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APPLICATION NUMBER

NDA 21-530

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-530

Brand Name: Mobic® Oral Suspension
Generic Name: Meloxicam
Dosage Form: Oral Suspension
Dosage Strength: 7.5 mg/5 mL
Indication: For relief of the signs and symptoms of osteoarthritis
NDA Type: Original NDA
Submission Date(s): 08/18/2003, 02/13/04, 03/12/04, 05/12/04
Sponsor: Boehringer Ingelheim
Reviewer: Chandra S. Chaurasia, Ph.D.
Team Leader: E. Dennis Bashaw, Pharm. D.
OCPB Division: DPE III (HFD-880)
OND Division: ODE V (HFD-550)

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I. EXECUTIVE SUMMARY

Mobic Oral Suspension contains the active ingredient meloxicam, a non-steroidal, anti-inflammatory agent. Solid oral formulations of meloxicam (Mobic 7.5 and 15 mg tablets, NDA 20-938) are approved in the US for relief of the signs and symptoms of osteoarthritis (OA). The

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15 mg tablet is listed as a reference drug in the Orange Book. Meloxicam is approved both as tablet and capsule dosage forms in Europe in 7.5 mg and 15 mg strengths.

The primary focus of this NDA is to establish bioequivalence of the oral suspension formulation of meloxicam to the solid oral dosage form. Support for the BE is based primarily on the results of Study 107.172 comparing the 15 mg meloxicam suspension with 15 mg meloxicam capsule. The 90% confidence intervals for the C_{max} and AUC under steady state conditions are within the acceptable range of 80-125%.

In the original NDA 20-938, the firm had conducted BE studies in Europe using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg tablet (Study 107.82) to link the safety and efficacy data of the tablet formulation with the meloxicam capsules. It is noted that pivotal clinical trials (in NDA 20-938) were conducted with the capsule formulations and, along with the BE determination, were the basis for approval of the 7.5 mg and 15 mg meloxicam tablets.

Since, the C_{max} and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulations were comparable, the Sponsor was directed by the FDA to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension. The Sponsor was also recommended to refer to the published report by Zintzaras, E. and Bouka, P., *Bioequivalence studies: biometrical concepts of alternative design and pooled analysis*, **Eur. J. Drug Metab. Pharmacokinet.** 1999, **24 (3):**225-32.

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUC_{ss} and C_{max,ss} measures of meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved meloxicam tablets, 15 mg

As bioequivalence comparisons are routinely done following a single dose, the single dose (day 1) data was re-analyzed at the request of the FDA for the purposes of investigating single dose bioequivalence. However, due to the fact that sampling was done only up to 6 hour post-dosing on Day 1, only a partial value for AUC could be obtained for the single dose fasted leg in the study 107.172. The results of this analysis showed that the products were not bioequivalent following a single dose (over a period of 0-6 hrs) in terms of AUC or C_{max}. For both parameters, the values for the suspension exceed that of the reference treatment. After evaluating the data and in consultation with the medical officer it was decided that the difference was not clinically relevant or meaningful. This is based on the following:

- 1.) The steady-state bioequivalence of the drug product and its chronic indication.
- 2.) The results of a supportive efficacy trial (Study 107.179) in patient with osteoarthritis suggesting that effectiveness of meloxicam oral suspension is comparable to that of meloxicam tablets in equal doses.

In the current NDA, Boehringer Ingelheim is seeking approval for meloxicam suspension 7.5 mg/5 mL strength. This submission did not contain a direct comparison of the 7.5 mg tablet to a suspension dose of 7.5 mg/5 mL. Given that for both formulations dose proportionality has been

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demonstrated, the finding of equivalency between the 15 mg tablet and a suspension dose of 15mg/10 mL can be extrapolated down to the 7.5 mg dose level.

The dissolution method and specifications were established based on previous recommendation by the FDA for the already approved tablet dosage form. The dissolution method using USP Apparatus 2 (paddle), at 100 rpm in 900 mL buffer pH 7.5 and the specification of NLT 75% Q in 15 minutes as proposed by the Sponsor are acceptable.

Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of the meloxicam oral suspension (7.5mg/5 mL) and found it to be acceptable for meeting the requirements of 21CFR320.

Phase IV Commitment: None requested at this time.

Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Bioequivalence Studies:

The sponsor Boehringer Ingelheim is seeking approval of Mobic Suspension (meloxicam oral suspension) 7.5 mg/5mL for the relief of the signs and symptoms of osteoarthritis in adult population. The NDA 21-530 is a 505 (b)(2) application. Mobic 7.5 mg and 15 mg oral tablets received FDA's approval (NDA 20-938, April 13, 2002 and Aug 23, 2000) for osteoarthritis indication in adults. In addition, meloxicam is approved both as tablet and capsule dosage form in Europe in 7.5 mg and 15 mg strengths.

In support of this application the sponsor submitted 4 bioequivalence/bioavailability studies conducted in healthy male and female volunteers. All of these studies were conducted in Europe. The pivotal BE study (107.172) included comparison of 15 mg meloxicam suspension with 15 mg meloxicam capsule. The original analysis called for the C_{max} and AUC under steady state to be within the acceptable range of 80-125% (Table 1). The metabolic profile of the suspension was comparable to that of the capsule (Table 2).

Table 1. Point estimates and 90% confidence intervals for pharmacokinetic parameters at steady state for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Point Estimate (suspension/capsule)	90% Confidence Interval
C _{maxss} (µg/L)	104%	96.1-112%
AUC _{ss} (µg·h/mL)	101%	95.7-106%
C _{minss} (µg/L)	96.0%	84.7-108%

Table 2. Mean (arithmetic) values of the amounts of meloxicam and its three metabolites excreted in urine for meloxicam suspension vs. meloxicam capsule on day 7 following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Suspension		Capsule	
	Mean	CV%	Mean	CV%
Meloxicam (%)	0.42	31.4	0.43	3.7
AF-UH 1 SE (%)	5.3	24.3	5.4	28.1
UH-AC 101 SE (%)	1.0	52.6	1.2	99.4
UH-AC 110 SE (%)	8.1	34.0	8.6	31.1

While this data is capable of demonstrating steady-state bioequivalence, the Agency's policy is to require a demonstration of bioequivalence under single dose conditions as it is more sensitive to changes in absorption rate. At the request of the Agency the sponsor undertook a re-analysis using the first dose 0-6 hr data. (Table 3 below).

Table 3. Point estimates and 90% confidence intervals for pharmacokinetic parameters for time of administration until 6 hours after administration for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage, N=16 (Study 107.172).

Parameters	Point Estimate (suspension/capsule)	90% Confidence Interval	Intra subject variability %CV
$C_{max, 0-6hr}$ ($\mu\text{g/L}$)	1.21	108-135%	17.66
$AUC_{0-6 hr}$ ($\mu\text{g}\cdot\text{h/mL}$)	1.29	116-143%	17.10

Ideally, the sponsor should have conducted bioequivalence study with a single dose paradigm under fasting conditions. The sponsor argues that based on the chronic nature of the disease, evaluation under steady state conditions is most reasonable. As noted the 90% confidence intervals for both C_{max} and AUC for the 0-6 hour single dose duration are beyond the acceptable range. However, considering a suspension dosage formulation, higher initial absorption leading to increased bioavailability in comparison to a solid oral formulation is not unexpected. This issue was also brought to the attention of the reviewing medical officer who did not feel that these differences were clinically meaningful, and cited the submitted efficacy trial (Study 107.179) as supportive proof of this conclusion.

Study 107.254 was conducted to evaluate dose-proportionality of meloxicam suspension over a dosage range of 7.5 mg to 22.5 mg, and also to assess the effect of food on the pharmacokinetics of meloxicam after a single oral administration of 22.5 mg meloxicam oral suspension. The study was a four-way crossover trial in 24 healthy male and female volunteers with single doses of meloxicam suspension 7.5 mg (treatment 1), 15 mg (treatment 2) and 22.5 mg (treatment 3 and 4) under fasted (treatments 1, 2 and 4) and fed (treatment 3) conditions, respectively.

Dose proportionality for $AUC_{0-\infty}$, AUC_{0-24} and C_{max} of the meloxicam oral suspension (7.5 mg, 15 mg and 22.5 mg) was demonstrated based on the outcome of the ANCOVA of the original values and ANOVA of the dose normalized values. The two-sided 90% confidence intervals for the slope provided by the ANCOVA and ANOVA were within 0.8 to 1.25 for all three parameters (Table 3). The point estimates for C_{max} , $AUC_{0-\infty}$, and AUC_{0-24} were 0.88, 0.97 and 0.99 in the ANCOVA model. The respective values for the ANOVA model were in the range of

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101-113%, 100-103% and 98-103% (Table 4). Mean Cmax, AUC_{0-∞} and AUC_{0-t} were proportional to meloxicam dose (Table 5). Furthermore, mean tmax for the 7.5 mg, 15 mg and 22.5 mg dosage ranged from 5.17-5.87 hour indicating dose-independence.

Table 3. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANCOVA analysis (Study 107.254)

Parameter	Lower Limit	Upper Limit	Point Estimate
Cmax ng/mL	0.8060	0.9637	0.8848
AUC _{0-∞} ng·h/mL	0.9218	1.0262	0.9740
AUC _{0-t} ng·h/mL	0.9437	1.0490	0.9963

Table 4. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANOVA analysis (Study 107.254)

Ratio (Test/Reference)	Parameter	Lower Limit	Upper Limit	Point Estimate
7.5 mg/15 mg	Cmax ng/mL	101.87	121.57	111.29
	AUC _{0-∞} ng·hr/mL	94.72	106.51	100.44
	AUC _{0-t} ng·hr/mL	92.64	104.21	98.26
7.5 mg/22.5 mg	Cmax ng/mL	103.37	123.35	112.91
	AUC _{0-∞} ng·hr/mL	97.36	109.47	103.24
	AUC _{0-t} ng·hr/mL	95.04	106.91	100.80
15 mg/22.5 mg	Cmax ng/mL	92.88	110.84	101.46
	AUC _{0-∞} ng·hr/mL	96.93	108.99	102.78
	AUC _{0-t} ng·hr/mL	96.73	108.81	102.59

Table 5. Pharmacokinetic parameter values following single oral administration of 7.5 mg, 15 mg and 22.5 mg meloxicam suspension under fasted condition (Study 107.254).

Parameters	Treatment	Geom. Mean	%CV
Cmax µg/mL	7.5 mg	0.576	30.5
	15 mg	1.04	30.6
	22.5 mg	1.53	23.8
AUC _{0-∞} µg·h/mL	7.5 mg	16.5	22.5
	15 mg	33.0	26.7
	22.5 mg	48.3	20.6
AUC _{0-t} µg·h/mL	7.5 mg	15.4	23.3
	15 mg	31.4	25.8
	22.5 mg	46.0	19.2
tmax * (hr)	7.5 mg	5.87	75.7
	15 mg	5.17	62.7
	22.5 mg	5.48	63.0

*arithmetic mean reported

Results obtained following administration of meloxicam suspension 22.5 mg under fed and fasted conditions (Study No. 107.254) provide evidence that administration of meloxicam suspension with high caloric high fat food has no effect on peak exposure (Cmax,fed 1.56 µg/mL, CV 25.4% vs. Cmax,fasted 1.53 µg/mL, CV 23.8%) and total exposure (AUC₀₋₂₄, fed

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45.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$, CV 19.9% vs AUC_{0-24} , 46.0 $\mu\text{g}\cdot\text{hr}/\text{mL}$, CV 19.2%). The 90% confidence intervals for C_{max} , AUC_{0-24} and $\text{AUC}_{0-\infty}$ were within the acceptable range of 0.8-1.25 (Table 6), and the ratios of fed/fasted for these parameters were close to the ideal value of 100%. However, the peak plasma concentration following food ingestion occurred almost three hours later as compared to the fasted treatment groups (mean t_{max} 7 hr vs 5.5 hr) presumably due to a longer gastric residence time.

Table 6. Relative bioavailability of meloxicam oral suspension following administration of 22.5 mg in a fasted and fed state, 90% confidence intervals and point estimate.

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate Fed/Fasted (%)
C_{max}	94.37	109.94	101.86
$\text{AUC}_{0-\infty}$	93.29	104.20	98.59
AUC_{0-t}	93.74	104.07	98.77

The sponsor had conducted BE studies in Europe using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg table (Study 107.82) to link the efficacy data obtained with meloxicam capsule. These studies were submitted in the original NDA 20-938 package also. The statistical analyses indicate that 7.5 mg tablets were not bioequivalent to the 7.5 mg capsules with the 90% confidence interval for the $\text{C}_{\text{max,ss}}$ value falling outside the 80-125% range (Table 7). However, the 15 mg tablets were shown to be bioequivalent to the 15 mg capsules with the 90% confidence interval of AUC and C_{max} in the acceptable range of 80-125% (Table 8).

