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: Movalis®,Mobic®				
Name of active ingredient: Meloxicam		**Page:**	**Number:**	
Ref. To Documentation:	**Volume:**	**Page:** **to**		**Addendum No.:**
Report date: October 3, 2001	**Number:** U01-3344	**Study period (years):** 1998 - 1999		

Title of study:	Double-blind study to compare efficacy and safety of meloxicam 7.5 mg and 15 mg vs. naproxen sodium 1100 mg in the symptomatic treatment of acute non bacterial pharyngitis or pharyngo-tonsillitis over a period of 5 days
Investigator:	Multicenter study. The names of the participating investigators are listed in Section 6 of this report.
Study centre(s):	Multicenter (10 total), bi-national (Mexico and Chile) trial.
Publication (reference):	Not applicable
Clinical phase:	IIb
Objectives:	To assess the efficacy and tolerability of Meloxicam once daily dose of 7 5 mg and 15 mg compared with 1100 mg of naproxen sodium in the symptomatic treatment of acute non bacterial pharyngitis or pharyngo-tonsillitis, over a period of 5 days.
Methodology:	Double-blind, double-dummy, randomized, parallel-group design. The study contemplated 3 scheduled visits and follow-up visit as required: screening-inclusion visit, within 24 hours from the start of symptoms (Visit 1), day 2 post-treatment visit (Visit 2), day 5 post-treatment and end of trial visit (Visit 3). At Visit 2 a clinical assessment was made to decide whether it was necessary or not to add an antibiotic (antimicrobials were not allowed during the first 48 hours of treatment). A patient diary was handed out for recording symptomatology within the first day every 8 hours and subsequently every day
No. of subjects entered:	
total:	390
each treatment:	Meloxicam 7.5 mg (132 patients), meloxicam 15 mg (127 patients) and naproxen sodium 1100 mg (131 patients)

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Diagnosis and main criteria for inclusion:

Diagnosis: acute non bacterial pharyngitis or pharyngo-tonsillitis, diagnosed based on spontaneous pharyngeal pain greater than 35 mm on a 110 mm visual analogue scale (VAS), pharyngeal pain on swallowing greater than 35 mm on a 110 mm VAS, pharyngeal and/or amygdaline hyperemia, absence of purulent plaques, and a negative test for ß-haemolytic Streptococcus on pharyngeal exudate.

A patient with the previous diagnosis was *included* in the study if: male or female aged 18 years or above; ambulatory patient; symptoms started within the previous 24 hours; therapy with a NSAID was required or recommended; and gave his/her written informed consent before inclusion in to the trial.

A patient was *excluded* from the study if: acute bacterial pharyngitis or pharyngo-tonsillitis was suspected by one or more of the following symptoms : an extremely rapid onset, very high fever (>38.5°C), severe pharyngeal pain, cervical adenopathy, intense headache, purulent pharyngeal plaques, evidence of peritonsillar abscess or phlegmon, known or suspected hypersensitivity to the trial drug or NSAIDs; positive test for ß-haemolytic Streptococcus on pharyngeal exudate; therapy with antimicrobial agents prior to start of the trial, chronic infections; infectious mononucleosis; active peptic ulcer within the past 6 months; pregnancy or breast feeding; Asthma, nasal polyps, angioneurotic edema or urticaria following the administration of aspirin or NSAIDs; concomitant treatment with anti-coagulants (including heparin), lithium or methotrexate, concomitant administration of other NSAIDs (including high-dose >150 mg a day aspirin) or analgesic agents; administration of any NSAID during the last three days or analgesics 6 hours prior to the first administration of the trial drug; present treatment or treatment within the last two months with corticosteroids, historical knowledge of impaired renal function (serum urea > 125 % of the upper limit of normal range; serum creatinine > 150 % of the upper limit of normal range); historical knowledge of severe liver injury (alanine amino transferase ALAT > 2 x the upper normal range limit or aspartate amino transferase ASAT > 2 x the upper normal range limit); historical knowledge of hematological disorder (platelet count < 100,000/mm^3, leukocyte count < 3,000/ mm^3), participation in another clinical trial during this study or during the previous month; previous participation in this trial; and/or, patient unable to comply with the protocol

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Test product:	Meloxicam	Meloxicam
dose:	15 mg	7.5 mg
mode of admin.:	Per os	Per os
batch no.:	9970026	9970025
Duration of treatment:	5 days	
Reference therapy:	Naproxen sodium	
dose:	1100 mg	
mode of admin.:	Per os	
batch no.:	K970405	

Criteria for evaluation:

Efficacy: *Primary endpoints* Spontaneous pharyngeal pain (during the last 24 hours) assessed on a Visual Analogue Scale (VAS) and pharyngeal pain intensity on swallowing (dysphagia) also assessed on a VAS By a CRF design error, the VAS line measured 11 cm and not 10 cm as it usually does. *Secondary endpoints*: Final global assessment of efficacy by patient, final global assessment of efficacy by investigator, disease systemic manifestations (fever, and general malaise), pharyngeal hyperemia, assessment of patient status and treatment withdrawal due to lack of efficacy.

