Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

2. SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: -				
Name of active ingredient: UH-AC 62 XX, meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 October 2002	**Number:** 107.254	**Study period (years):** 14 January – 29 April 2002		

Title of study:	An open, randomised, 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.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma KG, Ingelheim
Publication (reference):	No
Clinical phase:	I
Objectives:	To investigate dose-proportionality over the dosage range 7.5 mg to 22.5 mg, and to assess the effect of food on the pharmacokinetics of meloxicam after a single p.o. administration of 22.5 mg meloxicam oral suspension.
Methodology:	4-way crossover, randomised, open
No. of subjects entered:	
total:	24 subjects, 12 male and 12 female
each treatment:	24
Diagnosis and main criteria for inclusion:	Healthy male and female subjects
Test product:	Meloxicam oral suspension
dose:	7.5 mg meloxicam, fasted (Treatment 1) 15 mg meloxicam, fasted (Treatment 2) 22.5 mg meloxicam, fed (Treatment 3)
mode of admin.:	p.o.
batch no.:	156511A
Duration of treatment:	Single administration
Reference therapy:	Meloxicam oral suspension
dose:	22.5 mg meloxicam, fasted (Treatment 4)
mode of admin.:	p.o.
batch no.:	156511A

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: UH-AC 62 XX, meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 October 2002	**Number:** 107.254	**Study period (years):** 14 January – 29 April 2002		

Criteria for evaluation:

Efficacy: Primary endpoints: C_{max}, $AUC_{0-\infty}$

Secondary endpoints: t_{max}, AUC_{0-tf}, λ_z, $t_{1/2}$, MRT_{tot}, CL/f, V_z/f

Safety: Pulse rate, systolic and diastolic blood pressure, ECG, standard safety laboratory, adverse events

Statistical methods: The dependence of AUCs and C_{max} (y) on dose (x) was assessed by a general regression model of the type $y=a*dose^b$ with parameters a and b. Dose proportionality was to be concluded if the 90% confidence intervals for b were completely included in the interval 0.80 to 1.20. Confidence intervals were computed using the appropriate mean square errors obtained from the analysis of covariance. Criteria for an effect of food were that two-sided 90% CIs for the median intra-subject ratios are contained in the range of 80-125% for AUCs and within 70-143% for C_{max}. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". In addition to the calculation of CIs, the corresponding point estimates of the ratios for AUCs and C_{max} were provided.

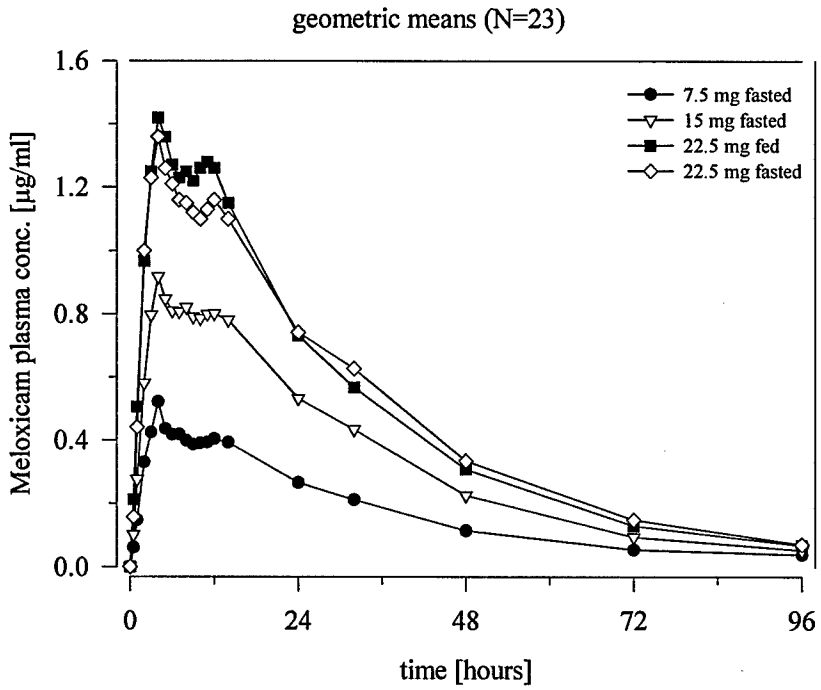
SUMMARY - CONCLUSIONS:

Efficacy / pharmacokinetics results: Meloxicam plasma concentrations were determined by means of a validated HPLC assay (25 -5000 ng/mL) with UV detection (assay precision within 4.8%, assay accuracy within ±1.9%)

Geometric mean concentrations for all four treatments are depicted in FIGURE 2: 1 below.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**	**(For National Authority Use only)**
Name of finished product: -		**SUPPLEMENTARY SHEET**	
Name of active ingredient: UH-AC 62 XX, meloxicam		**Page:** **Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to	**Addendum No.:**
Report date: 18 October 2002	**Number:** 107.254	**Study period (years):** 14 January – 29 April 2002	

FIGURE 2: 1 Geometric means following single dose administration of 7.5 mg, 15 mg and 22.5 mg meloxicam oral suspension under fasted conditions and 22.5 mg meloxicam oral suspension under fed conditions to healthy volunteers



cf. Appendix 16.3.2, TABLE 16.3.2: 2-5

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: UH-AC 62 XX, meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 October 2002	**Number:** 107.254	**Study period (years):** 14 January – 29 April 2002		

Dose proportionality of 7.5 mg, 15 mg, and 22.5 mg in a fasted state:

The results of the primary analysis of dose proportionality revealed that the 90% confidence intervals were contained within the predetermined acceptance range for all parameters. The common slope, b, was slightly lower than unity for C_{max}, whereas the slopes were fairly close to unity for the parameters $AUC_{0-\infty}$ and AUC_{0-tf} as can be seen in TABLE 2: 1 below.