Table 7. Relative bioavailability of meloxicam between the 7.5 mg tablet (test) and 7.5 mg capsule given as once per day for 7 days, N=18

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)
AUC_{ss} 7.5 mg tablet vs. 7.5 mg capsule	100.2	122.6	110.8
$\text{C}_{\text{max,ss}}$ 7.5 mg tablet vs. 7.5 mg capsule	108.3	133.1	120.1

Table 8. Relative bioavailability of meloxicam between the 15 mg tablet (test) and 15 mg capsules given as once per day for 7 days, N=18

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)
AUC_{ss} 15 mg tablet vs. 15 mg capsule	100.8	110.3	105.4
$\text{C}_{\text{max,ss}}$ 15 mg tablet vs. 15 mg capsule	100.9	113.7	107.1

In the current submission a direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. Since, the C_{max} and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulations were comparable, the Sponsor was recommended to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension.

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The sponsor reevaluated the pooled observations for AUC_{ss} and C_{max,ss} of both studies using SAS statistical program with the following model: “subject”, “period”, “treatment” (i.e., product), “study”, and “interaction between treatment (i.e., product) and study”.

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUC_{ss} and C_{max,ss} measures of meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved product meloxicam tablets, 15 mg (Table 9).

Table 9. Ninety percent confidence intervals for the AUC_{ss} and C_{max,ss} for meloxicam suspension vs. meloxicam tablet using pooled observations from studies 107.172 (suspension vs. capsule) and 107.74 (15 mg capsule vs. 15 mg tablet).

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)	Intrasubject variability (%CV)
AUC _{ss}	90.6	109.4	0.99	12.51
C _{max,ss}	87.1	110.5	0.98	15.88

Formulation:

In Study 107.172 the firm compared meloxicam suspension with 15 mg capsule, whereas in Study 107.74 15 mg tablet was compared with 15 mg capsule. It is noted that in the NDA 21-530 submission, the firm had referred the formulation as ‘syrup’ which indeed is a suspension formulation per e-mail clarification from the Sponsor dated April 14, 2004 (see attachment on page 69).

Dissolution:

The dissolution method and specifications for the meloxicam suspension 7.5 mg/5mL were essentially established based on previous recommendation by the FDA for the approved tablet dosage formulation. The dissolution testing was performed using USP apparatus 2 (paddle) at 100 rpm in [] buffer pH 7.5. The dissolution specification of NLT []Q in 15 minutes as proposed by the Sponsor is acceptable.

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

CC: NDA 21-530, HFD-850 (P. Lee), HFD-550 (BJ Gould), HFD-880 (J. Lazor, A. Selen)

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Question Based Review

2.1 General Attributes of Meloxicam

2.1.1 What regulatory background or history information contribute to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

This application is based on the following features that would support an NDA filing under the section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

Solid oral dosage formulations of meloxicam (Mobic NDA 20-938, 7.5 mg and 15 mg tablets) are approved in the US for use in treating the signs and symptoms of osteoarthritis. Meloxicam is approved both as tablet and capsule dosage form in Europe in 7.5 mg and 15 mg strengths.

The primary focus of this NDA is to establish the bioequivalence of the oral suspension formulation of meloxicam to the meloxicam tablets. Support for the BE is based primarily on the results of Study 107.172 comparing the 15 mg meloxicam suspension with 15 mg meloxicam capsule. In the original NDA 20-938, the firm had conducted BE studies in Europe using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg table (Study 107.82) to link the efficacy data obtained with meloxicam capsule.

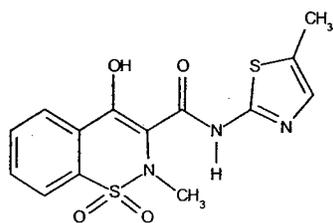
The formulation for the 7.5 mg and 15 mg meloxicam tablets marketed in the US is identical to the 7.5 mg and 15 mg meloxicam tablets used in the comparative bioavailability studies 107.74 and 107.82, respectively.

The Sponsor has submitted clinical trial study No. 107.179 also comparing efficacy and safety of 7.5 mg meloxicam oral suspension with 7.5 mg meloxicam tablet administered once daily over a period of 6 weeks in patients with osteoarthritis.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

Chemical Name: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

Structural formula



Empirical Formula: C₁₄H₁₃N₃O₄S₂

Molecular Weight: 351.4

Physicochemical Properties: Meloxicam is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. Meloxicam has pKa values of 1.1 and 4.2.

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2.1.3. What are the proposed mechanism of action and therapeutic indication of meloxicam?

Mechanism of Action: The mechanism of action of meloxicam, like that of other nonsteroidal anti-inflammatory drug, may be related to prostaglandin synthetase (cyclooxygenase) inhibition.

Indication: Meloxicam is indicated for relief of the signs and symptoms of osteoarthritis.

2.1.4 What is the proposed dosage and route of administration?

The proposed starting and maintenance dose of meloxicam for the treatment of osteoarthritis is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily. The maximum recommended daily oral dose of meloxicam is 15 mg. Meloxicam may be taken without regard to timing of meals.

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Sponsor conducted two pivotal phase I bioequivalence studies (study no. 107.172 and 107.254). Both of these studies were conducted in Europe. Study 107.172 was a single-center, open-label, multiple dose, two-way crossover trial in 18 healthy male volunteers under fasted conditions on day 1 and fed conditions days 2-7. The study was conducted to assess comparative bioavailability between the meloxicam suspension 15 mg and meloxicam capsule 15 mg using the 90% confidence interval approach for the C_{max} and AUC at steady state.

Study 107.254 was a single-center, open-label, randomized, four-way crossover trial in 24 healthy male and female volunteers with single doses of meloxicam suspension 7.5 mg (treatment 1), 15 mg (treatment 2) and 22.5 mg (treatment 3 and 4) under fasted (treatments 1, 2 and 4) and fed (treatment 3) conditions, respectively. The study was conducted to evaluate dose-proportionality over a dosage range of 7.5 mg to 22.5 mg, and also to assess the effect of food on the pharmacokinetics of meloxicam after a single oral administration of 22.5 mg meloxicam oral suspension.

In addition, the Sponsor also conducted supportive bioequivalence studies 107.74 and 107.82 comparing 15 mg capsule and 15 mg tablet and 7.5 mg capsule and 7.5 mg table, respectively. These studies were also conducted in Europe, and were submitted with the original meloxicam tablet formulation in NDA 20-938 to link the safety and efficacy data obtained with meloxicam capsule.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

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As this NDA is for a line extension, with the same indications as the original product, these types of studies were not performed.

2.2.3 Are the active moiety in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the Sponsor measured the appropriate meloxicam in clinical pharmacology studies. See Analytical section (page 35) for more details.

2.2.4. Exposure-response evaluations

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Based on NDA 20-938 for meloxicam tablets, no new information has been submitted for the current suspension dosage form. The exposure-response relationships for efficacy are expected to be comparable to those in Mobic tablets.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

A direct assessment of the exposure-response relationship was not contained in this NDA. As this is a line extension, the majority of the “clinical” database came from in vivo pk trials. These trials were conducted in healthy adult volunteers and were of insufficient duration to properly assess the exposure-response relationship in a definitive manner for safety. The finding of bioequivalency (at steady-state) was in the opinion of the medical officer, sufficient proof of a similar safety profile for this product.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Meloxicam is not known to affect the QT interval.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As this is a line extension with no changes in either dosing or indications, this does not apply here.

2.2.5 What are the pharmacokinetic characteristics of the drug and its metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Tables 1 and 2 present a comparison of the pharmacokinetic parameters determined following single (Day 1, 0-6 hr) and steady state oral doses of meloxicam suspension and capsule, 15 mg once daily for 7 days to healthy male volunteers. Table 2 presents the 90% confidence intervals and point ratios for AUC and C_{max} at steady state. As expected, after the single dose, the suspension showed a faster absorption in comparison to the capsule (median t_{max} 2 h vs 5 h), the maximum drug concentration in the first 6 hours post-dose tended to be higher for the suspension (C_{max,0-6h}: 0.92 µg/mL for suspension vs. 0.76 µg/mL for capsule). At steady state, the absorption from the suspension was comparable to

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that of the capsule. Similarly, the steady state $C_{max,ss}$ and AUC_{ss} values were very similar for both formulations, with a point estimate of 104% and 101%, respectively. The 90% confidence intervals for both these parameters ranged from 96.1-112% and 95.7-106%. Table 3 depicts the arithmetic mean of the amounts of meloxicam and its metabolites in urine collected on day 7 prior to drug intake and all urine voided within 24 hours after the last dose. As expected the urinary excretion of meloxicam and its three metabolites is very similar for both formulations.

Table 1. Pharmacokinetic parameters (geometric mean) of meloxicam suspension and capsule formulations determined in 16 healthy male subjects following single day 1 under fasted and steady state oral doses (days 2 to 7 after breakfast) of meloxicam 15 mg once daily (Study 107.172).

Parameters	Suspension (Test, N=16)		Capsule (Reference, N=16)	
	Geom. Mean	%CV	Geom. Mean	%CV
$C_{max_{0-6h}}$ ($\mu\text{g/L}$)	0.92	27.6	0.76	21.3
t_{max} (h)	2.0 (median)	1.5-5.0 (range)	5.0 (median)	2.0-6.0 (range)
AUC_{0-6h} ($\mu\text{g}\cdot\text{h/mL}$)	3.89	28.8	2.99	21.5
$C_{max,ss}$ ($\mu\text{g/L}$)	1.94	26.9	1.88	33.9
AUC_{ss} ($\mu\text{g}\cdot\text{h/mL}$)	31.0	34.2	30.7	39.0
$t_{max,ss}$ (h)	5.0	3.0-7.0	5.0	5.0-9.0
$C_{min,ss}$ ($\mu\text{g/L}$)	0.71	43.6	0.74	51.6
K_e (h^{-1})	0.0365	31.6	0.0367	27.7
$t_{1/2}$ (h)	18.7	31.6	18.9	27.7
MRT_{tot} (h)	29.3	33.5	34.5	27.1

Table 2. Point estimates and 90% confidence intervals for pharmacokinetic parameters at steady state for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Point Estimate (suspension/capsule)	90% Confidence Interval
$C_{max,ss}$ ($\mu\text{g/L}$)	104%	96.1-112%
AUC_{ss} ($\mu\text{g}\cdot\text{h/mL}$)	101%	95.7-106%
$C_{min,ss}$ ($\mu\text{g/L}$)	96.0%	84.7-108%

Table 3. Mean (arithmetic) values of the amounts of meloxicam and its three metabolites excreted in urine for meloxicam suspension vs. meloxicam capsule on day 7 following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Suspension		Capsule	
	Mean	CV%	Mean	CV%
Meloxicam (%)	0.42	31.4	0.43	3.7
AF-UH 1 SE (%)	5.3	24.3	5.4	28.1
UH-AC 101 SE (%)	1.0	52.6	1.2	99.4
UH-AC 110 SE (%)	8.1	34.0	8.6	31.1

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2.2.5.2 How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable

2.2.5.3 What are the characteristics of drug absorption?

As noted above from the concentration-time profiles of meloxicam suspension and capsules, the drug absorption characteristics of the suspension formulation is comparable to those in meloxicam capsules.

2.2.5.4 What are the characteristics of drug distribution?

Based on NDA 20-938 for meloxicam tablets, no new information has been submitted for the current suspension dosage form. The drug distribution characteristics of the suspension formulation is expected to be comparable to those in Mobic tablets.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted for this application.

2.2.5.6 What are the characteristics of drug metabolism?

As mentioned in 2.2.5.1 above, the urinary excretion of meloxicam and its three metabolites is very similar to those of the approved tablet formulation.

2.2.5.7 What are the characteristics of drug excretion?

Based on NDA 20-938 for meloxicam tablets, no new information has been submitted for the current suspension dosage form.

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity in the dose-concentration relationship?

The pharmacokinetics of meloxicam following single oral meloxicam suspension administration to 24 healthy male subjects over the dose range of 7.5 to 22.5 mg (Study No. 107.254) are presented in Tables 4-6 below. Dose proportionality for $AUC_{0-\infty}$, AUC_{0-24} and C_{max} of the meloxicam oral suspension (7.5 mg, 15 mg and 22.5 mg) was demonstrated based on the outcome of the ANCOVA of the original values and ANOVA of the dose normalized values. The two-sided 90% confidence intervals for the slope provided by the ANCOVA and ANOVA were within 0.8 to 1.25 for all three parameters (Table 4). The point estimates for C_{max} , $AUC_{0-\infty}$, and AUC_{0-24} were 0.88, 0.97 and 0.99 in the ANCOVA model. The respective values for the ANOVA model were in the range of 101-113%, 100-103% and 98-103% (Table 5). Mean C_{max} , $AUC_{0-\infty}$ and AUC_{0-t} were proportional to meloxicam dose (Table 6). Furthermore, mean t_{max} for the 7.5 mg, 15 mg and 22.5 mg dosage ranged from 5.17-5.87 hour indicating dose-independence.

