimination half-lives were not significantly different between age groups. Elderly male volunteers had a tendency towards shorter elimination half-lives. Comparison between study 107.039 and 107.078 (elderly and young females) is attached in the Appendix on page 54 for the other parameters.

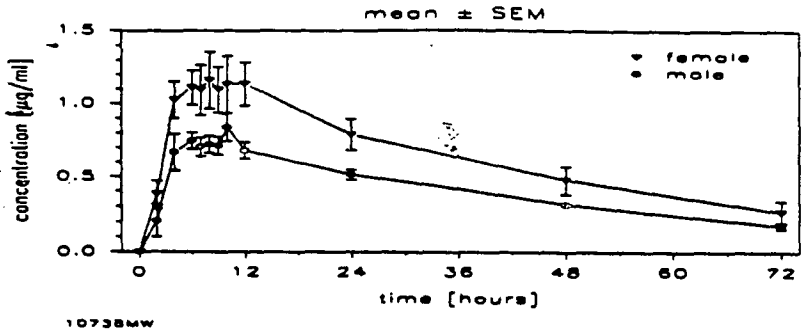
Conclusions

- Elderly females (N=6) had significantly higher $C_{MAX,SS}$, $C_{MIN,SS}$, $C_{PRE,SS}$, AUC_{SS} and CL as compared to elderly males (N=6), but after weight normalization only CL was significantly lower in elderly females.
- In the elderly females $C_{MAX,SS}$, $C_{MIN,SS}$, $C_{PRE,SS}$, AUC_{SS} were significantly higher as compared to the young females based on historical comparisons with Study 107.081 and these differences decreased only slightly after weight normalization and was still statistically significant.
- Elderly males the pharmacokinetic parameters were not significantly from the younger males in historical comparisons Study 107.074.

Study 107.038: Single-dose PK of 15 mg meloxicam capsules in elderly male and female healthy subjects

This trial was an open-label, single-dose pharmacokinetic study in six healthy male and six healthy-female volunteers older than 65 years. Details of study design are attached in the Appendix on page 55 along with subject demographics on page 56.

The mean plasma concentration time profile and the pharmacokinetic parameters for the elderly males and females with and without weight-adjustment is shown in the following figure.



parameter	units	Males (elderly) mean	%CV	median	Females (elderly) mean	%CV	Median	ANOVA p-value
C_{MAX}	[µg/mL]	0.917	26.5	0.870	1.25	25.0	1.17	0.653
t_{MAX}	[h]	6.7	36.3	7.00	7.5	39.3	6.50	0.6100
λ_Z	[h^{-1}]	0.0225	28.2	0.0229	0.0252	28.3	0.0254	0.5088
$t_{1/2}$	[h]	33.2	31.5	30.5	29.8	33.8	27.4	0.5805
MRT_{TOT}	[h]	49.8	31.2	46.9	44.9	34.0	41.5	0.6019
AUC_{0-TLOC}	[µg·h/mL]	30.20	12.5	30.29	46.43	36.5	40.65	**0.0449**
$AUC_{0-\infty}$	[µg·h/mL]	39.49	17.1	37.18	59.96	46.9	48.39	0.1137
Cl/f	[mL/min]	6.64	10.9	6.73	4.95	42.7	5.21	0.0947
Vd/f	[L]	18.2	25.4	17.7	11.5	21.9	12.10	**0.0113**
WNC_{MAX}	[µg/mL]	0.97	39.8	0.861	0.975	22.3	0.994	0.9707
$WNAUC_{0-TLOC}$	[µg·h/mL]	30.96	15.7	30.94	36.02	32.9	32.53	-
$WNAUC_{0-\infty}$	[µg·h/mL]	40.11	11.2	38.94	46.57	45.2	38.65	0.4869
WNCl/f	[mL/min]	6.95	25.6	6.96	3.92	44.5	4.10	**0.014**

WN weight-adjusted pharmacokinetic parameter (standardized weight was 75 kg).

Elderly female volunteers trended towards higher C_{MAX} (+36%) and $AUC_{0-\infty}$ (+52%), than elderly males, but this was not statistically significant. After normalizing the data for body weight, the trend either decreased (C_{MAX}) or disappeared ($AUC_{0-\infty}$).

