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: 21 March 1999	**Number:**	**Study period (years):** 1998		

Title of study:	A short term double-blind trial to compare the analgesic efficacy and tolerability of Meloxicam 15 mg, 7.5 mg, 3.75 mg and 1.875 mg oral (rapid release tablet) versus Placebo and Ibuprofen 400 mg and 200 mg oral in the treatment of pain after surgery of the third molar.			
Investigator:	Multicentre study without an official designation of a Coordinating Investigator.			
Study centre(s):	Multicenter, multi-national trial			
Publication (reference):				
Clinical phase:	II			
Objectives:	To assess the analgesic efficacy and tolerability of Meloxicam 15 mg, 7.5 mg, 3.75 mg and 1.875 mg oral (rapid release tablet) compared with Placebo and Ibuprofen 400 mg and 200 mg administered in a single dose, over an observation period of 6 hours in the treatment of pain after surgery of the third molar.			
Methodology:	Randomised, double-blind, double-dummy, 7 group-comparison.			
No. of subjects entered:				
total:	381			
each treatment:	Meloxicam 1.875 mg (53 patients); 3.75 mg (54 patients); 7.5 mg (58 patients) and 15 mg (49 patients). Ibuprofen 200 mg (59 patients) and 400 mg (56 patients). Placebo (52 patients).			
Diagnosis and main criteria for inclusion:	Patients undergoing removal of one impacted mandibular third molar under local anaesthesia. Only patients with type of inclusion II to IV were included.			
Test product:	Meloxicam MU	Meloxicam MU	Meloxicam MU	Meloxicam MU
dose:	15 mg	7.5 mg	3.75 mg	1.875 mg
mode of admin.:	Per os	Per os	per os	per os
batch no.:	B971011	B971011	B971012	B971014
Duration of treatment:	A single dose was administered. Observation time was between 3 and 7 days after treatment.			
Reference therapy:	Ibuprofen	Ibuprofen	Placebo	
dose:	400 mg	200 mg	-	
mode of admin.:	per os	per os	per os	
batch no.:	B951204	B951204	B971101; B971103; B971108; B970709	

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Criteria for evaluation:

Efficacy: *Primary endpoint*: Pain Intensity Differences (PID) on a VAS from one hour onwards. *Secondary endpoints*: Pain Intensity Differences (PID) on a VAS at all observed timepoints, Pain relief, assessed by the patient on a verbal rating scale (VRS) at all the observed timepoints, Sum of Pain Intensity Differences (SPID), Patients with pain decrease ≥ 50% at each observation point, Maximum Pain Decrease, Onset of analgesic action, Total Pain Relief (TOTPAR) assessed by the patients, Withdrawals due to inadequate efficacy, Final global assessment of efficacy by the patient on a VRS after six hours, Final assessment of efficacy by the investigator on a VRS after two hours.

Safety: Number, nature and severity of adverse events, Withdrawals due to safety reasons, Laboratory investigations, Healing of the extraction site, Patient's assessment of overall tolerability, Investigator's assessment of overall tolerability.

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Statistical methods:	An intent-to-treat analysis of all patients treated with a post baseline assessment was carried out. The parameters PID, SPID, PAR (pain relief) and TOTPAR were analysed parametrically by ANOVA followed by Tukey-tests for multiple comparisons. Baseline differences, centre effects, country effects or any confounding factors were investigated and included in the ANOVA model. The onset of analgesic action was analysed using the Log-Rank test. The other efficacy parameters were evaluated nonparametrically by a Kruskal-Wallis-test followed by two-sample Wilcoxon-tests. The incidence, severity and causal relationship of the adverse events were tabulated by body system organ class. The laboratory values were checked for any values that were outside the normal ranges and the frequency of these values were summarised. Baseline characteristics were tabulated and differences between the treatment groups were examined by means of descriptive statistics.			

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SUMMARY - CONCLUSIONS:

Efficacy results:

A clear dose-response for Meloxicam was observed. The results for placebo and Ibuprofen were comparable to those published previously. The results for the primary endpoint are consistent with those seen for the secondary endpoints assessed. The Meloxicam 1.875mg and 3.75mg treatments, although numerically slightly better, had a similar reduction in pain to the patients receiving placebo. The Meloxicam 7.5mg treatment showed a steady reduction in pain over time, however this reduction was not rapid enough or large enough to prove significantly different from placebo. The Meloxicam 15mg dose demonstrated a similar profile in the reduction of pain to the two Ibuprofen dosages. Both demonstrated a steep reduction in pain for the first 2 hours followed by a levelling of the reduction of pain over the 2 to 6 hour period. This reduction in pain was not as great as was seen with the two Ibuprofen treatments and was not significantly different from placebo. The Ibuprofen 200mg treatment was significantly better than placebo in reducing pain between 1½ and 4 hours and the Ibuprofen 400mg treatment was significantly better than placebo from 1 hour onwards. The Ibuprofen 400mg was significantly better than Meloxicam 15mg at the one hour and one and a half hour timepoints.

Safety results:

Three hundred and eighty one patients were included in the safety analysis. Sixty three patients (16.5%) suffered at least one adverse event during the study: 6 patients (1.6%) in the Meloxicam 15 mg group, 9 patients (2.4%) in the Meloxicam 7.5 mg group, 12 patients (3.1%) in the Meloxicam 3.75 mg group, 8 patients (2.1%) in the Meloxicam 1.875 mg group, 13 patients (3.4%) in the Ibuprofen 400 mg group, 6 patients (1.6%) in the Ibuprofen 200 mg group and 9 patients (2.4) in the placebo group. Only one patient, treated with 3.75 mg Meloxicam, suffered an adverse event considered as serious but not related to the study drug.

Gastrointestinal adverse events (35 patients, 9.2%) were the most frequent events observed. No patient died during the study and no patient discontinued due to an adverse events. No adverse event led to dose reduction of the trial drug since the study drugs were administered as a single dose.

All adverse events (dizziness, dyspepsia and nausea) considered as related to study drug were considered as expected.

Conclusions:

A clear dose-response for Meloxicam was observed. However, none of the doses of Meloxicam were significantly superior to placebo. The Ibuprofen 200mg treatment was significantly better than placebo in reducing pain between 1½ and 4 hours and the Ibuprofen 400mg treatment was significantly better than placebo from 1 hour onwards.

No patient died during the study and no patient discontinued due to adverse events. No adverse event led to dose reduction of the trial drug since the study drugs were administered as a single dose. All treatments were well tolerated.