Table 4. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANCOVA analysis (Study 107.254)

Parameter	Lower Limit	Upper Limit	Point Estimate
C _{max} ng/mL	0.8060	0.9637	0.8848
AUC _{0-∞} ng·h/mL	0.9218	1.0262	0.9740
AUC _{0-t} ng·h/mL	0.9437	1.0490	0.9963

Table 5. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANOVA analysis (Study 107.254)

Ratio (Test/Reference)	Parameter	Lower Limit	Upper Limit	Point Estimate
7.5 mg/15 mg	C _{max} ng/mL	101.87	121.57	111.29
	AUC _{0-∞} ng.hr/mL	94.72	106.51	100.44
	AUC _{0-t} ng.hr/mL	92.64	104.21	98.26
7.5 mg/22.5 mg	C _{max} ng/mL	103.37	123.35	112.91
	AUC _{0-∞} ng.hr/mL	97.36	109.47	103.24
	AUC _{0-t} ng.hr/mL	95.04	106.91	100.80
15 mg/22.5 mg	C _{max} ng/mL	92.88	110.84	101.46
	AUC _{0-∞} ng.hr/mL	96.93	108.99	102.78
	AUC _{0-t} ng.hr/mL	96.73	108.81	102.59

Table 6. Pharmacokinetic parameter values following single oral administration of 7.5 mg, 15 mg and 22.5 mg meloxicam suspension under fasted condition (Study 107.254).

Parameters	Treatment	Geom. Mean	%CV
C _{max} µg/mL	7.5 mg	0.576	30.5
	15 mg	1.04	30.6
	22.5 mg	1.53	23.8
AUC _{0-∞} µg·h/mL	7.5 mg	16.5	22.5
	15 mg	33.0	26.7
	22.5 mg	48.3	20.6
AUC _{0-t} µg·h/mL	7.5 mg	15.4	23.3
	15 mg	31.4	25.8
	22.5 mg	46.0	19.2
t _{max} * (hr)	7.5 mg	5.87	75.7
	15 mg	5.17	62.7
	22.5 mg	5.48	63.0
t _{1/2} (hr)*	7.5 mg	20.2	22.9
	15 mg	19.8	22.6
	22.5 mg	20.4	23.7
Ke (h ⁻¹)*	7.5 mg	0.0361	23.6
	15 mg	0.0367	22.2
	22.5 mg	0.0357	22.4

*arithmetic mean reported

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2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

Based on NDA 20-938 for meloxicam tablets, and on the lack of an observed change in meloxicam pharmacokinetics upon steady-state dosing, no change was noted.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability (CVs) in the C_{max} , ss was 27% and 34%, respectively for the suspension and capsule formulations. The respective CVs for AUC_{ss} were approximately 34% and 39% (Table 1 above in Section 2.2.5.1). The relatively high CV in capsule is presumably due to variation in the release of meloxicam from the capsule formulation. There were no remarkable differences in inter-subject variability in meloxicam AUC_{ss} (CVs 34% vs 39%). The intra-subject variability for the C_{max} , ss and AUC_{ss} in the pivotal BE study 107.172 was 20% and 17%, respectively (Module 5, Vol 1.6, pp. 461).

2.3. Intrinsic Factors

Based on NDA 20-938 for meloxicam tablets, no new information has been submitted for the current suspension dosage form.

2.4. Extrinsic factors

Based on NDA 20-938 for meloxicam tablets, no new information has been submitted for the current suspension dosage form.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

As indicated in Section 2.2.1, meloxicam is practically insoluble in water. The applicant has not provided any permeability data.

2.5.2. What is composition of the to-be-marketed formulation?

The proposed Mobic suspension is available for oral administration in strength of 7.5 mg/5mL. The inactive ingredients in MOBIC oral suspension include colloidal silicon dioxide, hydroxyethylcellulose, sorbitol, glycerol, xylitol, monobasic sodium phosphate (dihydrate), saccharin sodium, sodium benzoate, citric acid (monohydrate), raspberry flavor, and purified water.

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The proposed formulation for the to-be-marketed suspension is same as the formulation used in the pivotal BE studies.

2.5.4 What moieties should be assessed in bioequivalence studies?

The parent drug meloxicam.

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Food effect

Results obtained following administration of meloxicam suspension 22.5 mg under fed and fasted conditions (Study No. 107.254) provide evidence that administration of meloxicam suspension with high caloric high fat food has no effect on peak exposure ($C_{max, fed}$ 1.56 $\mu\text{g/mL}$, CV 25.4% vs. $C_{max, fasted}$ 1.53 $\mu\text{g/mL}$, CV 23.8%) and total exposure ($AUC_{0-24, fed}$ 45.2 $\mu\text{g}\cdot\text{hr/mL}$, CV 19.9% vs $AUC_{0-24, fasted}$ 46.0 $\mu\text{g}\cdot\text{hr/mL}$, CV 19.2%). The 90% confidence intervals for C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ were within the acceptable range of 0.8-1.25, and the ratios of fed/fasted for these parameters were close to the ideal value of 100%. However, the peak plasma concentration following food ingestion occurred almost three hours later as compared to the fasted treatment groups (mean t_{max} 7 hr vs 5.5 hr) presumably due to a longer gastric residence time.

2.5.7 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Yes., the applicant has conducted dissolution testing under various stability conditions, and has proposed the following method and specification based on the results of the dissolution testing (for detail description please see In Vitro Dissolution under Appendix:

Apparatus: USP Apparatus 2 (paddle)
Rotation: 75 rpm
Medium: 900 mL of 0.1N HCl buffer, pH 7.5 at 37 C
Specification: NLT 75% (Q) of the labeled amount of meloxicam dissolved in 75 minutes.

The method is similar to that for the meloxicam (Mobic) tablet dosage formulation (NDA 21-938) except for rotational speed, which was reduced from 100 rpm to avoid excessive agitation.

2.6 Analytical Section

2.6.1 Were relevant metabolite concentration measured in the clinical pharmacology and biopharmaceutics studies?

The applicant measured the active moiety meloxicam in all the BE studies, and urinary metabolites in the pivotal BE study #107.172.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis of that decision, and is it appropriate?

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Not Applicable

2.6.3 Were the analytical procedures used to determine drug concentration in this NDA acceptable?

Yes. Meloxicam in plasma and meloxicam and its metabolites in urine were quantified by means of a validated HPLC assays using UV detection. The assay methods have adequate linearity, precision, accuracy, reproducibility and sensitivity (LOQ 1 µg/mL in plasma and 1 ng/mL in urine matrix) for meloxicam and its metabolites. The applicant has provided adequate documentation of method validation and in-study validation.

It is further noted that an inspection of analytical laboratories and Human Pharmacology Center, Boehringer Ingelheim Pharma KG, Ingelheim am Rhein, Germany and associated with pivotal studies No. 107.171 and 107.254, was requested through the Division of Scientific Investigation (HFD-48). Following the inspection, no Form 483 was issued at Human Pharmacology Center, Boehringer Ingelheim Pharma KG, Ingelheim am Rhein, Germany and Form FDA 483 was issued at due to concern on long term and freeze-thaw stabilities data for meloxicam. Subsequent FDA inspection found adequate documentation on long term and freeze-thaw stability of meloxicam. Based on these findings, the DSI recommended data from studies no. 107.171 and 107.254 to be accepted for review. This reviewer concurs with the DSI recommendation. DSI summary report is attached in Appendix section.

3. Labeling Recommendations

The following changes in the Clinical Pharmacology section of the proposed labeling is recommended based on the pharmacokinetic results following meloxicam suspension administration under fasted and fed conditions (Study No. 107.254). The recommended insertions are marked by bold and underlined and deletions by strikethrough.

Food and Antacid Effects

Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e. C_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T_{max}) was achieved between 5 and 6 hours. In comparison, neither the AUC nor the C_{max} values for meloxicam suspension were affected following a similar high fat meal, while mean T_{max} values were increased to approximately 7 hours.

No pharmacokinetic interaction was detected with concomitant administration of antacids. **Based on the results**, MOBIC can be administered without regard to timing of meals **or concomitant administration of antacids.**²

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4. Appendices

4.1 Proposed Package Insert (Original and Annotated)

**Proposed by the Sponsor in the original NDA 21-530 submission dated 08/18/2003
(see next page)**

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17 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

 _____ § 552(b)(5) Draft Labeling

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Review

Study 107.172: Relative Bioavailability of 15 mg meloxicam suspension p.o. in comparison to 15 mg meloxicam capsule p.o. after steady state in healthy subjects.

Study Design: This was a Phase I, single-center, open-label, randomized, multiple dose, two-way crossover trial in 18 healthy male volunteers under fasted conditions on day 1 and fed conditions days 2-7. A washout period of at least 7 days was set between both trial periods.

Study Center/Investigator: The study was conducted [redacted]

[redacted] supervised by the Clinical Investigator [redacted]

Study Subjects: Eighteen healthy male volunteers participated in the study, 17 subjects completed the trial, however data from only 16 subjects were included in the pharmacokinetic evaluation. Subject 1 was excluded for noncompliance and subject 13 withdrew prior to second steady state profile due to personal reasons. The mean and range for age, weight and height were 35 years (range 22-45), 78.34 kg (range 59-99) and 179.7 cm (range 163-189), respectively. Inclusion and exclusion criteria are described on pages 19-20, Module 5, Vol. 1.5.

Treatment: The subjects received seven once daily 15 mg doses of meloxicam as suspension or as capsule in a crossover design. The drug was given in fasted state on day 1 and subsequent dose after a breakfast on days 2-7 with 100 ml of water.

Study Dates: Clinical study was performed between 10/14/1996 to 11/24/ 1996. Analytical: Urine samples were analyzed between 12/3-12/13, 1996, and the PK evaluation was performed between 01/10-23, 1997.

Drug Formulations: Test: Meloxicam suspension, UH-AC 62XX-SI 1D 1A, lot B960923.

Reference: Meloxicam Capsule, 15 mg, UH-AC 62XX-KAH 30 10A, lot 50813.

Sampling: Plasma Sampling: Blood 4.5 mL pre-dose (0) and at 0.25, 0.5, 0.75, 1, 1.5, 2,3,4,5 and 6 hours post-dose on day 1, immediately before the next dose from day 2 through 7 (24 h, 48 h, 72 h, 96 h and 120 h) as well as 0.5,1,1.5,2,3,4,5,6,7,8,9,19,12,14,24,36,48 and 72 hours after the last dose on day 7.

Urine Sampling: Collected on day 7 prior to drug intake and all urine voided within 24 hours after the last dose.

All blood and urine samples were stored at -20 °C pending analysis.

Analytical Determinations:

Meloxicam in Plasma: Drug was quantified in plasma by means of a validated HPLC assay using UV detection. The limit of detection (LOQ) was [redacted] µg/mL. Calibration standards employed drug concentrations from [redacted] µg/mL. The assay precision and accuracy values were within [redacted] respectively. The analytical validation is described in detail in Module 5, Vol. 1.5. pp. 212-242.

Meloxicam in Urine: Meloxicam and its metabolites AU-FH 1 SE, UH-AC 101 SE and UH-AC 110 SE were quantified in urine by means of a validated HPLC assay using a UV detection. The limit of quantification (LOQ) was [redacted] ng/mL for each analyte. Calibration standards employed drug concentrations from [redacted] ng/mL. The assay precision values were within [redacted] and assay accuracy were within [redacted] for meloxicam, and three metabolites, respectively. The analytical validation is described in detail in Module 5, Vol. 1.6. pp. 271.

The Division of Scientific Investigation (HFD-48, report by Dr. Martin K Yau) found the analytical method validation and procedures in the current study acceptable for reviewing the data (please also see above section 2.6.3 page 17).

Pharmacokinetic Results:

Plasma Data:

Pharmacokinetic Analysis: A comparison of the mean (geometric) pharmacokinetic parameters values for day 1 (0-6h) and at steady state is summarized in the Table 1, and Point estimates and 90% confidence intervals for pharmacokinetic parameter values at steady state are summarized in the Table 2 below. Figure 1 depicts the steady-state plasma-concentration time profile.

Table 1. Pharmacokinetic parameters (geometric mean) of meloxicam suspension and capsule formulations determined in 16 healthy male subjects following single day 1 under fasted and steady state oral doses (days 2 to 7 after breakfast) of meloxicam 15 mg once daily (Study 107.172).

Parameters	Suspension (Test, N=16)		Capsule (Reference, N=16)	
	Geom. Mean	%CV	Geom. Mean	%CV
C _{max} _{0-6h} (µg/L)	0.92	27.6	0.76	21.3
t _{max} (h)	2.0 (median)	1.5-5.0 (range)	5.0 (median)	2.0-6.0 (range)
AUC _{0-6h} (µg·h/mL)	3.89	28.8	2.99	21.5
C _{max,ss} (µg/L)	1.94	26.9	1.88	33.9
AUC _{ss} (µg·h/mL)	31.0	34.2	30.7	39.0
t _{max,ss} (h)	5.0	3.0-7.0	5.0	5.0-9.0
C _{min,ss} (µg/L)	0.71	43.6	0.74	51.6
Ke (h ⁻¹)	0.0365	31.6	0.0367	27.7
t _{1/2} (h)	18.7	31.6	18.9	27.7
MRT _{tot} (h)	29.3	33.5	34.5	27.1

Table 2. Point estimates and 90% confidence intervals for pharmacokinetic parameters at steady state for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Point Estimate (suspension/capsule)	90% Confidence Interval
C _{max,ss} (µg/L)	104%	96.1-112%
AUC _{ss} (µg·h/mL)	101%	95.7-106%
C _{min,ss} (µg/L)	96.0%	84.7-108%

Table 3. Mean (arithmetic) values of the amounts of meloxicam and its three metabolites excreted in urine for meloxicam suspension vs. meloxicam capsule on day 7 following 15 mg oral dosage once daily for 7 days, N=16 (Study 107.172).

