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 Pharma KG		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Meloxicam				
Name of active ingredient: Meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**To:**	**Addendum No.:**
Report date: June 14, 1999	**Number:** 107.214	**Study period (years):** 1998		

Title of study:	Pharmacokinetics and tolerability of 2 x 15 mg meloxicam (2 x 0.3 g topical gel) over 7 days compared to 7.5 mg meloxicam tablet (single oral dose) in healthy subjects. A two-way cross-over, randomised, open study.
Investigator:	[redacted]
Study center (s):	Human Pharmacology Center, Biberach, Germany
Publication (reference):	not yet published
Clinical phase:	I
Objectives:	To gain information on the percutaneous absorption of meloxicam after administration of a topical gel over 7 days.
Methodology:	two-way cross-over, randomised, open design.
No. of subjects entered:	12
total:	12, 6 male and 6 female
each treatment:	12, 6 male and 6 female
Diagnosis and main criteria for inclusion:	healthy male and female subjects
Test Product:	meloxicam gel
dose:	2 x 15 mg UH-AC 62 XX daily over 7 days
mode of admin.:	topical on the back, alternating between the left and right sites
batch no.:	B980606
Duration of treatment:	7 days
Reference therapy:	meloxicam tablet
dose:	7.5 mg UH-AC 62 XX, single dose
mode of admin.:	p.o., fasted with 150 ml tap water
batch no.:	9970025
Duration of treatment:	1 day

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Criteria for evaluation:	
Efficacy:	primary endpoints: plasma concentration-time course after topical dose, oral pharmacokinetics of meloxicam, ratio AUC_{SS} topical / $AUC_{0-\infty}$ oral of meloxicam
Safety:	adverse events, local and systemic tolerability, laboratory findings
Statistical methods:	Descriptive statistics, 90% confidence intervals for test / reference ratio of AUC.

SUMMARY CONCLUSIONS:

Efficacy results: see pharmacokinetic results

Pharmacokinetic results:

Meloxicam in plasma was measured by an HPLC ultraviolet assay and quality controls with an assay precision within 5.8 % and a deviation from theory within ±6.8 % demonstrated adequate assay performance.

Twelve subjects included in the pharmacokinetic analysis had a mean age of 31.8 (range 20 to 39) years, a mean weight of 72.3 kg (range 55 to 92 kg) and a mean height of 173 cm (range 160 to 187 cm).

For the new gel the geometric mean (%gCV) AUCss values on day 7 (dosing interval 144-156 and 156-168 hours) were 316.1 and 306.1 ng·h/ml (68.1 and 66.3 %), respectively. Meloxicam given as an oral application (tablet) revealed after a single dose of 7.5 mg a mean value of 29350 ng·h/ml (41.0%). Geometric mean meloxicam plasma concentration during a 12 hour profile (dosing interval 144-156 and 156-168 hours) at steady state ranged from 22.47 and 21.35 ng/ml (70.0 and 70.3 %) to 31.35 and 32.89ng/ml (70.8 and 62.6 %), respectively.

Results of the noncompartmental pharmacokinetic evaluation (n=12):

TABLE 2: 1 **Results of single dose administration: 7.5mg meloxicam tablet (reference)**

parameter	unit	n	gmean	%gCV	mean	%CV
C_{max}	[ng/ml]	12	930.8	21.4	951.5	23.7
t_{max}	[h]	12	4 #	2-10 §	5.333	54.4
AUC_{0-t}	[ng·h/ml]	12	26450	35.4	27820	31.3
AUC	[ng·h/ml]	12	29350	41.0	31440	37.6
$\%AUC_{calc}$	(%)	12	8.064	66.4	9.665	68.4
$t_{½}$	[h]	12	25.35	39.1	27.06	38.1
λ_z	[1/h]	12	0.02734	39.1	0.02917	38.1
MRT_{tot}	[h]	12	36.00	39.4	38.43	38.1
CL/f	[ml/min]	12	4.259	41.0	4.578	40.8
V_z/f	[l]	12	9.346	23.5	9.607	27.5