A historical comparison to young male (mean age-38 years- Study 107.071) and female (mean age-33 years- Study 107.078) volunteers was performed. Medians were chosen for comparison using a nonparametric test [redacted] A non-parametric test was used due to unequal standard deviations between the groups and deviations from the normal distribution. The data are summarized in Table below.

parameter	units	males 107.038 elderly	107.071 young	% diff. per 10 y	p-value	females 107.038 elderly	107.078 young	% diff. per 10 y	p-value
WNC_{MAX}	[µg/mL]	0.861	0.975	-11.7	0.961	0.994	1.03[a]	-0.9	0.688
$WNAUC_{0-\infty}$	[µg.h/mL]	38.9	34.5	3.8	0.508	38.7	24.4[a]	15.4	**0.031**
WNCL/f	[ml/min]	6.96	8.37	-	0.1900	4.10	8.66	-	**0.0008**
MRTtot	[h]	46.9	31.9	-	**0.0014**	41.5	31.4	-	**0.0592**
Vz/f	[l]	17.7	12.7	-	**0.0033**	12.1	14.9	-	**0.0239**
$t_{1/2}$	[h]	30.5	19.3	17.1	**<0.001**	27.4	19.8	10.1	**0.037**

WN weight-adjusted parameter

[a]adjusted to 15 mg dose

In males, weight-normalized C_{MAX} and AUC were similar for both young and elderly males. In females, a significantly larger weight-adjusted AUC in the elderly female group (15.4% difference per 10 years of age) was found. There was no age related change in either gender. This may be due to delayed absorption as indicated by a trend towards a later tmax value. The MRT_{tot} was higher in the elderly in both the genders. This comparison also revealed significantly longer elimination half-lives in the elderly group of both genders. Volume of distribution was higher in the older men as compared to the younger men. In contrast, volume of distribution decreased in elderly females.

Conclusions

- Female volunteers showed higher concentrations compared to male volunteers. Weight adjustment could not explain the differences in most cases, although the differences in the parameters decreased. Other NSAIDS cleared by CYP 2C9 and 3A4 like piroxicam showed a similar gender related effect.
- Elderly females also differed from young females, which can probably be explained by age related reduced hepatic function. Reduced renal function is unlikely to be the reason, since meloxicam is primarily cleared by metabolism. The free fraction of meloxicam in plasma tended to be lower in elderly females and this may explain a part of the difference. Furthermore, body muscle mass changes with age and is accompanied with lower weight, which may be the reason for higher total drug concentrations in elderly females.

Report U93-0205: Effect of age on meloxicam pharmacokinetics in humans based on clinical trials.

Prior to the conduct of study 107.085, the sponsor collected blood samples during the conduct of clinical Phase 2 and 3 safety and efficacy trials to check the compliance of the patients enrolled. Plasma concentrations from trials 107.014/030/036/040/041/042/043/044 were taken to evaluate the effect of age and gender. Multiple values per patient were averaged and compared by gender and age. Taking together all data from the selected rheumatoid and osteoarthritis studies, there was a statistically significant correlation between age and drug concentration for both genders. This indicated higher drug plasma concentrations in elderly patients compared to young adult patients. Results of regression analyses are tabulated below.

		Regression analysis (MELX15norm vs. age)					
gender	age group	corr. coeff.	estimate slope	confidence interval (95%)		p value	n
Male	All	0.1457	0.0106	0.0031 - 0.0180		0.0055 *	362
	< 65 years	0.1634	0.0178	0.0035 - 0.0320		0.0146 *	223
	≥ 65 years	0.1388	0.0187	-0.0039 - 0.0413		0.1031	139
Female	All	0.1549	0.0168	0.0103 - 0.0234		0.0000 *	1048
	< 65 years	0.0588	0.0061	-0.0022 - 0.0144		0.1481	606
	≥ 65 years	-0.0201	0.0057	-0.0326 - 0.0211		0.6738	442

MELX15norm Meloxicam plasma concentrations, individual values per patient averaged and normalized to a 15-mg dose. * Statistically significant ($p<0.05$).

