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: MOBEC®				
Name of active ingredient: Meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:** to		**Addendum No.:**
Report date: 10 January 2000	**Number:** 107.226	**Study period (years):** 1999		

Title of study:	An open, randomised, three-way cross-over study in healthy volunteers to evaluate the relative bioavailability of Meloxicam after single p.o. administration of 2 x 7.5 mg Meloxicam tablets compared to 15 mg Meloxicam tablet, and dose-proportionality over a dosage range of 7.5 mg and 15 mg.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Biberach, Germany
Publication (reference):	No
Clinical phase:	I
Objectives:	To assess the relative bioavailability of two 7.5 mg Meloxicam tablets (American type) compared to one 15 mg Meloxicam tablet (American type), and to investigate dose-proportionality over the dosage range 7.5 mg to 15 mg.
Methodology:	3-way cross-over, randomised, open
No. of subjects entered:	
total:	18 subjects, 9 male and 9 female
each treatment:	18 subjects, 9 male and 9 female
Diagnosis and main criteria for inclusion:	Healthy male and female subjects
Test product:	Meloxicam, tablet (American type)
dose:	7.5 mg UH-AC 62 XX (Treatment 1) 2 x 7.5 mg UH-AC 62 XX (Treatment 2)
mode of admin.:	p.o.
batch no.:	902261
Duration of treatment:	Single administration
Reference therapy:	Meloxicam, tablet (American type)
dose:	15 mg UH-AC 62 XX (Treatment 3)
mode of admin.:	p.o.
batch no.:	901823
Criteria for evaluation:	Primary endpoints: C_{max}, $AUC_{0-\infty,}$
Efficacy:	Secondary endpoints: t_{max}, AUC_{0-t}, λ_z, $t_{1/2}$, MRT, CL/f, Vz/f
Safety:	Pulse rate, systolic and diastolic blood pressure, laboratory, adverse events
Statistical methods:	Descriptive statistics including geometric mean values and 90 % confidence intervals for pharmacokinetic parameters.

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SUMMARY - CONCLUSIONS:

Efficacy /pharmacokinetic results:

Meloxicam plasma concentrations were determined by means of a validated HPLC assay (0.02-5.0 µg/mL) with UV detection (assay precision within 5.9 %, assay accuracy within ± 1.0 %). Mean age of the 18 subjects was 35 years, the mean weight 70 kg (females 62 kg, males 78 kg)

The parameters of the primary and secondary endpoints of the pharmacokinetic analysis are shown descriptively in the following table:

TABLE 2.1: Results of the non-compartmental evaluation (n=18)

IP. 107.226			1 x 7.5 mg tablet (US) (treatment 1)		2 x 7.5 mg tablet (US) (treatment 2)		1 x 15 mg tablet (US) (treatment 3)	
parameter	unit	n	gMean	gCV (%)	gMean	gCV (%)	gMean	gCV (%)
C_{max}	[ng/mL]	18	485.2	20.1	1000	19.5	961.0	15.5
t_{max}	[h]	18	4.5 #	4.0 -12.0 §	7.0 #	4.0 - 11.0 §	6.5 #	4.0 - 11.0 §
λ_z	[1/h]	18	0.0338	26.9	0.0329	31.0	0.0331	27.7
$t_{½}$	[h]	18	20.49	26.9	21.06	31.0	20.94	27.7
AUC_{0-t}	[ng·h/mL]	18	15090	34.6	31400	31.2	30620	26.1
$AUC_{0-\infty}$	[ng·h/mL]	18	16140	36.3	33640	35.5	32650	29.7
$AUC_{t-\infty}$	(%)	18	5.793	46.7	5.195	70.8	5.175	61.6
MRT_{tot}	[h]	18	32.70	24.3	33.88	28.4	33.71	24.0
CL/f	[mL/min]	18	7.746	36.3	7.433	35.6	7.657	29.7
Vz/f	[L]	18	13.74	20.0	13.55	20.5	13.88	14.6
C_{max} ^{S}	[ng/mL]	18	970.5	20.1				
$AUC_{0-\infty}$ ^{S}	[ng·h/mL]	18	32280	36.3				

Source data: TABLEs 14.4.1: 4 to 14.4.1: 6

#: median; §: range

S: parameters normalised to 15 mg

Test of bioequivalence between treatment 2 (2 x 7.5 mg tablet) and treatment 3 (1 x 15 mg tablet):

Geometric mean (%gCV) maximum drug plasma concentrations were 1000 ng/mL (19.5 %) and 961 ng/mL (15.5 %) for treatment 2 (2 x 7.5 mg tablet) [T=Test] and treatment 3 (1 x 15 mg tablet) [R=Reference], respectively. In addition, almost identical results were obtained for $AUC_{0-\infty}$: 33640 ng.h/mL (35.5 %) [T] and 32650 ng.h/mL (29.7 %) [R] for both treatments.