TABLE 2: 1 Two-sided 90% confidence intervals and point estimates to assess dose proportionality of meloxicam oral suspension following administration of 7.5 mg, 15 mg and 22.5 mg doses ($y = a \cdot dose^b$), N=23; acceptance range: 0.80 to 1.20

Parameter	Unit	Lower limit	b	Upper limit
C_{max}	ng/mL	0.8060	0.8848	0.9637
$AUC_{0-\infty}$	ng·h/mL	0.9218	0.9740	1.0262
AUC_{0-tf}	ng·h/mL	0.9437	0.9963	1.0490

Source Data: section 11.4.2.2, TABLE 11.4.2.2: 1

The secondary analysis involving pairwise comparisons of 7.5 mg vs. 15 mg, 7.5 mg vs. 22.5 mg and 15 mg vs. 22.5 mg all in a fasted state used dose normalised data. The results revealed that the confidence intervals were contained within the predetermined acceptance range of 80 to 125%: for C_{max} 101.87% - 121.57%, 103.37% - 123.35% and 92.88% - 110.84%, respectively; for $AUC_{0-\infty}$ 94.72% - 106.51%, 97.36% - 109.47% and 96.93% - 108.99%, respectively, and very similar ranges for AUC_{0-tf}. The ratios of the 7.5 mg dose compared to the 15 mg and 22.5 mg doses were slightly higher than 100% for C_{max}, whereas the ratio of the 15 mg and 22.5 mg doses for C_{max} and all three ratios comparing doses for $AUC_{0-\infty}$ and AUC_{0-tf} were very close to 100%.

Within-treatment geometric means (gCV%) of maximum plasma concentrations (C_{max}) were 0.576 µg/mL (30.5%) and 1.04 µg/mL (30.6%) and 1.53 µg/mL (23.8%) for the doses 7.5 mg, 15 mg and 22.5 mg, respectively. The corresponding geometric means (gCV%) for $AUC_{0-\infty}$ were 16.5 µg*h/mL (22.5%), 33.0 µg*h/mL (26.7%) and 48.3 µg*h/mL (20.6%).

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: -		**SUPPLEMENTARY SHEET**		
Name of active ingredient: UH-AC 62 XX, meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 18 October 2002	**Number:** 107.254	**Study period (years):** 14 January – 29 April 2002		

	Food effect of the 22.5 mg dose in a fasted and fed state: All 90% confidence intervals were contained within the predetermined acceptance ranges of 70 to 143% for C_{max} and 80 to 125% for AUCs, which were 94.37% - 109.94% for C_{max} and 93.29% -104.20% for $AUC_{0-\infty}$. The median ratios for the primary parameters, C_{max} and $AUC_{0-\infty}$, as well as for the secondary parameter AUC_{0-tf} were fairly close to 100%. These results provide confidence that even a high fat, high caloric breakfast has no effect on both, peak and total exposure of meloxicam. Within-treatment geometric means (gCV%) of maximum plasma concentrations (C_{max}) were 1.56 µg/mL (25.4%) and 1.53 µg/mL (23.8%) in a fed and fasted state, respectively. Corresponding geometric means (gCV%) for $AUC_{0-\infty}$ were 47.4 µg*h/mL (21.7%) and 48.3 µg*h/mL (20.6%), respectively.
Safety results:	Treatment with meloxicam oral suspension, 7.5 mg (fasted), 15.0 mg (fasted) and 22.5 mg (with and without food) was safe and well tolerated. There were no serious and no severe adverse events. No adverse events were considered to be drug-related. The highest number of AEs was seen in the MedDRA System Organ Classes *Gastrointestinal disorders*, *Infections and infestations* and *Nervous system disorders*. Although the total number of AEs was slightly higher in the 22.5 mg compared to the 7.5 mg and 15.0 mg dose groups, no dose-dependent increase of individual AEs, or specific System Organ Class AEs, was seen. The total number of AEs in this study was too low to draw meaningful conclusions on dose-dependency. Furthermore, the slightly higher number of AEs in the 22.5 mg dose groups may partly be attributable to the open design of the study. There were no relevant changes in vital signs, ECG, and laboratory analyses.
Conclusions:	Treatment with meloxicam oral suspension was safe and well tolerated. Dose proportionality was confirmed over the dose range of 7.5 mg (fasted) to 22.5 mg (fasted). No food effect was observed for the highest investigated dose (22.5 mg) following a standardised high fat breakfast.