Boehringer Ingelheim

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**.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: MOBIC®				
Name of active ingredient: UH-AC 62 XX, Meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 21 May 2004	**Number:** U04-3227-01	**Study period (dates):** 06 December 2000 – 25 June 2003		**Revision date:** 07 December 2004

Title of study:	A 12 week double-blind randomized trial, with a 12 week open-label extension, to investigate the efficacy and safety of meloxicam oral suspension administered once daily and naproxen oral suspension administered twice daily in children with Juvenile Rheumatoid Arthritis
Investigator:	Multicenter study conducted by pediatric rheumatologists and rheumatologists experienced in pediatric rheumatology without official designation of a Principal or Coordinating Investigator
Study centers:	Multicenter study, c.f. Appendix 16.1.4
Publication (reference):	Data from this study have not been published
Clinical phase:	III
Objectives:	To obtain safety, efficacy, pharmacokinetic and dosing information for meloxicam oral suspension in children with Juvenile Rheumatoid Arthritis (JRA)
Methodology:	Randomized, double-blind, double-dummy, parallel group trial with active comparator followed by an open-label extension
No. of subjects: **planned:** **actual:**	Entered: 180 with 60 in each of 3 treatment groups Enrolled: 225 Treatment Group 1 Entered: 62 Treated: 62 Analysed (for primary endpoint): 62 Treatment Group 2: Entered: 72 Treated: 72 Analysed (for primary endpoint): 72 Treatment Group 3: Entered: 75 Treated: 75 Analysed (for primary endpoint): 75 Pharmacokinetic sub-study: Planned: 20 Actual: 29 Analyzed: 28
Diagnosis and main criteria for inclusion:	Children 2-17 years old with a diagnosis of JRA (pauci- and polyarticular course of disease) according to International League Against Rheumatism criteria

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Test product:	Meloxicam oral suspension
dose:	Treatment Group 1 : 0.125 mg/kg body weight once daily (increased to 0.25 mg/kg daily after 4 weeks) Treatment Group 2: 0.25 mg/kg body weight once daily (increased to 0.375 mg/kg daily after 4 weeks) Open label extension: 0.375 mg/kg body weight once daily (Weeks 12-24)
mode of admin.:	Oral
batch no.:	Meloxicam oral suspension 7.5mg/5mL: 009035A, 009037A Placebo meloxicam oral suspension 7.5mg/5mL: 009033A
Duration of treatment:	6 months (3 months double-blind followed by 3 months open-label treatment)
Reference therapy:	Naproxen oral suspension
dose:	Treatment Group 3: 5 mg/kg body weight twice daily (increased to 7.5 mg/kg twice daily after 4 weeks)
mode of admin.:	Oral
batch no.:	Naproxen oral suspension 125 mg/5mL: 999060A, 019006A, 019028A Placebo naproxen oral suspension 125 mg/5 mL: 999066A, 019053A, 009077A
Criteria for evaluation:	
Efficacy:	Primary: The rate of responders according to core set of outcome criteria (JRA pediatric 30) after 12 weeks of treatment Secondary: Investigator global assessment of overall disease activity, parent global assessment of overall well-being, number of joints with active arthritis, assessment of functional disability by means of Childhood Health Assessment Questionnaire (CHAQ), number of joints with limited range of motion, erythrocyte sedimentation rate (ESR), final global assessment of efficacy by parent, final global assessment of efficacy by investigator, withdrawals due to lack of efficacy and acetaminophen consumption

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Safety:	Incidence and intensity of adverse events, withdrawals due to adverse events, laboratory parameters, slit lamp eye exam, final global assessment of tolerability by parent and investigator, physical exam, additional physician visits due to gastrointestinal adverse event (GI-AE), hospital stay due to gastrointestinal serious adverse event (GI-SAE), hospital stay due to adverse events related to study drug administration, vital signs
Pharmacokinetics:	Pharmacokinetic endpoints: AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$, $C_{pre,ss}$, C_{av}, $t_{max,ss}$, $t_{1/2}$, CL/F, V_z/F, λ_z, PTF for meloxicam
Statistical methods:	Descriptive statistics, Cochran's test for binomial response, ANOVA, logistic regression, Wilcoxon's rank sum test, Fisher's exact test and Kaplan- Meier estimates

SUMMARY – CONCLUSIONS:

Efficacy results:	For the primary endpoint of ACR Pediatric 30 responders, meloxicam oral suspension in doses of 0.25 mg/kg and 0.375 mg/kg were non-inferior to treatment with naproxen oral suspension at a dose of 15 mg/kg after twelve weeks of treatment. For the secondary endpoints that comprised the core set of outcome variables, all endpoints except ESR demonstrated substantial improvement over the 12 weeks of treatment. For the other secondary endpoints, i.e., discomfort, parent's global assessment of arthritis (CHAQ), parent and investigator assessments of efficacy, all treatment groups showed comparable improvements over the 12 weeks of study.
Safety results:	This 24 week trial showed that all three doses of meloxicam (0.125 mg/kg/day, 0.25 mg/kg/day and 0.375 mg/kg/day) were safe, well tolerated and similar to naproxen with regards to the safety profile.