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The 90 % confidence limits for $AUC_{0-\infty}$ as well as for Cmax of both 15 mg doses (2 x 7.5 mg tablet vs. 15 mg tablet) were clearly within the preset range of 80 - 125 % (97 % - 109 % and 98 % - 111 % , respectively), and thus bioequivalence between both investigated treatments can be stated.

Test of dose proportionality between treatment 1 (1 x 7.5 mg tablet) and treatment 3 (1 x 15 mg tablet):

Geometric means (CV%) for normalised (to 15 mg) C_{max} values amounted 970.5 ng/mL (20.1 %) [T] vs. 961.0 ng/mL (15.5 %) [R] and for normalised $AUC_{0-\infty}$ values 32280 ng·h/mL (36.3 %) [T] vs. 32650 ng·h/mL (29.7 %) [R] for the 7.5 mg tablet (T=Test; treatment 1) and the 15 mg tablet (R=Reference; treatment 3), respectively.

Dose proportionality between the 7.5 mg tablet and the 15 mg tablet was confirmed, since 90 % confidence limits for normalised $AUC_{0-\infty}$ and C_{max} values ranged between 94 % - 104 % and 95 % - 107 % , respectively.

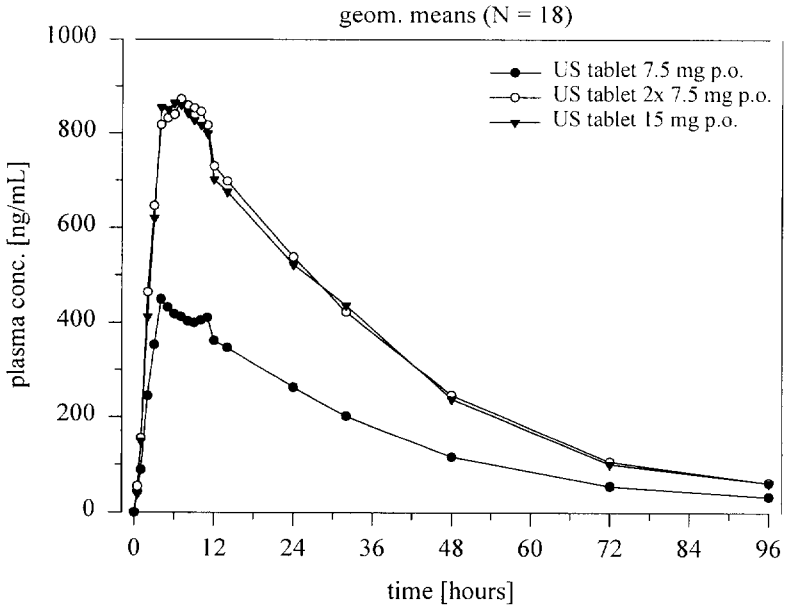

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FIGURE 2.1: Geom. means after single dose administration of 7.5 mg, 2 x 7.5 mg and 15 mg Meloxicam tablet (American type) to healthy volunteers.

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Safety results:	Unspecific adverse events, e.g. headache, herpes labialis, back pain, vaso-vagal syncope and haematoma, were regarded not related to the test drugs. Meloxicam was well tolerated, and global assessment of tolerability was judged as good in all visits except for one event of severe headache in one subject, in which tolerability was judged as satisfactory.
Conclusions:	Both 15 mg doses (2 x 7.5 mg tablet vs. 15 mg tablet) were shown to be bioequivalent and dose proportionality between the 7.5 mg and the 15 mg tablet (treatment 1 vs. treatment 3) was confirmed. All tested formulations were well tolerated and there was no significant difference with regard to tolerability between the three administrations.