The correlation was only significant for the total age range, not for the young or elderly group alone. Thus a linear correlation seemed inappropriate to describe the age-related changes. To further elucidate the nature and extent of the elevation in males and females, data for both genders were split into age classes as given in the following tables.

age [y]	dose-adjusted (15 mg) drug concentrations [µg/mL]						% dev.*
	males			females			
	mean	% CV	N	mean	% CV	N	
<30	0.922	58.6	3	1.577	48.3	26	71
30-39	0.968	42.2	14	1.632	65.2	57	69
40-49	1.534	51.8	46	1.718	66.1	123	12
50-59	1.547	67.0	100	1.667	54.9	260	8
60-69	1.597	53.2	108	2.143	98.7	303	34
70-79	1.597	53.1	65	2.291	62.0	186	44
>80	1.839	66.4	26	2.219	72.0	93	21
age [y]	dose (15 mg)-and weight-adjusted drug concentrations [µg/mL]						% dev.*
	males			females			
	mean	% CV	N	mean	% CV	N	
<30	0.856	40.9	3	1.266	42.7	26	48
30-39	0.996	45.1	14	1.361	62.7	57	37
40-49	1.606	55.1	46	1.565	66.4	123	-3
50-59	1.619	68.1	100	1.545	53.6	260	-5
60-69	1.628	50.4	108	1.993	110.1	303	22
70-79	1.629	50.3	65	2.078	65.7	186	28
>80	1.889	65.9	26	1.936	72.8	93	3

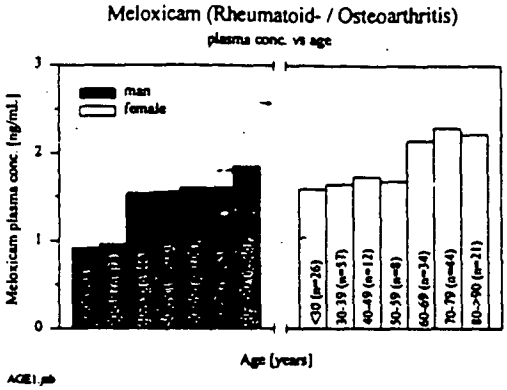
*difference between males and females

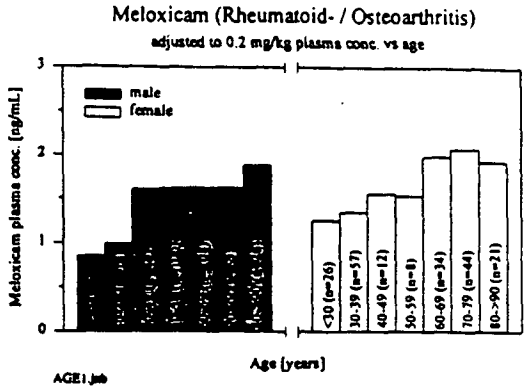
age group		males [µg/mL]*	females [µg/mL]*	female / male % dev.	males [µg/mL]**	females [µg/mL]**	female / male % dev.
all	mean	1.58	1.97	24.5	1.64	1.79	9.0
	%CV	58.4	78.3		58.6	84.7	
	N	362	1048		362	1048	
<65 years	mean	1.53	1.72	12.4	1.59	1.56	-1.9
	%CV	61.0	61.3		59.7	59.8	
	N	223	606		223	606	
= 65 years	mean	1.65	2.30	39.0	1.72	2.10	22.1
	%CV	54.5	86.9		54.7	96.2	
	N	139	442		139	442	
= 65/< 65 y.	% dev.	7.8	33.4		8.2	34.7	

* Normalized to a 15 mg dose.

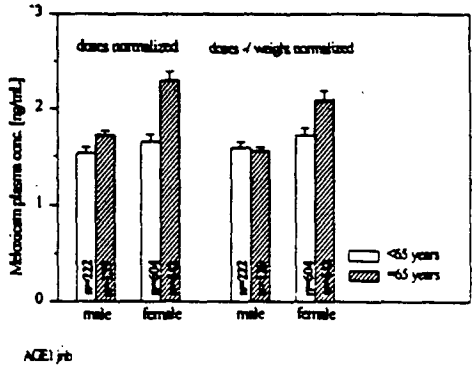
** Normalized to a 15 mg dose and a standard weight of 75 kg.