Parameters	Suspension		Capsule	
	Mean	CV%	Mean	CV%
Meloxicam (%)	0.42	31.4	0.43	3.7
AF-UH 1 SE (%)	5.3	24.3	5.4	28.1
UH-AC 101 SE (%)	1.0	52.6	1.2	99.4
UH-AC 110 SE (%)	8.1	34.0	8.6	31.1

Figure 1. Geometric mean and individual plasma concentrations on Day 7 after multiple once daily 15 mg meloxicam doses given as suspension or capsule to 16 healthy male volunteers: 0-24 h in steady state.

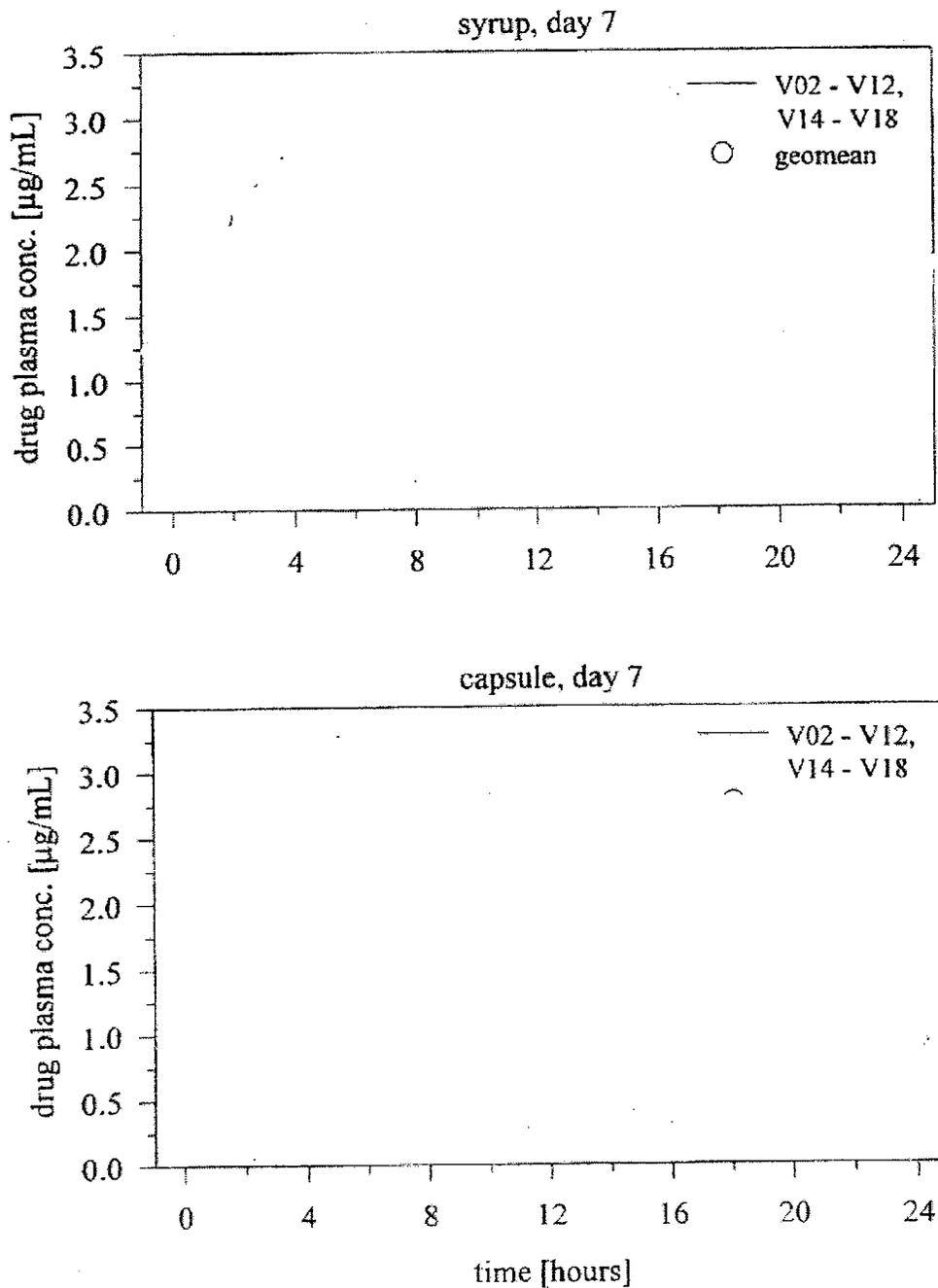
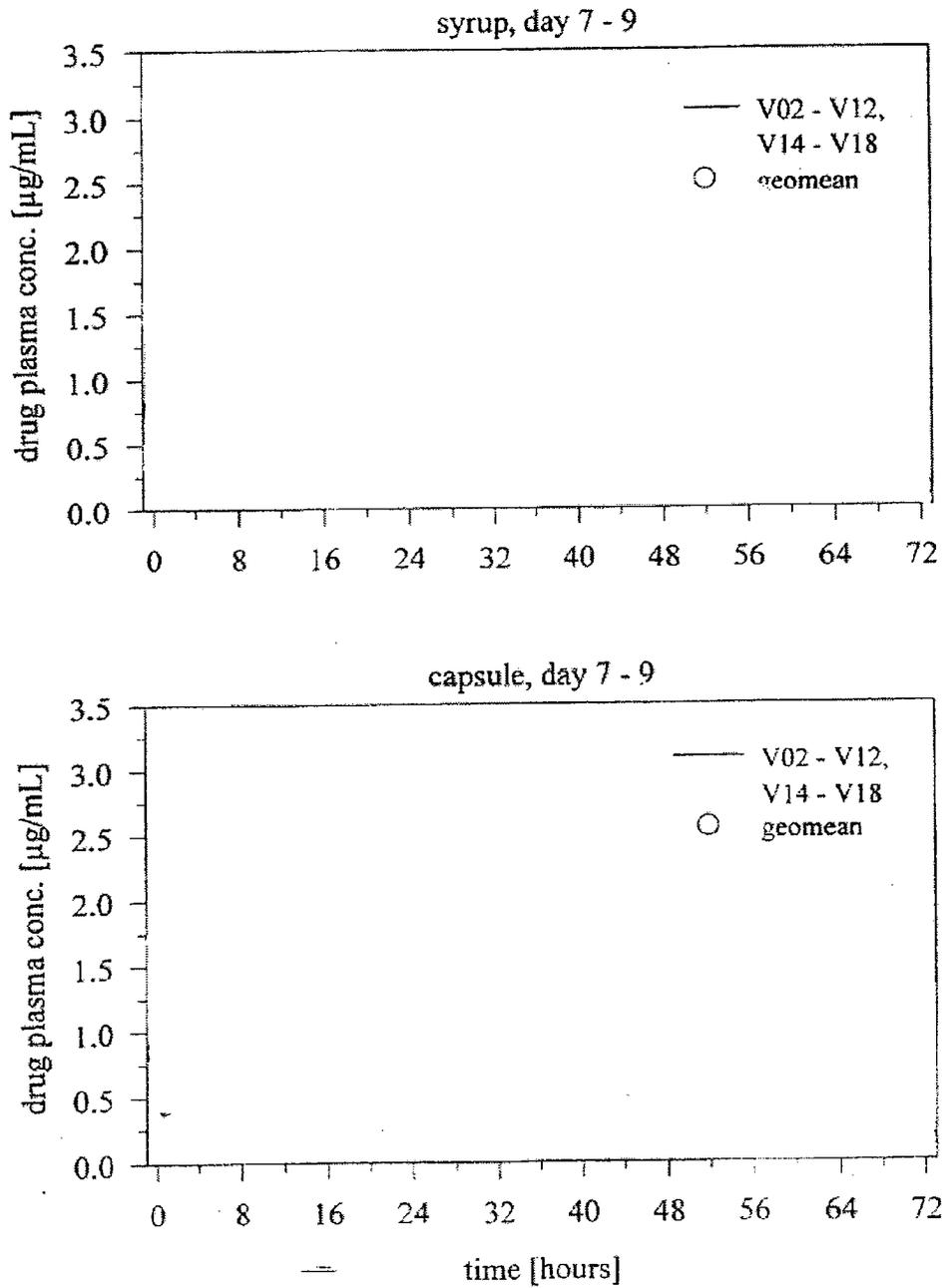
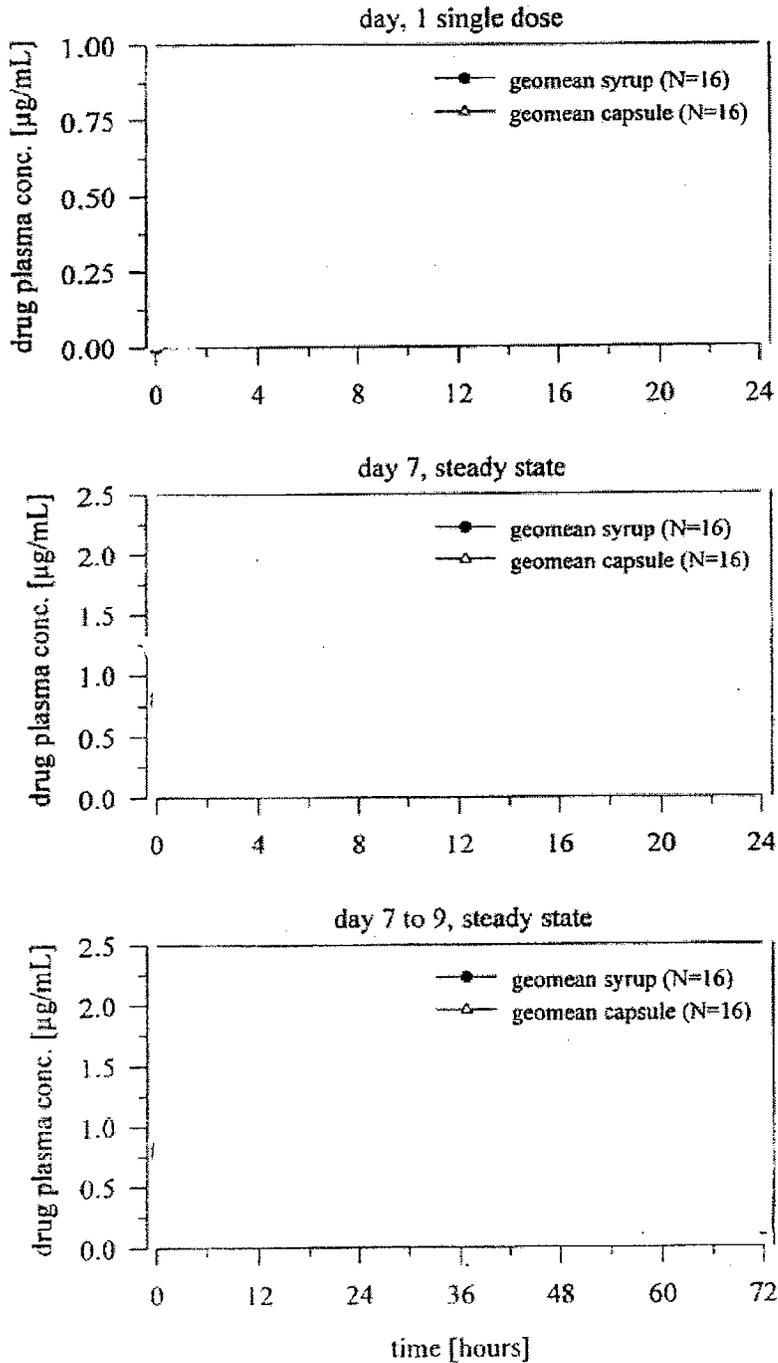


Figure 2. Geometric mean and individual plasma concentrations on Day 7 after multiple once daily 15 mg meloxicam doses given as suspension or capsule to 16 healthy male volunteers: 0-72 h in steady state.



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Figure 3. Geometric mean and individual plasma concentrations on Day 7 after multiple once daily 15 mg meloxicam doses given as suspension or capsule to 16 healthy male volunteers: 0-72 h in steady state.



Based on the fact that pharmacokinetic parameter especially C_{max} value has less propensity of variation when compared as a single dose rather than at steady state, the sponsor was requested to provide statistical analysis data 90% (confidence intervals and point estimate ratios on the 0-6 hours Day 1 fasting stage C_{max,0-6h} and AUC_{0-6h}) parameters for this study. The data for the 0 to 6 hours following the first dose administration are summarized in Table 4 below:

Table 4. Point estimates and 90% confidence intervals for pharmacokinetic parameters for time of administration until 6 hours after administration for meloxicam suspension vs. meloxicam capsule following 15 mg oral dosage, N=16 (Study 107.172).

Parameters	Point Estimate (suspension/capsule)	90% Confidence Interval	Intra subject variability %CV
C _{max, 0-6hr} (µg/L)	1.21	108-135%	17.66
AUC _{0-6 hr} (µg·h/mL)	1.29	116-143%	17.10

Adverse Events: No serious adverse event occurred in this trial. Six volunteers reported adverse events under treatment with suspension only. One adverse event (nausea immediately after drug administration) in Subject #1 was considered drug related. No therapy was required. Other events included headache (Sub #1), gastric pain (Sub #3, mild intensity beginning in the morning of day 7 one hour before drug administration), common cold of moderate intensity (Sub #3, beginning in the morning of day 5), constipation, flatulence and fatigue of mild intensity (from day 2-5, Sub #10), common cold of mild intensity (Sub #16 from day 4-7) and sore throat of mild intensity (Sub #17, day 6-7) were considered not drug related.

