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.

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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 International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: MOBIC®			
Name of active ingredient: Meloxicam		**Page: 1 of 5**	
Report date: 17 December 2003	**Trial-Number:** 107.258	**Study period (years):** 03 Jul 2002 - 22 Jul 2003	**Date of Revision:**

Title of study:	A Multi-Center, Double-Blind, Randomized, Parallel-Group Trial to Compare the Efficacy and Safety of Three Doses of Meloxicam (7.5, 15, and 22.5 mg) and Placebo in Patients with Rheumatoid Arthritis
Investigator:	Multicentre study without official designation of a Principal or Coordinating Investigator
Study center(s):	Multicentre Study
Publication (reference):	
Clinical phase:	III
Objectives:	To evaluate the efficacy and safety of three doses (7.5, 15, and 22.5 mg) of meloxicam compared with placebo in the treatment of patients with active rheumatoid arthritis.
Methodology:	Multicenter, multinational, double-blind, randomized, parallel-group trial.
No. of subjects: **planned:** **actual:**	 Enrolled: 1400, entered:1000 Enrolled: 1593, entered: 1191, treated: 1191 Placebo: treated: 293, analyzed (for primary endpoint): 292 Meloxicam 7.5 mg: treated: 308, analyzed (for primary endpoint): 306 Meloxicam 15 mg: treated: 295, analyzed (for primary endpoint): 293 Meloxicam 22.5 mg: treated: 295, analyzed (for primary endpoint): 293
Diagnosis and main criteria for inclusion:	Patients between the ages of 18 and 80 years, inclusive, with a diagnosis of rheumatoid arthritis, as defined by the American College of Rheumatology. After NSAID washout, patients must have had at least 6 painful or tender joints which must have been an increase of at least 2 joints and at least 20% over screening; at least 3 swollen joints which must have been an increase of at least 2 joints and at least 20% over screening; physician 's global assessment of no better than moderate; patient's global assessment of ≥40 mm on the 100-mm visual analogue scale (VAS); and at least one of the following criteria: morning stiffness lasting at least 45 minutes and an increase of at least 15 minutes over screening, or worsening of ≥10mm and at least 20% increase from screening on the 100-mm VAS patient's assessment of pain to at least 40mm.

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Test product:	Meloxicam
Dose:	7.5 mg, 15 mg, or 22.5 mg once daily
mode of admin.:	Tablet, administered orally after food with a glass of water.
batch no.:	PD 2181
Duration of treatment:	12 weeks
Reference therapy:	Placebo
mode of admin.:	Administered orally after food with a glass of water.
batch no.:	PD 2182
Criteria for evaluation:	
Efficacy:	Primary Variable: ACR20 Secondary Variables: the number of painful or tender joints; the number of swollen joints; patient's global (overall) assessment of disease activity; investigator's global (overall) assessment of disease activity; and the patient's assessment of pain; patient's assessment of physical function (mHAQ); CRP; withdrawal due to lack of efficacy; duration of morning stiffness; the patient's final global (overall) assessment of efficacy; the investigator's final global (overall) assessment of efficacy; the patient's assessment of status with regard to change in arthritic condition and use of rescue medication.
Safety:	The incidence and intensity of adverse events; patient's final global assessment of tolerability; the investigator's final global assessment of tolerability; withdrawals due to adverse events; laboratory tests; vital signs and physical examination.
Statistical methods:	Cochran-Mantel-Haenszel test; Analysis of Variance; Logistic Regression; Analysis of Covariance; Kaplan-Meier survival analysis; log rank test; Wilcoxon rank sum test and Fisher's Exact test

SUMMARY – CONCLUSIONS:

Efficacy results:

For the primary efficacy parameter of ACR20 responder criteria, meloxicam in doses of 22.5 mg, 15 mg, and 7.5 mg was more effective than placebo throughout 12 weeks of treatment. Efficacy reached a plateau at the 15 mg dose level.

Across the endpoints that comprised the ACR20 criteria, each of the meloxicam groups was superior to placebo at all visits except for CRP. When meloxicam groups were compared, different trends were noted between the patient-evaluated endpoint and others. In patient evaluated endpoints of patient global assessment of disease activity, patient assessment of pain, and mHAQ, a clear plateau at the middle dose of 15 mg dose was demonstrated. Furthermore, patients appeared to discriminate between meloxicam doses with a numerical trend toward larger improvements in efficacy parameters for the 22.5 mg dose. This trend was not seen for the investigator-assessed endpoints including the number of painful or tender joints, number of swollen joints, and investigator global assessment of disease activity. For all parameters, the evaluation of the change from baseline compared to the magnitude of the flare indicated that the 15 mg and 22.5 mg groups had returned to a pre-flare condition. While the 7.5 mg dose group showed a change from baseline approaching the size of the flare, the placebo-treated patients clearly did not return to pre-flare functionality.