Safety: Incidence of adverse events (AE), nature, severity and relationship to treatment; withdrawal due to AE; perforation, ulceration, bleeding (PUB) of the upper gastro-intestinal tract (stomach or duodenum), duration of hospital stay due to gastro-intestinal serious AE, duration of hospital stay due to AE related to trial drug administration, additional visits to the physician due to gastro-intestinal AE; incidence of significant laboratory AE; and, final global assessment of tolerability by the patient and by the investigator.

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Statistical methods:	*Efficacy analyses (for the ITT population)*: for all efficacy variables, adequate statistical test were applied for the between-treatment comparisons at different point intervals during treatment (analysis of covariance, Cochran-Mantel-Haenszel test or Kruskal-Wallis Rank Sum test). *Safety analyses*: The incidence, severity and relationship to treatment of adverse events were tabulated by WHO-ART body system and class (patients reporting more than one adverse event for a WHO-ART preferred term were counted only once for that term, using the most severe event) Laboratory values were also evaluated. Adequate statistical test were applied for the between-treatment comparisons at different point intervals during treatment (analysis of covariance, Fisher Exact test or Kruskal-Wallis Rank Sum test)			

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SUMMARY - CONCLUSIONS:

The three treatment groups were comparable in their demographic and baseline characteristics. About two thirds of the patients had an inclusion diagnosis of pharyngitis and the remaining one third a diagnosis of pharyngo-tonsillitis. For all treatment groups, almost all patients (95%) were compliant with their treatment.

Efficacy results:

- All three treatments demonstrated a clinically important improvement in all primary and secondary efficacy endpoints Between baseline and the end of treatment, there was an approximately 86 % decrease in spontaneous and when swallowing pharyngeal pain severity; within the first two days of treatment (for both primary efficacy variables, the within-treatment differences between baseline and visits 2 and 3 were clinically important but also statistically significant), there was an approximately 70% decrease in the percentage of patients with the secondary endpoints present at baseline (bad general well-being, fever, severe pharyngeal hyperemia and severe cough); and, for close to 90% of the patients their final status was judged by the investigator as improved
- The only statistically significant between-treatment difference was for the percent of patients who reported severe spontaneous pharyngeal pain after 8 hours of treatment initiation (p=0 0006) (baseline %/8 hr %)· NAPRO decreased from 22.1% to 15.0%, M-7.5 decreased from 18 0% to 10 9% and M-15 decreased from 31.2% to 9.8%.
- Among patients who received concomitantly antimicrobial agents after 48 hours, the mean reductions for both primary efficacy variables (spontaneous pharyngeal pain and pharyngeal pain on swallowing) at Visit 3 was about half the reduction observed for the total ITT population (N=377), however, there were only few patients (NAPRO= 9 patients, M-7.5= 14 patients and M-15=8 patients) and there was no statistically significant difference between treatments.

Therefore, the results of this trial showed that meloxicam at either dose (7 5 mg or 15 mg) were comparable to naproxen sodium (1100 mg) with regard to efficacy in the symptomatic treatment of acute non-bacterial pharyngitis or pharyngo-tonsillitis.

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Safety results·

- The incidence of adverse events was about twice among the naproxen sodium 1100 mg patients (20.6%) as compared to the meloxicam patients (12.1% with the 7.5 mg dose and 11.8% with the 15 mg dose).
- For all treatment groups, the most frequently reported adverse events were the ones related to the gastro-intestinal system. Overall, the incidence of gastro-intestinal adverse event among the naproxen sodium patients was much higher (13.0%) as compared to the meloxicam 7.5 mg patients (4 5%) and the meloxicam 15 mg patients (5 5%), and the difference was statistically significant (p=0.0249)
- Overall and among the gastro-intestinal adverse events, abdominal pain was the most frequently reported, and the difference between treatment groups was borderline statistically significant (p=0.0724).
- The vast majority of the total 83 reported adverse events were mild to moderate in severity in all treatment groups (90% to 100%).
- There was only one serious adverse event in the meloxicam 15 mg group. It was a severe, treatment-related bronchospasm that, although the patient was hospitalized for few hours and the random code was broken, it resolved without study treatment discontinuation.
- There were no deaths. Only 3% of the patients, mostly from the naproxen sodium 1100 mg group, discontinued prematurely from the study due to adverse events
- The overall final assessment of safety, by the investigator and by the patient, was mostly good (for at least 84% of the patients)
- For all treatment groups, practically all patients were exposed to the expected number of treatment days (5 days)

Conclusions:

Meloxicam at both doses registered for the treatment of rheumatic diseases (7.5 mg and 15 mg) and administered once a day for five days, had a clinically relevant improvement of the signs and symptoms of acute non bacterial pharyngitis or pharyngo-tonsillitis. Results with both meloxicam doses were comparable to those of naproxen sodium 1100 mg per day. Meloxicam was well tolerated and patients treated with meloxicam experienced fewer adverse events from the gastro-intestinal tract as compared to naproxen sodium.