The plasma concentration in the different age groups can be represented by the following bar graphs, without and with weight adjustment. All data has been normalized for dose.





As seen in the figures males showed a nonsignificant increase in meloxicam plasma concentrations with increasing age. It should be noted that the number of subjects below the age of 40 were few and hence the lower concentrations observed in this age group could be influenced by this. The drug concentrations in the males were slightly lower than the females of the same age group. Female subjects showed an increase in plasma concentrations in the age group 60-69 years and remained constant in the older group. The mean value for female patients 65 years and older was 33% higher than the value for female patients younger than 65 years (see previous table). Males showed no such differences. Gender differences in the elderly may in part be explained by body weight and composition differences. Dose- and weight-adjusted concentrations differed less than only dose-adjusted concentrations as shown in the previous tables.



Conclusions

Based on all the studies pooled together and the clinical safety data, no meaningful differences were seen in the adverse event profile, hence, no dosage adjustment is necessary, as these drugs are normally titrated to effect. (Safety Review by Dr. Kent Johnson).

(C) EFFECT OF RENAL IMPAIRMENT

The effect of renal impairment on the pharmacokinetics has been studied in two studies, a third study is supportive study and is a more mechanistic study (influence of meloxicam in intra-renal prostaglandin synthesis).

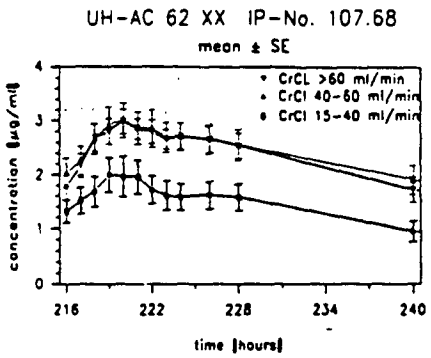
Study 107.068: Phase I study to determine steady state PK of 15 mg meloxicam capsules given orally in subjects with moderate, mild or no renal impairment

Meloxicam is extensively metabolized in the liver with only few percent of the drug

appearing unchanged in urine and feces. The metabolites are excreted in equal parts in the urine and feces. Since renal excretion of unchanged meloxicam does not play an important role in the elimination, it would be expected that the elimination rate would be normal in subjects with impaired renal function. However, there is evidence that non-renal clearance of various drugs is impaired in subjects with decreased renal function, with renal insufficiency affecting the hepatic metabolism of drugs. Further more, the serum protein binding of most anionic drugs is decreased in subjects with renal impairment. Hence, this study was conducted to evaluate the effect of renal impairment on the excretion of meloxicam.

This was an open-label, multiple-dose pharmacokinetic study in patients (18M & 18F) with various stages of renal impairment. Patients were assigned to groups by means of their creatinine clearance. Three groups (Moderate, Mild, No Impairment) had creatinine clearance of 20 - 40 mL/min, 40 - 60 mL/min and >60 mL/min, respectively. Twelve volunteers were recruited for each group. They were given one 15 mg capsule of meloxicam per day for nine days, in the morning after breakfast. Blood samples were taken predose on Days 1, 5, 6, 7, 8 and 9 and serially for 96 hours after the last dose on Day 9. The demographic data for each group is attached in the Appendix on page 58, along with the other details of study design on page 57. The demographic data has not been broken down by gender.

Results



The mean pharmacokinetic parameters and the plasma concentration time profile after multiple doses of 15 mg meloxicam per day are given in the adjacent figure. The mean plasma concentrations decreased in moderately renally impaired patients. Related to this was a higher meloxicam clearance in these group of patients. Lower clearance values were observed in the group of healthy subjects. Reason for this is not known, the sponsor speculates that elderly and more women were enrolled in this group. However, there were no elderly subjects in this group (age>65 years) and same number of females as in the mild group.