Discussion:

Plasma Study:

Meloxicam suspension showed a faster absorption in comparison to the capsule on day 1, when both formulations were given in fasted state (median t_{max} = 2 hr vs. 5 h). Also, the maximum drug concentration in the first 6 hours post-dose tended to be higher for the suspension (C_{max 0-6h}, 0.92 vs. 0.76 µg/mL). As noted from the steady state concentration-time profiles of meloxicam suspension and capsules, the drug absorption characteristics of the suspension formulation is comparable to those in meloxicam capsules with the mean t_{max,ss} of 5 hr for each formulation.

Meloxicam minimum plasma concentration at steady state were also very similar for suspension and capsule with 0.711 (CV 43.6%) and 0.74 (CV 51.6%) µg/mL, respectively. The 90% confidence interval for C_{max,ss} and AUC_{ss} were within the 80-125% range, and point ratios were close to 1.

Ideally, the sponsor should have conducted bioequivalence study with a single dose paradigm under fasting conditions. The sponsor argues that based on the chronic nature of the disease, evaluation under steady state conditions is most reasonable. As noted the 90% confidence intervals for both C_{max} and AUC for the 0-6 hour single dose duration are beyond the acceptable range. However, considering a suspension dosage formulation, higher initial absorption leading to increased bioavailability in comparison to the tablet formulation is not unexpected. Additionally, taking into account that the systemic exposure of meloxicam from the suspension formulation under chronic use situation is similar to that of the meloxicam capsule, the consultation with the medical officer it was decided that the difference was not clinically relevant or meaningful. This is based on the following:

- 3.) The steady-state bioequivalence of the drug product and its chronic indication.
- 4.) The results of a supportive efficacy trial (Study 107.179) in patient with osteoarthritis suggesting that effectiveness of meloxicam oral suspension is comparable to that of meloxicam tablets in equal doses.

Urine Study:

As expected the urinary excretion of meloxicam and its three known metabolites AF-UH 1SE, UH-AC 101 SE and UH-AC 110 SE is very similar for both formulations.

Conclusion:

Based on the results of BE study #107.72, meloxicam suspension 15 mg is bioequivalent to meloxicam capsule 15 mg.

Report No. 107.243: An open, randomized, 4-way crossover study in healthy volunteers to evaluate the effect of food on the pharmacokinetics of meloxicam after a single p.o. administration of 22.5 mg meloxicam oral suspension and dose-proportionality over a dosage range of 7.5 mg to 22.5 mg. (N=24, 12 males and 12 females, age 23-47, average 33.1. Dose: 7.5 mg fasted, 15 mg fasted and 22.5 mg fed.

Note: As reported by the Sponsor (Vol .1.2) due to technical difficulty (mixing up of a relevant no. of samples) the study was not conclusive. The study was repeated in Protocol No. 107.254. Report No. 107.243 was therefore not reviewed by this reviewer.

Protocol No. 107.254. An open, randomized, four-way crossover study in healthy volunteers to evaluate the effect of food on the pharmacokinetics of meloxicam after a single p.o. administration of 22.5 mg meloxicam oral suspension and dose-proportionality over a dosage range of 7.5 mg to 22.5 mg.

Study Objectives: The primary aim of this trial was to investigate dose-proportionality over the dose range of 7.5 mg to 22.5 mg. The secondary objective was to assess the effect of food on the pharmacokinetics of meloxicam after a single oral administration of 22.5 mg meloxicam suspension.

Study Design: This was a Phase I, single-center, open-label, randomized, four-way crossover trial in 24 healthy male and female volunteers with single doses of 7.5 mg (treatment 1), 15 mg (treatment 2) and 22.5 mg (treatment 3 and 4) under fasted (treatments 1, 2 and 4) and fed (treatment 3) conditions, respectively. The crossover to the alternate treatments was performed after a wash out phase of at least 10 days, respectively.

Study Center/Investigator: The study was conducted at Human Pharmacology Center, Department of Clinical Research, Boehringer Ingelheim Pharma KG, Rhein, Germany supervised by the Clinical Investigator Dr. M. Klueglich.

Analytical Center: []

Study Subjects: Twenty-four healthy male (N=12) and female (N=12) volunteers participated in the study, 23 subjects completed the trial. One subject (#12 dropped out of the trial during wash out period 1 due to nausea and vertigo (unrelated to study drugs). The median and range for age, weight and height were 33.9 years (range 24-48), 71 kg (range 51-99) and 174.0 cm (range

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153-188), respectively. Inclusion and exclusion criteria are described on pages 25-27, Module 5, Vol. 1.3.

Treatments: The subjects received single dose of the following:

Treatment 1 (Test): 7.5 mg of meloxicam suspension, fasted

Treatment 2 (Test): 15 mg of meloxicam suspension, fasted

Treatment 3 (Test): 22.5 mg of meloxicam suspension, fed

Treatment 4 (Reference): 7.5 mg of meloxicam suspension, fasted

Study Dates: Clinical study was performed between 01/14/2002 to 04/29/2002.

Drug Formulations: Meloxicam Suspension, UH-AC 62XX-SI 1D 1A, batch no. 156511A

Sampling: Plasma Sampling: Blood samples 4.9 mL each were collected at pre-dose (0) and at 0.5, 1, 2,3,4,5,6,7,8,9,10,11,12,14,24,32,48,72 and 96 hours after post-dose.

Analytical Determinations:

Meloxicam in Plasma: Drug was quantified in plasma by means of a validated HPLC assay using UV detection. The assay was validated from $—$ ng/mL to $—$ ng/mL with a mean r^2 for the standard curve of $\text{[} \quad \text{]}$. The assay precision was in the range of $\text{[} \quad \text{]}$ and assay accuracy in the range of $\text{[} \quad \text{]}$. The limit of quantification was $—$ ng/mL. The analytical validation is described in detail in Module 5, Amendment volume 1 of the original NDA.

Pharmacokinetic and Statistical Methods:

The primary aim of this trial was to investigate dose-proportionality over the dose range of 7.5 mg to 22.5 mg. The secondary objective was to assess the effect of food on the pharmacokinetics of meloxicam after a single oral administration of 22.5 mg meloxicam suspension. Dose proportionality ($AUC_{0-\infty}$, AUC_{0-t} and C_{max}) of the meloxicam suspension was demonstrated based on the outcome of both ANCOVA (analysis of covariance) of original values and ANOVA (analysis of variance) of dose normalized values. Mean values for C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ were compared using an analysis of variance (ANOVA) statistical model with calculation of 90% confidence intervals for the ratio of test formulation to reference formulation. Bioequivalence was concluded if the 90% confidence intervals were within the 80%-125%.

Results

Dose Proportionality

Mean PK values for meloxicam suspension 7.5 mg, 15 mg and 22.5 mg under fasted conditions are summarized in Table 4 below. The results of the analyses of dose-proportionality using the ANCOVA model for C_{max} and AUCs and ANOVA model using the dose normalized data are summarized in Tables 5 and 6 below. Figures 3,4 and 5 depict individual and geometric mean plasma concentrations for 7.5 mg, 15 mg, 22.5 mg suspensions under fasted conditions. Figure 6 depicts geometric means after single dose administration of 7.5 mg, 15 mg and 22 mg meloxicam under fasted under fed conditions.

Table 4. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANCOVA analysis (Study 107.254)

Parameter	Lower Limit	Upper Limit	Point Estimate
C _{max} ng/mL	0.8060	0.9637	0.8848
AUC _{0-∞} ng·h/mL	0.9218	1.0262	0.9740
AUC _{0-t} ng·h/mL	0.9437	1.0490	0.9963

Table 5. 90% Confidence Intervals and Point Estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5, 15 and 22.5 mg doses, under fasted condition, N=23, ANOVA analysis (Study 107.254)

Ratio (Test/Reference)	Parameter	Lower Limit	Upper Limit	Point Estimate
7.5 mg/15 mg	C _{max} ng/mL	101.87	121.57	111.29
	AUC _{0-∞} ng.hr/mL	94.72	106.51	100.44
	AUC _{0-t} ng.hr/mL	92.64	104.21	98.26
7.5 mg/22.5 mg	C _{max} ng/mL	103.37	123.35	112.91
	AUC _{0-∞} ng.hr/mL	97.36	109.47	103.24
	AUC _{0-t} ng.hr/mL	95.04	106.91	100.80
15 mg/22.5 mg	C _{max} ng/mL	92.88	110.84	101.46
	AUC _{0-∞} ng.hr/mL	96.93	108.99	102.78
	AUC _{0-t} ng.hr/mL	96.73	108.81	102.59

Table 6. Pharmacokinetic parameter values following single oral administration of 7.5 mg, 15 mg and 22.5 mg meloxicam suspension under fasted condition (Study 107.254).

Parameters	Treatment	Geom. Mean	%CV
C _{max} µg/mL	7.5 mg	0.576	30.5
	15 mg	1.04	30.6
	22.5 mg	1.53	23.8
AUC _{0-∞} µg·h/mL	7.5 mg	16.5	22.5
	15 mg	33.0	26.7
	22.5 mg	48.3	20.6
AUC _{0-t} µg·h/mL	7.5 mg	15.4	23.3
	15 mg	31.4	25.8
	22.5 mg	46.0	19.2
t _{max} * (hr)	7.5 mg	5.87	75.7
	15 mg	5.17	62.7
	22.5 mg	5.48	63.0
t _{1/2} (hr)*	7.5 mg	20.2	22.9
	15 mg	19.8	22.6
	22.5 mg	20.4	23.7
K _e (h ⁻¹)*	7.5 mg	0.0361	23.6
	15 mg	0.0367	22.2
	22.5 mg	0.0357	22.4

*arithmetic mean reported

Food Effect

The results of the analysis of the food effect for C_{max} and AUCs are shown in the Tables 7 and 8 below. Figure 7 depicts individual and geometric mean plasma concentrations of meloxicam following single dose administration of 22.5 mg meloxicam suspension under fed conditions, and Figure 8 depicts geometric means after single dose administration of 7.5 mg, 15 mg and 22 mg meloxicam under fasted and 22.5 mg meloxicam suspension under fed conditions.

Table 7. Pharmacokinetic parameter values following single oral administration of 22.5 mg meloxicam suspension under fasted and fed conditions.

Parameters	Fed (N=23)		Fasted (N=23)	
	Geom. Mean	%CV	Geom. Mean	%CV
C _{max} µg/mL	1.56	25.4	1.53	23.8
AUC _{0-∞} µg·h/mL	47.4	21.7	48.3	20.6
AUC _{0-t} µg·h/mL	45.2	19.9	46.0	19.2
t _{max}	7.0*	45.8	5.5*	63.0
t _{1/2} (h)	20.6*	22.3	20.4*	23.7
Ke (h ⁻¹)	0.0354*	24.9	0.0357*	22.4

*arithmetic mean reported

Table 8. Relative bioavailability of meloxicam oral suspension following administration of 22.5 mg in a fasted and fed state, 90% confidence intervals and point estimate.

