Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**	
Name of finished product: Meloxicam			
Name of active ingredient: Meloxicam		**Page:**	**Number:**
Report date: **Dec 2, 2003**	**Trial-Number:** **107.208**	**Study period (dates):** **Sep 4, 2000- Jan 14, 2003**	

Title of study:	A one year double-blind trial to investigate the efficacy and safety of meloxicam oral suspension 0.25 mg/kg and 0.125 mg/kg administered once daily in comparison to naproxen oral suspension 5 mg/kg administered twice daily in children with Juvenile Rheumatoid Arthritis.
Investigator:	[redacted] (ITALY)
Study centers:	Multi-national (7 countries), multi-centre (34 centres); paediatric rheumatologists and paediatricians in hospital and practices
Publication (reference):	N/A
Clinical phase:	III
Objectives:	Analysis of efficacy and safety of meloxicam oral suspension in children with Juvenile Rheumatoid Arthritis (JRA)
Methodology:	Randomised, double-blind, double-dummy, active-comparator, parallel, multi-centre, multinational.
No. of subjects planned:	Enrolled 240, entered 180
actual:	Enrolled: 232, entered 226, treated 225 Treatment A (meloxicam 0.25 mg/kg Body Weight (BW): entered: 74 treated: 74 analysed (for primary endpoint): N/A, 74 in this report Treatment B (meloxicam 0.125 mg/kg BW): entered: 74 treated: 73 analysed (for primary endpoint): N/A, 73 in this report Treatment C (naproxen 5 mg/kg BW twice daily): entered: 78 treated: 78 analysed (for primary endpoint): N/A, 78 in this report
Diagnosis and main criteria for inclusion:	Children 2-16 years old with a diagnosis of juvenile idiopathic arthritis (oligo- and polyarticular course of disease) according to International League Against Rheumatism (ILAR) criteria
Test product:	Meloxicam oral suspension
dose:	Treatment A: 0.25 mg/kg BW once daily (meloxicam high dose (Mel H)) Treatment B: 0.125 mg/kg BW once daily (meloxicam low dose (Mel L))
mode of admin.:	Oral
batch no.:	009027A, 009035A, 156511A
Duration of treatment:	12 months (primary analysis after 12 weeks)

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Reference therapy:	Naproxen oral suspension
dose:	Treatment C: 5 mg/kg BW twice daily (10mg/kg total daily dose (Nap))
mode of admin.:	Oral
batch no.:	009026A, 009079A, 019006A, 019028A
Criteria for evaluation:	
Efficacy:	Primary: rate of responders according to core set of outcome criteria (R97-2518) 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, number of joints with limited range of motion, assessment of functional disability by means of Childhood Health Assessment Questionnaire (CHAQ), Erythrocyte Sedimentation Rate (ESR) including children's assessment of discomfort and parents global assessment of pain and arthritis, change in functional classification (Steinbrocker classification), final global assessment of efficacy by investigator, final global assessment of efficacy by parent, withdrawals due to inadequate efficacy, paracetamol / acetaminophen consumption.
Safety:	Final global assessment of tolerability by investigator, final global assessment of tolerability by parents, incidence of adverse events, intensity of adverse events, withdrawals due to adverse events, incidence of laboratory adverse events, duration of hospital stay due to gastrointestinal serious adverse event (GI-SAE), duration of hospital stay due to adverse events related to trial drug administration, additional physician visits due to gastrointestinal adverse event (GI-AE)
Statistical methods:	Intent-to-treat analysis for all parameters. Efficacy: Chi-square test, Fisher's exact test, logistic regression Safety: tabulation by body system organ class, logistic regression, score analysis

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SUMMARY – CONCLUSIONS:

Efficacy results:

The analysis of the primary endpoint parameter American College of Rheumatology (ACR) Ped 30 up to one year suggests that meloxicam oral suspension administered to children in doses of 0.125 mg/kg and 0.25 mg/kg once daily is not inferior to naproxen oral suspension in a dose of 5 mg/kg twice daily in the treatment of JRA. The meloxicam responder rates over time were numerically larger compared to naproxen at all time points beyond 12 weeks. After 12 months, the responder rates were 76.7% (56 of 73 patients) for Mel L, 75.7% (56/74) for Mel H, and 74.4% for Nap (58/78), respectively. The responder rates separate all treatment groups from a placebo responder rate of 28.9% calculated in a meta-analysis.

At month 12, 19.1% of patients had terminated the study prematurely. The number of drop-outs due to AE and lack of efficacy was significantly higher in the Nap group compared to Mel H. To limit the associated information loss, all dropouts were counted as non-responders according to a WCA. This approach changed the above responder rates to 68.5% (50/73) for Mel L, to 68.9% (51/74) for Mel H, and to 62.8% for Nap (49/78), respectively, thus further increasing the numerical difference in favour of meloxicam treatment.

In an AUC approach, the mean responder rates over 12 months were 56.5% for Mel L, 54.9% for Mel H, and 53.7% for Nap.

In the secondary endpoint analysis, no remarkable differences were observed. All treatments induced mean improvements to baseline in an order of magnitude mostly between 50 and 60% at month 12. Only the improvement in ESR remained below 20% with exception of the Mel H group that achieved a more than 30% decrease in ESR. The only significant difference observed in secondary endpoints was in favour of Mel L compared to Mel H for the reduction of the number of joints with limitation in movement at month 12.

Within all treatment groups, patients with higher individual doses did not respond better than patients with lower doses. There was no dose-dependency observed between the two meloxicam doses.

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Safety results:

The safety data suggest an advantage of meloxicam treatment over naproxen. Despite a slightly longer mean time on drug, the absolute numbers of patients with AEs, SAEs and significant AEs were lower in the two groups treated with meloxicam, as were the drop-outs due to AE. Over one year of treatment, 84.6% of patients on Nap had at least one AE, compared to 79.7% in the Mel H and 74.0% in the Mel L groups. At least one SAE occurred in 12.8% of patients in the Nap group compared to 9.5% in the Mel H and 5.5% in the Mel L group. Significant AEs, always triggered by the event drop-out due to AE, were recorded in 12.8% (Nap), 2.7% (Mel H) and 9.6% (Mel L).

AEs related to skin and to bleeding were more frequently seen on naproxen. There was no difference in AEs related to the gastrointestinal tract.

No unexpected safety issues could be identified above those known from adults.

There was no evidence for an increase in AE incidence if meloxicam is given in the higher dose.

Laboratory data were unremarkable. Individual subject changes were observed very infrequently and in all cases without clinical significance.

Conclusions:

- The efficacy of meloxicam oral suspension administered to children with JRA in doses of 0.125 mg/kg/day and 0.25 mg/kg/day once daily over one year is not different from naproxen oral suspension in a standard dose of 10 mg/kg daily divided in two doses. Over time, the efficacy rates of the two meloxicam doses compared to naproxen were numerically larger.
- The magnitude of responses of all treatments is superior to placebo based on a historic comparison.
- There is no difference between the two doses of meloxicam for efficacy and safety.
- The safety data support that the treatments applied in this trial are equally safe in children except for skin and bleeding events, where an increased frequency was observed in the naproxen group. These differences to meloxicam can be explained with the properties of the compounds.