For other secondary endpoints including: withdrawal due to lack of efficacy, duration of morning stiffness, patient final global assessment of efficacy, investigator final global assessment of efficacy, and patient assessment of status with regard to change in arthritic condition, all meloxicam doses demonstrated efficacy in the treatment of rheumatoid arthritis.

Safety results:

This 12-week trial showed that all three doses of meloxicam (7.5, 15, and 22.5 mg per day) were safe and well tolerated. The overall incidence of AEs was similar among the three meloxicam dose groups (7.5 mg, 46.1%; 15 mg, 42.7%; and 22.5 mg, 44.7%, respectively) and lower in the placebo group (35.6%). The severity of AEs (i.e., mild, moderate, or severe) was similar among all three meloxicam doses. The number of patients who reported a "severe" AE was higher in the meloxicam 22.5 mg treatment group, compared with the meloxicam 7.5 mg and 15 mg and placebo treatment groups.

Approximately 12% (143) of all evaluable patients had at least one AE considered by the investigator to be related to trial medication, with the least occurring in the placebo group (8.6%) compared with the meloxicam 7.5, 15, and 22.5 mg groups (15.0%, 10.6%, and 14.0%, respectively). The incidence of patients discontinuing the trial due to an AE was comparable for the meloxicam 7.5 mg, meloxicam 22.5 mg, and placebo groups (8.2%, 7.5%, and 6.8%, respectively) and lower in the meloxicam 15 mg group (3.4%). The incidence of patients discontinuing the trial due to a related AE was also lower in the meloxicam 15 mg group (2.4%) compared with the meloxicam 7.5 mg, meloxicam 22.5 mg, and placebo groups (4.9%, 4.1%, and 3.4%, respectively).

The incidence of serious AEs was similar across all treatment groups (≤3.1%). Two deaths were reported, both in the meloxicam 22.5 mg group (0.7%); neither was judged as related to study medication.

The incidence of gastrointestinal (GI) events for patients treated with meloxicam 7.5 mg, 15 mg, and 22.5 mg was 15.0%, 10.6%, and 13.3%, respectively. The incidence of patients with GI events in the placebo group was slightly lower (8.9%). No patient experienced an upper GI perforation or bleed during the trial. One (0.1%) patient in the meloxicam 22.5 mg group experienced a duodenal ulcer; this event was classified as significant, but not serious and resulted in discontinuation from the trial. One (0.3%) patient in the placebo group experienced a serious GI event (gastroduodenitis). This event was considered by the investigator to be of moderate intensity and related to study medication. The patient discontinued the trial and the event resolved.

Among patients treated with meloxicam 22.5 mg, there was a higher incidence of overall and GI-AEs in patients >65 years of age compared with patients ≤65 years. No apparent differences were seen with the 7.5 and 15 mg meloxicam doses or placebo in overall or GI-AEs in either age group.

Safety results cont.:	Laboratory, ECG, vital signs and physical exam results showed no unexpected pattern among treatment groups. The slight abnormalities in blood pressure and laboratory values observed in this trial are not considered problematic and are expected considering both the patient population and previous knowledge of NSAID effects. For the both the patient's and investigator's final global assessment of tolerability, the highest proportion of "good" ratings occurred in the meloxicam 15 mg and 22.5 mg groups and lowest in the placebo and 7.5 mg groups. Statistically significant differences between the meloxicam 15 mg and 22.5 mg groups versus placebo and for meloxicam 15 mg versus 7.5 mg were seen for the patient's assessment. For the investigator's assessment, only the 15 mg dose was significantly different from placebo. No other pairwise comparisons yielded significant differences.
Conclusions:	Meloxicam is effective and safe for the treatment of rheumatoid arthritis in a dose range from 7.5 mg to 22.5 mg. In this trial, where flare criteria were strictly applied, efficacy appeared to plateau at the 15 mg dose. Patients treated with 15 mg and 22.5 mg meloxicam returned to pre-flare conditions, i.e., while on the NSAID taken prior to entering the trial. The 7.5 mg dose group showed improvement in efficacy scores, but it did not fully restore pre-flare conditions. The efficacy results combined with an advantageous safety profile support beginning meloxicam at a dose of 7.5 mg and escalating to a maximum dose of 15 mg if needed, to maximise benefit while minimising risk of potential adverse events in the treatment of the signs and symptoms of RA.