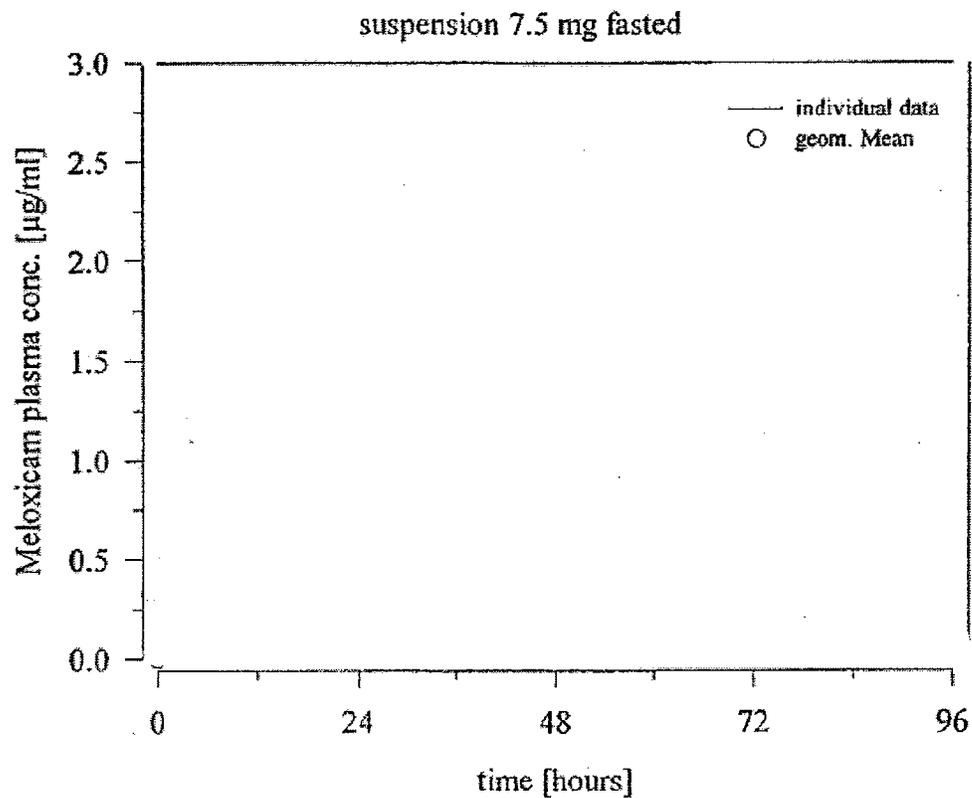
Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate Fed/Fasted (%)
C _{max}	94.37	109.94	101.86
AUC _{0-∞}	93.29	104.20	98.59
AUC _{0-t}	93.74	104.07	98.77

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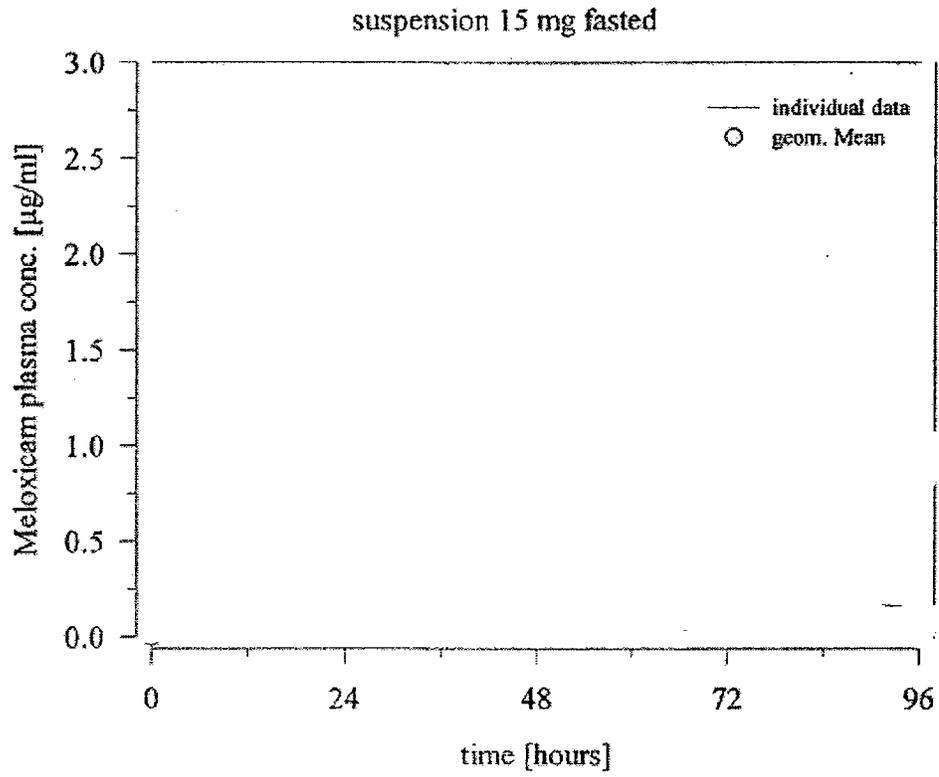
Figure 4. Individual (line) and geometric mean (symbols) plasma concentrations of meloxicam following single dose administration of 7.5 mg oral suspension under fasted conditions in healthy volunteers.



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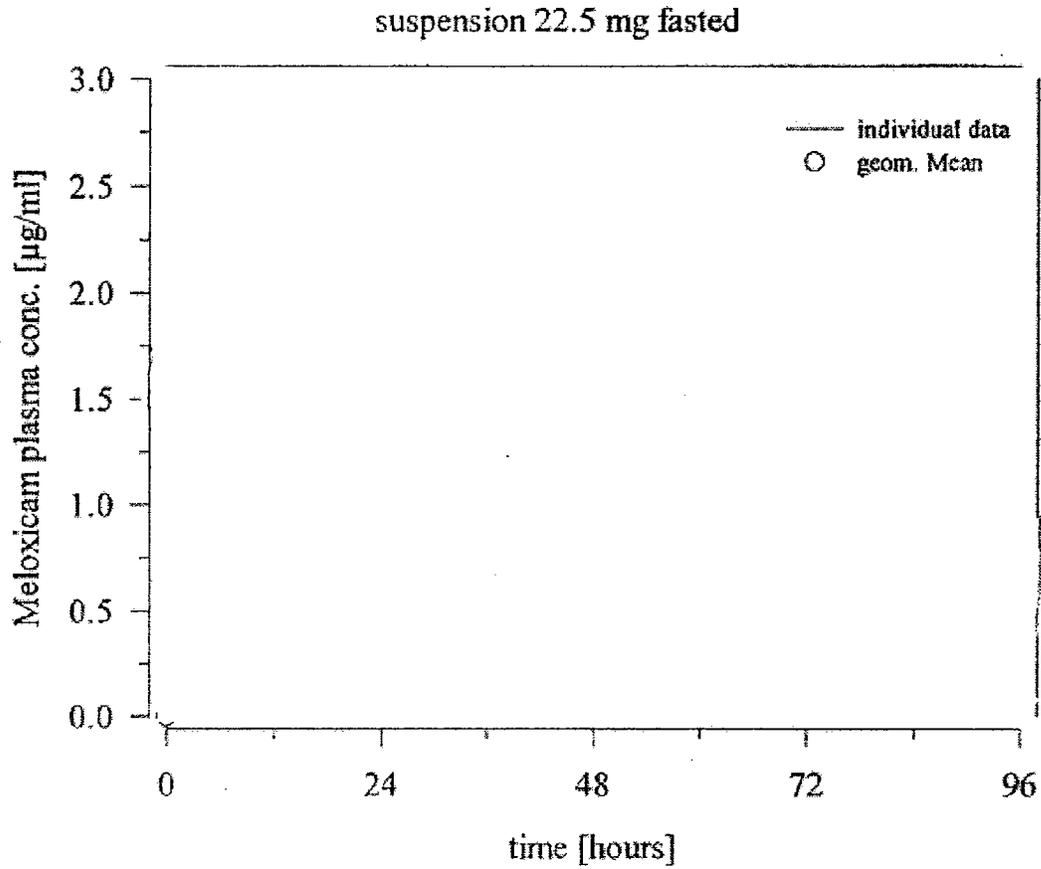
Figure 5. Individual (line) and geometric mean (symbols) plasma concentrations of meloxicam following single dose administration of 15 mg oral suspension under fasted conditions in healthy volunteers.



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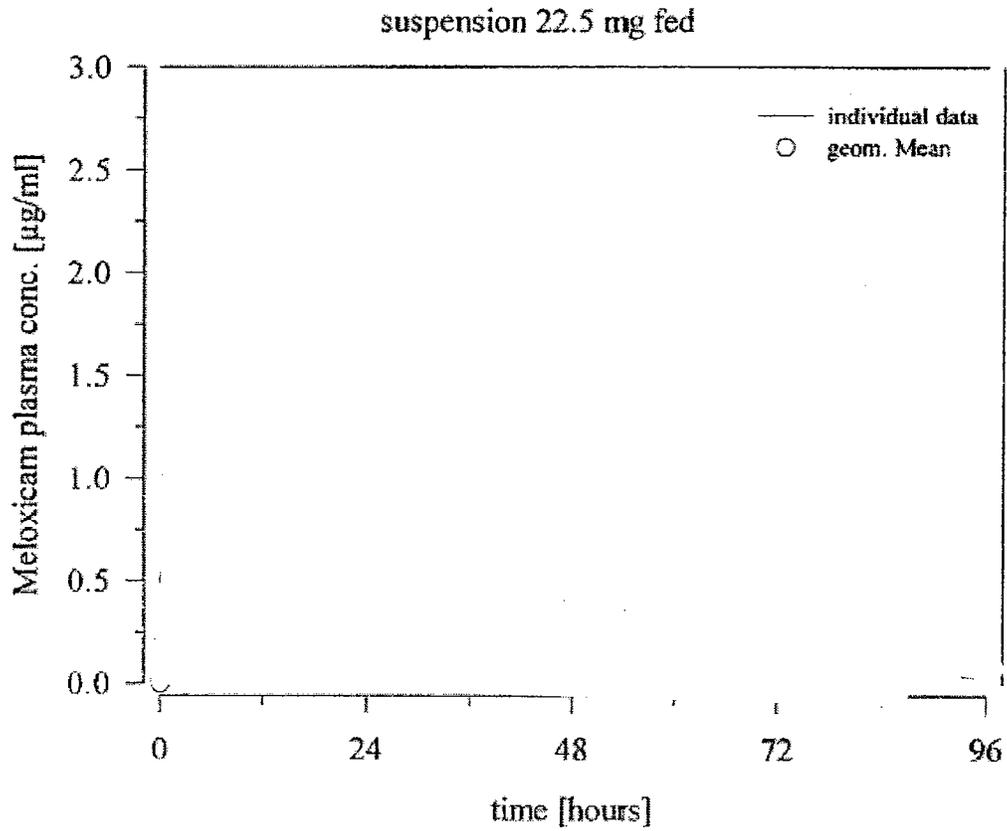
Figure 6. Individual (line) and geometric mean (symbols) plasma concentrations of meloxicam following single dose administration of 22.5 mg oral suspension under fasted conditions in healthy volunteers.



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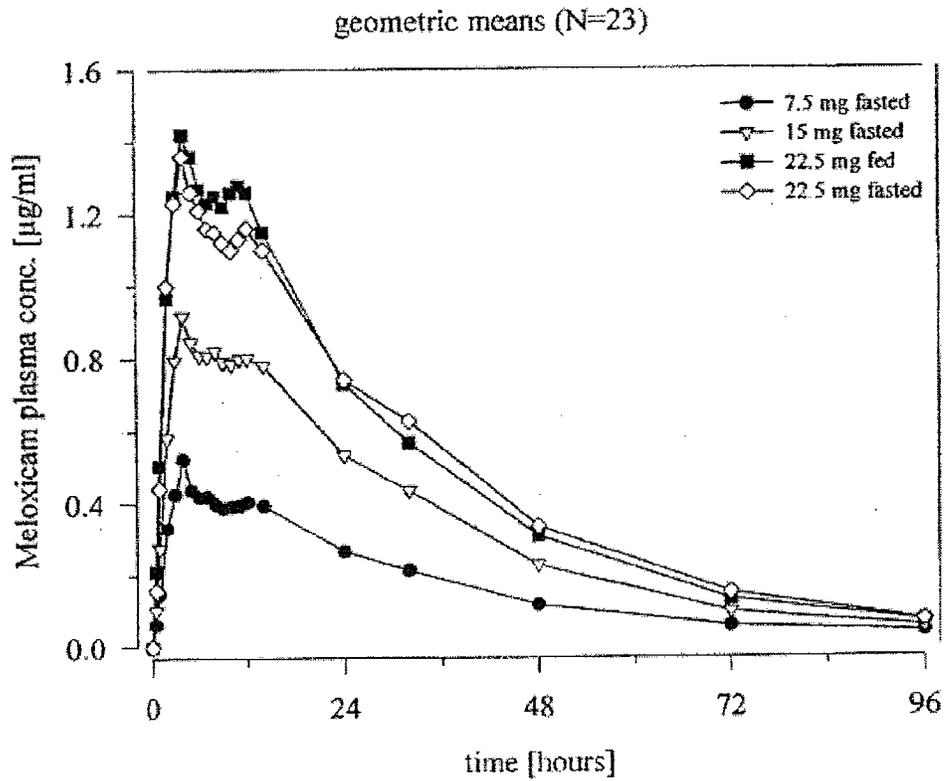
Figure 7. Individual (line) and geometric mean (symbols) plasma concentrations of meloxicam following single dose administration of 22.5 mg oral suspension under fed conditions in healthy volunteers.



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Figure 8. Geometric mean after single dose administration of 7.5 mg, 15 mg and 22.5 mg meloxicam suspension under fasted conditions and 22.5 mg meloxicam suspension under fed condition to healthy volunteers.



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Safety and Tolerability: Eighteen subjects experienced adverse events (5 nasopharyngitis, 4 headache, 3 arthralgia, back and neck pain, 2 cough, and 1 each of Herpes Zoster, skin disorder and sports injury). The AEs were of mild intensity. The overall AE was slightly higher in the 22.5 mg meloxicam treatment groups compared to the 7.5 mg and 15 mg treatment groups. The AEs are summarized on page 59 module 5, Vol. 1.3.

Comments

Dose proportionality

Dose proportionality for $AUC_{0-\infty}$, AUC_{0-24} and C_{max} of the meloxicam oral suspension (7.5 mg, 15 mg and 22.5 mg under fasting condition) was demonstrated based on the outcome of the ANCOVA of the original values and ANOVA of the dose normalized values. The two-sided 90% confidence intervals for the slope provided by the ANCOVA and ANOVA were within 0.8 to 1.25 for all three parameters. The point estimates were 0.88 C_{max} , 0.97 and 0.99 for C_{max} , $AUC_{0-\infty}$ and AUC_{0-24} , respectively (ANCOVA model, Table 5).