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Pharmacokinetic results: TABLE 2: 1 Pharmacokinetic parameters

		0.375 mg/kg Meloxicam oral suspension			
		Age group 2-6 years (n=5)		Age group 7-17 years (n=23)	
Parameter	Unit	gMean	% gCV	gMean	% gCV
age	[years]	3.73	45.5	12.1	20.8
weight	[kg]	15.0	35.8	46.3	35.1
dose	[mg]	5.64	35.4	16.6	27.7
dose	[mg/kg]	0.375	0	0.375	0
$C_{max,ss}$	[ng/mL]	2440	35.3	3030	45.2
$t_{max,ss}$	[h]	1.00#	0.45 – 7.58$	2.73#	1.00 – 11.9$
AUC_{ss}	[ng·h/mL]	32400	47.9	44600	43.4
$C_{min,ss}$	[ng/mL]	626	71.1	944	92.0
$C_{pre,ss}$	[ng/mL]	843	78.4	1160	110
C_{av}	[ng/mL]	1350	47.9	1860	43.4
$t_{½}$	[h]	11.3	19.7	15.8	24.2
λ_z	[h^{-1}]	0.0611	19.7	0.0439	24.2
CL/F	[mL/min]	2.90	29.9	6.20	41.3
V_z/F	[L]	2.85	44.6	8.47	43.2
PTF	[%]	131	26.8	103	37.6
CL/F§	[mL/min/kg]	0.193	48.0	0.134	46.3
V_z/F§	[L/kg]	0.190	57.8	0.182	45.3

Source data: TABLEs 15.5.2.1: 2 and 3

median; $ range

§ adjusted to body weight

Mean maximum plasma concentration (2440 ng/mL) as well as total exposure (32400 ng·h/mL) for the younger children was approximately 20-30% lower as compared to older children ($C_{max,ss}$: 3030 ng/mL; AUC_{ss}: 44600 ng·h/mL). Maximum plasma concentrations for all children are on average achieved between 1 to 3 hours following drug administration (range: 0.45 - 11.9 hours). Weight adjusted oral clearance (0.193 mL/min/kg) was higher, and the terminal half-life (11.3 h) for the younger children was lower than in the older age group (+ 44% and -28%, respectively).

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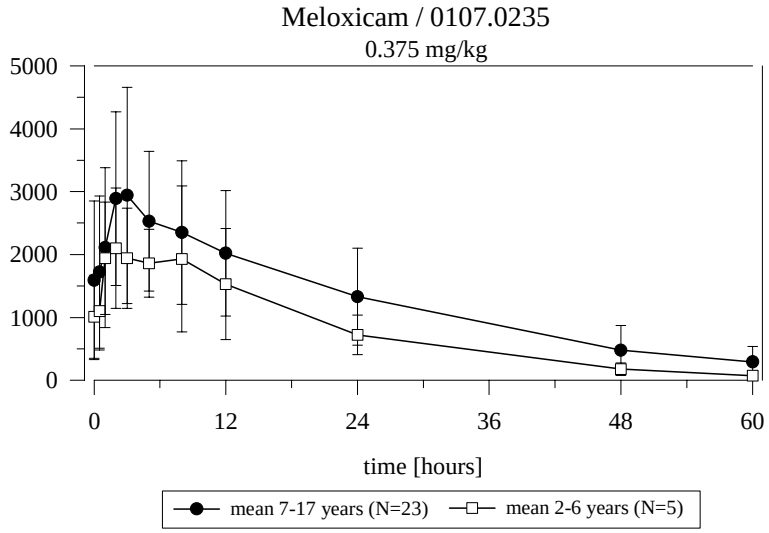
FIGURE 2: 1 Arithmetic mean plasma concentrations (±SD) following 0.375 mg/kg Meloxicam oral suspension in children aged 2-6 years and 7-17 years



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Conclusions:

- Meloxicam oral suspension at 0.125 mg/kg/day 4 weeks followed by 0.25 mg/kg/day 8 weeks, and meloxicam oral suspension at 0.25 mg/kg/day 4 weeks followed by 0.375 mg/kg/day 8 weeks was as clinically efficacious as naproxen oral suspension at 5 mg/kg twice daily 4 weeks followed by 7.5 mg/kg twice daily 8 weeks in the treatment of children with JRA. The efficacy response was sustained during the 12 week open-label phase with meloxicam 0.375 mg/kg/day.
- The twelve week comparative phase of the trial showed that the two meloxicam regimens were safe and well- tolerated, as was the naproxen regimen. The twelve week open-label phase with 0.375 mg/kg/day meloxicam showed that this dose of meloxicam was safe and well-tolerated with extended use.
- Lower mean meloxicam plasma concentrations were observed in the younger age group (age 2 to 6 years) compared to the older age group (age 7 to 17 years). Elimination half-life tended to be lower and body weight adjusted clearance was slightly higher in younger children compared to older children. These results are consistent with the previous Phase IIa study (U00-1093). However, those differences in PK parameters between age groups on the basis of mean values may not be significant given the variability observed and the limited sample size.
- No difference in efficacy and safety was observed between the younger age group (age 2 to 6 years) compared to the older age group (age 7 to 17 years).
- Meloxicam oral suspension demonstrates a positive benefit-risk ratio for use in children with Juvenile Rheumatoid Arthritis and offers the advantage of once per day dosing.