median; § range

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TABLE 2: 1 **Results of multiple dose administration: 15mg meloxicam gel (test)** - continued

parameter	unit	n	gmean	%gCV	mean	%CV
$C_{max,144\text{-}156h}$	[ng/ml]	12	31.35	70.8	38.02	68.0
$t_{max,144\text{-}156h}$	[h]	12	4 #	0-12 §	4.67	108.6
$C_{min\ 144\text{-}156h}$	[ng/ml]	12	22.47	70.0	27.71	82.1
$C_{pre,ss\ 144\text{-}156h}$	[ng/ml]	12	27.54	64.1	32.90	72.1
$AUC_{144\text{-}156h}$	[ng·h/ml]	12	316.1	68.1	382.9	74.0
$t_{½}$	[h]	7	50.87	28.2	52.55	27.2
λ_z	[1/h]	7	0.01363	28.2	0.01408	28.0
$C_{max,156\text{-}168h}$	[ng/ml]	12	32.89	62.6	38.49	62.4
$t_{max,156\text{-}168h}$	[h]	12	7 #	0-12 §	6.33	94.1
$C_{min\ 156\text{-}168h}$	[ng/ml]	12	21.35	70.3	26.27	80.2
$C_{pre,ss\ 156\text{-}168h}$	[ng/ml]	12	26.93	79.6	33.84	74.6
$AUC_{156\text{-}168h}$	[ng·h/ml]	12	306.1	66.3	366.8	71.9

median; § range
Source Data: TABLEs 16.3.2.6 and 16.3.2.8

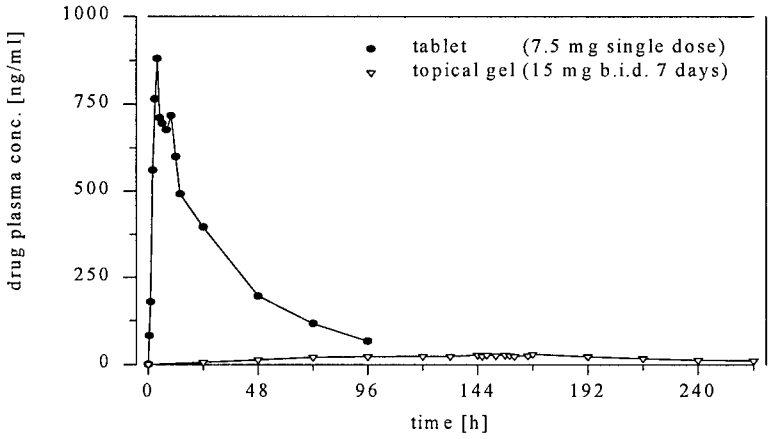

FIGURE 2: 1 Geometric mean of Meloxicam plasma concentration-time profiles in healthy male and female subjects after single dose of 7.5 mg Meloxicam tablet (reference) or 15 mg BID Meloxicam topical gel over 7 days (test).
Source data: TABLEs 16.3.2.2 and 16.3.2.4

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Safety results:
Tolerability was rated as good in all cases for all formulations. Six of 12 subjects reported a collective total of 8 episodes of adverse events: 4 episodes rash, 3 episodes upper respiratory tract infection, 1 episode migraine. None of the reactions were considered drug related by the investigator. Two episodes of rash in the same patient were associated with latex glove use in a latex allergic patient. Two episodes of rash in another patient existed prior to drug administration with worsening after gel administration in a site distant to drug administration. Except for one episode of migraine, all of the adverse events had an intensity of mild or moderate. One patient used one tablet of Thomapyrin C® in association with an upper respiratory tract infection. There was no association between treatment group and reaction.

Conclusions:
Plasma concentrations obtained after topical meloxicam gel were approximately 0.5 % (0.52 to 0.54%) of those obtained after oral application of 7.5 mg (tablet), i.e. assuming an absorption of 90% after oral dosing, approximately 0.6 % of the topically applied meloxicam was absorbed from the newly developed gel formulation. Thus the primary aim to achieve absorption rates of around 5% was not reached. The local and systemic tolerability of meloxicam as topical formulation was good.