Food effect

The 90% confidence intervals for C_{max} , AUC_{0-24} and $AUC_{0-\infty}$ were within the acceptable range of 0.8-1.25, and the ratios of fed/fasted for these parameters were close to the ideal value of 100%. These results provide evidence that administration of meloxicam suspension with high caloric high fat food has no effect on peak exposure (C_{max}) and total exposure (AUCs). However, the peak plasma concentration following food ingestion occurred almost three hours later as compared to the fasted treatment groups (mean t_{max} 7 hr vs 5.5 hr) presumably due to a longer gastric residence time.

Conclusion: Based on the results submitted, meloxicam oral suspension demonstrates dose proportionality over the dose range of 7.5 mg to 22.5 mg under fasted condition. No food effect was observed for the highest investigated dose (22.5 mg) of meloxicam suspension following a standardized high fat breakfast.

Report No. IP 107.82 IPHAR 92/193: Determination of the relative bioavailability of meloxicam 7.5 mg tablets q.d. compared with 7.5 mg meloxicam capsules q.d. and dose-proportionality between 7.5 mg and 15 mg capsules q.d. after oral administration over 7 days to healthy volunteers.

Study Objectives: The primary aim of this trial was to demonstrate bioequivalence of meloxicam between 7.5 mg tablet (test) and the 7.5 mg capsule (reference). The secondary objective was to show dose-proportionality over the range 7.5 mg to 15 mg for capsules.

Study Design: This was a Phase I, single-center, open-label, randomized, three-way crossover trial in 18 healthy male volunteers with 7.5 mg of meloxicam tablets (treatment 1), 7.5 mg meloxicam capsules (treatment 2) and 15 mg meloxicam capsules (treatment 3) once a day for 7 days. The washout period between different treatments was one week.

Study Center/Investigator: The study was conducted at [

]

Clinical Investigator [

]

], supervised by the

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Study Subjects: Nineteen healthy male volunteers participated in the study, 18 subjects age 20-50 years (mean age 32.6 ± 7.9 years, mean body wt. 71.6 ± 8.7 kg) completed the trial.

Inclusion and exclusion criteria are described on pages 205-207, Module 5, Vol. 1.4

Treatments: The subjects received single dose of the following:

Treatment 1: 7.5 mg of meloxicam tablets Code UHAC 62 XX TA 30 3B 1A Batch 20820

Treatment 2: 7.5 mg of meloxicam capsules Code UHAC 62 XX KAH 30 12A 1A Batch 00617

Treatment 3: 15 mg of meloxicam capsules Code UHAC 62 XX KAH 30 10A 1A Batch 01001

All doses were administered at about 8 am within 10 min of breakfast and swallowed with 150 mL water

Study Dates: Clinical study was performed between November 1992 to February 1993.

Sampling: Blood samples 5 mL each were collected at pre-dose on days 1 to 6 and at 0.5, 1, 2,3,4,5,6,7,8,9,10,11,12,14 hours after study drug administration. Further blood samples were taken at 24, 36 and 48 hr post dose on day 7.

Analytical Determinations:

Drug was quantified in plasma by means of a validated HPLC assay using UV detection. The assay was validated from 0.1 to 10 $\mu\text{g/mL}$. The assay precision was within $\pm 5\%$ and assay accuracy within $\pm 5\%$. The limit of quantitation (LOQ) was 0.1 $\mu\text{g/mL}$. The assay precision and accuracy values were within $\pm 5\%$ and $\pm 5\%$, respectively. The analytical validation is described in detail in Module 5, Vol. 1.4. pp. 39-40.

Pharmacokinetic and Statistical Methods:

Equivalence of the parameters AUC_{ss} and C_{max,ss} was by a comparison of the two one-sided test procedure and the 90% confidence intervals for the ratio of the AUC_{ss} tablet/AUC_{ss} capsule and C_{max,ss} tablet/C_{max,ss} capsule were determined based on average bioavailability. Dose proportionality was analyzed by normalizing AUC_{ss} of the 15 mg capsule to the 7.5 mg dosage and the 90% confidence intervals were determined as above.

Results

Of the 19 volunteers enrolled for the study, 18 completed the study per protocol. One subject #10) was excluded from the study due to carry-over effect after first (7.5 mg capsule) and second (15 mg capsule) study treatments. Figure 9a and 9b illustrate individual concentration-time profiles on day 7 of 7.5 mg tablet and 7.5 mg capsule, respectively. Figure 10 shows plasma-concentration time profiles on day 7 for the 7.5 mg tablet and capsules, and 15 mg capsules.

The results of the pharmacokinetic analyses and relative bioavailability of the 7.5 mg tablets, 7.5 mg capsules and 15 mg capsules, and dose-proportionality between 7.5 mg and 15 mg capsule formulations are summarized Tables 9 and 10 below:

Table 9. Pharmacokinetic parameter values Analysis: A comparison of the mean (geometric) pharmacokinetic parameters values at steady state following once daily oral administration of 7.5 mg tablet, 7.5 mg capsule and 15 mg capsule (N=18).

Parameters	Treatment	Geom. Mean	%CV
C _{max,ss} µg/mL	7.5 mg tablet	1.03	19.87
	7.5 mg capsule	0.86	22.49
	15 mg capsule	1.88	22.60
AUC _{ss} µg·h/mL	7.5 mg tablet	14.77	29.36
	7.5 mg capsule	13.32	30.19
	15 mg capsule	28.49	31.80
t _{max}	7.5 mg tablet	4.9	8.4
	7.5 mg capsule	5.1	26.7
	15 mg capsule	5.6	39.2
t _{1/2} (h)	7.5 mg tablet	19.3	28.7
	7.5 mg capsule	19.5	31.2
	15 mg capsule	21.2	34.6

Table 10. Relative bioavailability of meloxicam between the 7.5 mg tablet (test) and 7.5 mg capsules and the dose proportionality between the 7.5 mg capsule vs. the 15 mg capsules, given as once per day for 7 days, N=18

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)
AUC _{ss} 7.5 mg tablet vs. 7.5 mg capsule	100.2	122.6	110.8
C _{max,ss} 7.5 mg tablet vs. 7.5 mg capsule	108.3	133.1	120.1
Dose Proportionality AUC _{ss} 7.5 mg capsule vs. 15 mg capsule	84.5	103.5	93.5

Adverse Events:

A total of 3 adverse events have been reported. Two volunteers reported mild headache one each with the 7.5 mg tablet and 7.5 mg capsule, respectively. One volunteer had mild nose bleeding after meloxicam 7.5 mg tablet on day 15, 9 hours after the morning administration lasting for a short period of 4 minutes. These adverse events were considered possibly related to the study medications.

Comments:

The Sponsor conducted this study to establish the bioequivalence between the meloxicam table and capsules dosage formulations. It is noted that the formulation for the 7.5 mg tablet used in this study is identical to that of the marketed product in the US.

The study design included once daily dose for 7 days for each formulation, and thus the C_{max} and AUC parameters at steady state were compared for the confidence intervals between the test (tablet) and reference (capsule) products. The confidence limit for AUC_{ss} of the 7.5 mg tablet was in the range of 80 to 125%, however, the range for the confidence interval of 108-133% for C_{max,ss} was outside the acceptable range per BA/BE guidance.

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The confidence interval of AUC_{0-∞} for the 7.5 mg and 15 mg capsule formulations was in the range of 80-125% indicating a dose proportionality between the 7.5 mg and 15 mg capsules.

Conclusions:

Based on the results of the statistical analysis obtained in the study protocol 107.82, meloxicam 7.5 mg tablet Lot UHAC 62 XX failed to meet the bioequivalence criteria for the C_{max} parameter, and may not be considered bioequivalent to that of the capsule dosage form.

Report No. IP 107.74: Determination of the relative bioavailability of 15 mg meloxicam tablets compared with 15 mg meloxicam capsules after oral administration over 7 days to healthy volunteers.

Study Design: This was a Phase I, single-center, open-label, randomized, two-way crossover trial in 24 healthy male volunteers with 15 mg of meloxicam tablets (treatment 1, test) and 15 mg meloxicam capsules (treatment 2, reference) once a day for 7 days. The washout period between treatments was 8-12 days.

Study Center/Investigator: The study was conducted at Center of Clinical Pharmacology, B.I. Deutschland GmbH, Biberach, Germany, and was supervised by the Clinical Investigator

Study Subjects: Twenty-eight healthy male volunteers were enrolled in the study. Twenty-five volunteers were treated and 24 volunteers completed the protocol. Volunteer #10 discontinued due to adverse events in the first period and was replaced by volunteer 26. The mean age of the volunteers treated was 35 ±8 (range 23-50 years), the mean weight was 77±6 kg (range 64-98 kg) and the mean height was 178 ±17 cm (range 165-190 cm).

Inclusion and exclusion criteria are described on page 230, Module 5, Vol. 1.7.

Treatments: The subjects received single dose of the following:

Treatment 1: 15 mg of meloxicam tablets Code UHAC 62 XX TA 30 1B 1A Batch 10518

Treatment 2: 15 mg of meloxicam capsules Code UHAC 62 XX KAH 30 10A 1A Batch 01001

All doses were administered within 10 min after the end of a standardized breakfast and 12 hours after the last meal on Days 6. All doses were swallowed with 150 mL water.

Study Dates: Clinical study was performed between November 1991 to December 1991

Sampling: Blood samples 5 mL each were collected at pre-dose on days 1 to 7 and at 0.5, 1, 2,3,4,5,6,7,8,9,10,11,12,14, as well as 24 hours after drug administration on Day 7 of each treatment period.

Analytical Determinations:

Drug was quantified in plasma by means of a validated HPLC assay using UV detection. The assay was validated from 0.5 to 10 µg/mL. The assay precision was within 10% and assay accuracy within 10%. The limit of quantitation (LOQ) was 0.5 µg/mL. The assay precision and accuracy values were within 10%, respectively. The analytical validation is described in detail in Module 5, Vol. 1.7. pp. 280-316.

The Division of Scientific Investigation (HFD-48, report by Dr. Martin K Yau) found the analytical method validation and procedures in the current study acceptable for reviewing the data (please also see above section 2.6.3 page 17).

Pharmacokinetic and Statistical Methods:

Equivalence of the parameters AUC_{ss} and C_{max,ss} was by a comparison of the two one-sided test procedure and the 90% confidence intervals for the ratio of the AUC_{ss} tablet/AUC_{ss} capsule and C_{max,ss} tablet/C_{max,ss} capsule were determined based on average bioavailability. Dose proportionality was analyzed by normalizing AUC_{ss} of the 15 mg capsule to the 7.5 mg dosage and the 90% confidence intervals were determined as above.

Results

Of the 25 volunteers treated 24 completed the study per protocol. One subject (#10) was excluded from the study after treatment in the first period.

The results of the pharmacokinetic analyses and relative bioavailability of the 15 mg tablets and 15 mg capsules formulations are summarized in Table 11 and 12 below:

Table 11. Pharmacokinetic parameter values Analysis: A comparison of the mean (geometric) pharmacokinetic parameters values at steady state following once daily oral administration of 15 mg tablet and 15 mg capsule (N=24).

Parameters	Treatment	Geom. Mean	%CV
C _{max,ss} µg/mL	15 mg tablet	2.396	24.33
	15 mg capsule	2.236	30.22
C _{av} µg/mL	15 mg tablet	1.513	34.29
	15 mg capsule	1.435	34.43
C _{min, ss} µg/mL	15 mg tablet	0.900	48.74
	15 mg capsule	0.884	41.95
AUC _{ss} µg·h/mL	15 mg tablet	36.3	34.3
	15 mg capsule	34.4	34.4
t _{max} hr	15 mg tablet	149.0	0.5
	15 mg capsule	149.1	0.4
t _{1/2} (h)	15 mg tablet		
	15 mg capsule		

Table 12. Relative bioavailability of meloxicam between the 7.5 mg tablet (test) and 7.5 mg capsules and the dose proportionality between the 7.5 mg capsule vs. the 15 mg capsules, given as once per day for 7 days, N=18

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)
AUC _{ss} 15 mg tablet vs. 15 mg capsule	100.8	110.3	105.4
C _{max,ss} 15 mg tablet vs. 15 mg capsule	100.9	113.7	107.1

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Adverse Events: No serious adverse event occurred in this trial. Four episodes of headache, 2 somnolence, 1 dyspepsia, 1 hot flushes and 3 influenza like symptoms were reported in 10 subjects in the tablet treatment group. In the capsule treatment group, 5 episodes of headache, 1 diarrhea, 2 fatigue, and 3 influenza like symptoms were reported in 9 volunteers reported adverse events under treatment with tablet and capsule, respectively.

Comments:

The Sponsor conducted this study to establish the bioequivalence between the meloxicam tablet and capsules dosage formulations each 15 mg strength.

The study design included once daily dose for 7 days for each formulation, and thus the C_{max} and AUC parameters at steady state were compared for the confidence intervals between the test (tablet) and reference (capsule) products. The 90% confidence intervals for AUC_{ss} and C_{max,ss} of the 15 mg tablet were in the acceptable range of 80 to 125%. The 15 mg meloxicam capsule meets the bioequivalence criteria in reference to the 15 mg meloxicam capsule marketed in Europe.

Conclusions

Based on the results of bioequivalence study 107.74, meloxicam 15 mg tablet manufactured by Boehringer Ingelheim Pharmaceutical is equivalent to its 15 mg capsules.

Bioequivalence Analysis Based on Pooled Observations from Studies 107.172 and 107.74:

As observed from the studies above, the Sponsor has established indirect bioequivalence of meloxicam suspension to the approved tablet dosage form (via the capsules). Study 107.172 demonstrates that meloxicam suspension 15 mg is bioequivalent to meloxicam capsule 15 mg, whereas bioequivalence between meloxicam 15 mg tablet and capsule was established in study 107.74. However, a direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. The Sponsor was therefore recommended to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension—based on published report by Zintzaras, E. and Bouka, P., *Bioequivalence studies: biometrical concepts of alternative design and pooled analysis*, *Eur. J. Metab. Pharmacokinet.* 1999, 24 (3):225-32.

The sponsor reevaluated the pooled observations for AUC_{ss} and C_{max,ss} of both studies using SAS statistical program with the following model:

“subject, “period”, “treatment” (i.e., product), “study”, and “treatment*study”.

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUC_{ss} and C_{max,ss} measures of meloxicam suspension are within the acceptable range of 80-125% when compared to the meloxicam tablets (Table 9). The ratios of the geometric means for AUC_{ss}, and C_{max,ss} for the tablet/suspension are 0.99 and 0.98, respectively. Additionally, there was no significant difference in the results of interactions between the study and treatments ($p > 0.15$) for both the AUC_{ss} and C_{max,ss} measures.

Table 9. Ninety percent confidence intervals for the AUC_{ss} and C_{max,ss} for meloxicam suspension vs. meloxicam tablet using pooled observations from studies 107.172 (suspension vs. capsule) and 107.74 (15 mg capsule vs. 15 mg tablet).

Parameter	Lower Limit (%)	Upper Limit (%)	Point Estimate (%)	Intrasubject variability (%CV)
AUC _{ss}	90.6	109.4	0.99	12.51
C _{max,ss}	87.1	110.5	0.98	15.88

Overall Comments on Bioavailability and Bioequivalence Studies:

The primary focus of this NDA is to establish bioequivalence of the oral suspension formulation of meloxicam to the meloxicam 15 mg oral tablets, the reference listed drug in the Orange Book. Meloxicam 15 mg capsule is marketed in Europe.

Support for the bioequivalence is based primarily on the results of comparative bioavailability Study 107.172 between the 15 mg meloxicam suspension and 15 mg meloxicam capsule. The 90% confidence intervals for the C_{max} and AUC under steady state are within the acceptable range of 80-125%.

In the original NDA 20-938 submission, the Sponsor had conducted BE studies using the 15 mg capsule and 15 mg tablet (Study No. 107.74) and 7.5 mg capsule and 7.5 mg table (Study 107.82) to link the efficacy data obtained with meloxicam capsule. Both of these studies were conducted in Europe.

In the current submission although the Sponsor has established indirect bioequivalence of the suspension to the approved tablet dosage form (via the capsules), a direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. Thus, although the C_{max} and AUC levels between the meloxicam suspension and capsule, and those between the suspension and tablet formulation are comparable, the same relationship may not necessarily hold true between the suspension and tablet formulations. The Agency therefore recommended the Sponsor to provide additional statistical analysis using the pooled observations from the two studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% CI for a comparison of the tablet to suspension.

Based on the results of the meta-analysis of studies 107.172 and 107.74, the 90% confidence intervals for the AUC_{ss} and C_{max,ss} measures of meloxicam suspension are within the acceptable range of 80-125% when compared to the meloxicam tablets, the meloxicam suspension 7.5 mg is therefore deemed bioequivalent to the meloxicam tablet 7.5 mg, and is expected to have safety and efficacy profile similar to that of the 7.5 mg tablet dosage formulation.

With regards to food effect, it is noted the package insert label for meloxicam tablets states, "Drug intake after a high fat breakfast (75 g of fat) did not affect extent of absorption of meloxicam capsules, but led to 22% higher C_{max} values". However, with respect to meloxicam

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suspension, no effect on peak exposure (C_{max}) and total exposure (AUCs) was observed for the highest investigated dose (22.5 mg) of meloxicam suspension following a standardized high fat breakfast. The 90% confidence intervals for C_{max}, AUC₀₋₂₄ and AUC_{0-∞} were within the acceptable range of 0.8-1.25, and the ratios of fed/fasted for these parameters were close to the ideal value of 100%.

The labeling for the suspension should therefore include the fact that no food effect on the total and peak exposure was observed with meloxicam suspension following a standardized high fat diet.

Composition of Meloxicam Oral Suspension

Ingredient	mg/ mL
Meloxicam (UH-AC 62 XX)	1.50
Colloidal Silicon Dioxide, NF	
Hydroxyethylcellulose, NF	
Sorbitol, NF	
Glycerol	
Xylitol, NF	
Monobasic Sodium Phosphate Dihydrate, USP	
Saccharin Sodium, USP	
Citric Acid, USP	
Raspberry Flavor	
Water, Purified, USP	

In vitro Dissolution Study

The firm has reported an in vitro dissolution testing on the meloxicam oral suspension 7.5 mg/5 mL in the Chemistry section of the application. The dissolution conditions used were as follow:

Apparatus: USP 2 with a paddle rotation speed of — rpm

Medium: ζ buffer, pH 7.5 at 37 °C, 900 mL

Specifications (as proposed by the sponsor): NLT ζ 1 (Q) of the labeled amount dissolved in 15 minutes.

The dissolution results from a representative 6 month stability sample for batch 156427A are summarized in the Table below:

Sampling time (min)	% dissolved (N=6)		
	Mean	Range	%CV
5	80	ζ	
10	91		
15	94		
30	96		1

Similar dissolution results as provided above have been reported for 156428A and 156429A during the stability studies (N=6 in each experiment) conducted at 6, 12, 18 and 24-month

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periods. The profiles generated for each time point during the 24-month stability studies show the following average dissolution ranges:

5 minutes: []

10 minutes:

15 minutes:

30 minutes: []

Comments on Dissolution Results:

The dissolution method is identical to that approved Mobic (meloxicam) tablets (NDA 20-938) with the exception of paddle speed, which was [] rpm from [] rpm for the Mobic tablets. The Sponsor states that a slower rate is used for the suspension formulation to avoid excessive agitation according to recommendation given in USP <1088>.

The specification for Mobic tablets is NLT [] (Q) of the labeled amount dissolved in [] minutes. The Sponsor's proposed specification for Mobic Suspension is NLT [] (Q) of the labeled amount dissolved in 15 minutes. The proposed dissolution specification of NLT [] (Q) in 15 minutes is acceptable.

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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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4.4. Cover Sheet and OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information about the Submission</u>				
	Information		Information	
NDA Number	21-530	Brand Name	Mobic Suspension 7.5mg/5 mL	
OCPB Division (I, II, III)	DPE III, HFD 880	Generic Name	Meloxicam	
Medical Division	ODE V, HFD 550	Drug Class	NSAID	
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	For the relief of the signs and symptoms of osteoarthritis.	
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Oral Suspension	
		Dosing Regimen	For the treatment of osteoarthritis the recommended starting and maintenance oral dose of MOBIC is 7.5 mg once daily. The maximum recommended daily oral dose of MOBIC is 15 mg. <u>MOBIC oral suspension 7.5 mg/5 mL or 15 mg/10 mL may be substituted for MOBIC tablets 7.5 mg or 15 mg, respectively</u>	
Related INDs	IND 51,268			
Date of Submission	Aug 18, 2003	Route of Administration	Oral	
Estimated Due Date of OCPB Review	Feb 28, 2004	Sponsor	Boehringer Ingelheim Pharmaceutical Inc.	
PDUFA Due Date	June 18, 2004	Priority Classification		
Division Due Date				
<i>Clin. Pharm. and Biopharm. Information</i>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Validated HPLC assay $\{ \}$ $\} \text{ng/mL}$ range.
I. Clinical Pharmacology				

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Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -	X			Ascending Dose
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X			Pooled Data
pediatrics:				At the PreIND 51,268 meeting July 19, 2001, the Sponsor had noted (under Q 10) that pediatric studies using oral suspension was being addressed in separate proposal supplemental NDA 20-938/S004. Also, the sponsor had requested a formal waiver of the (then) requirement to provide pediatric study.
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

NDA 21-530
 Meloxicam Oral Suspension: DFS

Phase 1 and/or 2, proof of concept:	Phase 1	5		<p>1. Report No. 107.172: Relative bioavailability of 15 mg meloxicam suspension p.o vs. 15 mg meloxicam capsules p.o. after steady state in healthy subjects.</p> <p>2. Report No. 107.243: An open, randomized, 4-way crossover study in healthy volunteers to evaluate the effect of food on the pharmacokinetics of meloxicam after a single p.o. administration of 22.5 mg meloxicam oral suspension and dose-proportionality over a dosage range of 7.5 mg to 22.5 mg. (N=24, 12 males and 12 females, age 23-47, average 33.1. Dose: 7.5 mg fasted, 15 mg fasted and 22.5 mg fed. Note: Due to technical difficulty (mixing up of a relevant no. of samples) the study was not conclusive and was repeated. Vol. 1.2. Protocol No. 107.254. Repeat of above, N =24, 12 females and 12 males, age 23-48. Results (as reported by the Sponsor): 90% CI for Cmax and AUC for the dose proportionality studies fasted 7.5 mg vs. 15 mg, fasted 7.5 mg vs. 22.5 mg and fasted 15 mg vs. 22.5 mg, and for food effect study 22.5 mg fasted vs. 22.5 mg fed within the acceptable range of 0.8 to 1.25. Vol. 1.3.</p>
				<p>4. Report No. No. 92/193: determination of the relative bioavailability of 7.5 mg tablets q.d. compared with 7.5 mg capsules q.d. and dose-proportionality between 7.5 mg and 15 mg capsules qd after oral administration over 7 days to healthy volunteers.</p> <p>5. Report No. 107.74 Relative BA of 15 mg tab compared with 15 mg capsules in healthy volunteers.</p>
Phase 3 clinical trial:		1		<p>Protocol No. 107.179 A multi-center double blind, double dummy, randomized, parallel group trial to compare the efficacy and safety of 7.5 mg meloxicam oral suspension with 7.5 mg meloxicam tablets administered orally administered once daily over a period of 6 weeks in patients with osteoarthritis. Note: Plasma concentration was measured, however, it is NOT a BE study. Conducted in June 1997-March 1998, Vol. 1.8</p>
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				

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Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • What are the properties of the formulation of the drug product? • What are the basic pharmacokinetic parameters of meloxicam (ADME)? • Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters? • What studies have been conducted for bioequivalence/bioavailability evaluation of the drug product? What are the outcomes of these studies? • Are the study populations relevant to the proposed indication? • Are dose and dosing regimen appropriate for the treatment of the proposed indication? • Are there any differences between clinical and to-be-marketed formulations? • Are there any in vitro data for meloxicam suspension formulation? 			
Other comments or information not included above	<ul style="list-style-type: none"> • In addition, the firm has provided summary of post-marketing experience of meloxicam oral suspension from Switzerland, Ecuador, Columbia and Mexico. • Preliminary screening of the document did not indicate any dissolution data on the suspension. If not submitted, the sponsor will be requested to do so. 			

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Primary reviewer Signature and Date	Chandra S. Chaurasia, Ph. D.
Secondary reviewer Signature and Date	E. Dennis Bashaw, Pharm. D.

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

CC: NDA 21-530, HFD-850 (P. Lee), HFD-550 (BJ Gould), HFD-880 (J. Lazor, A. Selen)

NDA 21-530

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Attachment: E-mail letter from Sponsor providing clarification that the dosage formulation used in study 107.172 is a suspension in contrast to syrup as indicated in the NDA 21-540 submission.

-----Original Message-----

From: cmazzare@rdg.boehringer-ingenelheim.com [mailto:cmazzare@rdg.boehringer-ingenelheim.com]

Sent: Wednesday, April 14, 2004 2:09 PM

To: GouldB@cder.fda.gov

Subject: Mobic OS NDA 21-530 - Dosage forms for Studies 107.172 and 107.25 4

Dear Ms. Gould,

In response to your fax dated 13-April-2004 I would like to confirm that the dosage forms used in studies 107.172 and 107.254 were oral suspensions. Study 107.172 used Meloxicam oral suspension batch # B960923 and study 107.254 used batch # 156511A. The attachment below contains the Batch Analyses section (3.2.P.5.4) from Module 3 of NDA 21-530 and lists all referenced batches including B980923 and 156511A. The report itself states that "all batches tested have the same qualitative composition as the proposed commercial Meloxicam Oral Suspension, 7.5mg/5mL; with the exception that **L**

J used for batch # B960923 was of a different grade."

<<Pages from Module 3.pdf>>

If you should require additional information please feel free to contact me.

Sincerely,

Charlie Mazzarella

Associate Director, Drug Regulatory Affairs

Boehringer Ingelheim Pharmaceuticals Inc.

Tele: (203) 798-5462

Fax: (203) 791-6262

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Chandra S. Chaurasia
5/27/04 04:42:33 PM
BIOPHARMACEUTICS

Dennis Bashaw
5/27/04 04:56:07 PM
BIOPHARMACEUTICS