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 do Brasil Quim. e Farm. Ltda.		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Meloxicam				
Name of active ingredient: Meloxicam		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**	**To**	**Addendum No.:**
Report date: 19 September 2001	**Number:** U01-3305	**Study period (years):** Jan 1998 to Apr 1999		

Title of study:	Double-blind study to evaluate efficacy and safety of Meloxicam 7.5 mg and 15 mg *versus* Mefenamic acid 1500 mg in the treatment of dysmenorrhea	
Investigator:	Multicentre study without an official designation of a Coordinating Investigator.	
Study centre(s):	Multicentre (seven centres), multi-national trial (two countries)	
Publication (reference):		
Clinical phase:	IIb	
Objectives:	To assess the efficacy and safety of Meloxicam 7.5 mg and 15 mg once daily compared with Mefenamic acid 500 mg t.i.d., over a treatment period of 3-5 days, during an observation period of 3 menstrual cycles, for the symptomatic relief of primary dysmenorrhea.	
Methodology:	Double-blind, double-dummy, parallel 3 group comparison, randomised.	
No. of subjects entered:		
total:	337	
each treatment:	Meloxicam 7.5 mg (113 patients) and 15 mg (114 patients). Mefenamic acid 1500 mg (110 patients).	
Diagnosis and main criteria for inclusion:	Subjects presenting with primary dysmenorrhea for at least 3 consecutive menstrual periods. Only subjects whose baseline evaluation of lumbar and/or abdomino-pelvic pain due to dysmenorrhea was assigned as greater than 35 mm on a 0-100 mm visual analogue scale were included.	
Test product:	Meloxicam	Meloxicam
dose:	7.5 mg	15 mg
mode of admin.:	Per Oral	Per Oral
batch no.:	9970025	9970026
Duration of treatment:	Test products were administered once a day for the duration of the observation time (3 to 5 days during each cycle).	

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Reference therapy:	Mefenamic acid		
dose:	500 mg t.i.d.		
mode of admin.:	Per Oral		
batch no.:	K97046		
Placebo:	For blinding purposes (double-dummy method), placebo tablets identical in appearance and weight to the following tablets were used:		
	Meloxicam 7.5 mg	Meloxicam 15 mg	Mefenamic acid 500 mg
mode of admin.:	Per Oral	Per Oral	Per Oral
batch no.:	9970031	9970036	B970612

Criteria for evaluation:

Efficacy: All assessments were made after interruption of the vaginal bleeding on each menstrual cycle. *Primary endpoint*: Evaluation of severity of lumbar and/or abdominopelvic pain on a VAS. *Secondary endpoints*: Final global efficacy evaluation by patient and investigator, referred as "good"(=1), "satisfactory"(=2), "non satisfactory"(=3), or "poor"(=4); evaluation of severity of disability to work and disability on daily life on a VAS; evaluation of severity of dysmenorrhea-associated symptoms, namely irritability, vomiting, headache, dizziness, fatigue, diaphoresis and diarrhoea assessed as "absent"(=1), "mild"(=2), "moderate"(=3), or "severe"(=4).

Safety: Number, nature and severity of adverse events; incidence of GI-AEs, withdrawals due to safety reasons; incidence of significant Laboratory Adverse Events; additional visits to a physician due to gastro-intestinal adverse events; incidence of bleeding and/or perforation of gastro-intestinal ulcers (PUB); duration of hospital stay due to significant and/or serious Gastro-Intestinal Adverse Events (GI-SAE) and / or AEs related to trial drug administration; patient's assessment of global tolerability; investigator's assessment of global tolerability.

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Statistical methods: A per-protocol efficacy analysis of all treated subjects for whom at least one post baseline assessment has been carried out. The efficacy parameters were evaluated nonparametrically. Treatment group comparisons of continuous variables were done using the Kruskal-Wallis-test. Same treatment group comparisons between menstrual cycles were performed for continuous variables using Wilcoxon signed rank tests. Categorical efficacy parameters were analysed using contingency tables (Fisher and Chi-square tests) and were also treated as discrete numeric variables and analysed using the same nonparametrical tests described for the continuous ones. The incidence, severity and causal relationship of the adverse events were tabulated for all treated subjects (intent-to-treat analysis) 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.

SUMMARY – CONCLUSIONS:
Efficacy results: Meloxicam 7.5mg and Meloxicam 15mg showed a similar profile in the reduction of pain and dysmenorrhea associated symptoms when compared to the subjects receiving Mefenamic Acid 1500mg. No dose related differences in response to Meloxicam were detected in the study. The results for the efficacy parameters in the primary endpoint were consistent with the ones observed in the secondary endpoints.

Safety results: Three hundred and thirty-seven subjects were included in the safety analysis. Thirty-three (9.8%) out of those 337 subjects presented with one or more adverse events during the course of the trial. Two thirds of those thirty-three subjects were included in the Mefenamic Acid group. The number of subjects on each group who presented with at least one adverse event was eleven (10%) in the Mel 7.5 mg group (N=113), ten (9%) in the Mel 15 mg group (N=114), and 22 (20%) in the Mefenamic Acid group (N=110) (see Section 12.1 for details). One serious adverse event was reported in the mefenamic acid group, which was not considered to be drug related. There were no detectable differences between the safety profiles of the two Meloxicam dosages used in this trial. The most common adverse events were gastrointestinal system diseases, with incidence rates of six, eight, and 20% respectively for the Mel 7.5 mg, Mel 15 mg, and Mefenamic Acid groups (see TABLE 12.2.3.1). Among those GI adverse events, dyspepsia and gastritis were the ones with an incidence higher than 1%. Dyspepsia was reported by four (3.5%) of the Mel 7.5 mg treated subjects, four (3.5%) of the Mel 15 mg treated subjects, and 15 (13.6%) of the Mefenamic Acid treated subjects (source: Appendix 16.1.9.2: TABLE 5.2.5). Significant laboratory abnormalities were rare and did not differ significantly in incidence between the considered treatment groups considered.

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Conclusions: The present study has shown that both tested daily oral doses of Meloxicam (7.5mg and 15 mg) were comparable to 500 mg PO Mefenamic Acid *t.i.d.* in relieving dysmenorrhea related symptoms, and also showed that Meloxicam seems to have a better gastro-intestinal tolerability profile when used for this indication. The results concerning treatment emergent gastrointestinal adverse events with the use of Meloxicam are consistent with previous descriptions and do not impose substantial contraindications to its use under these conditions. The efficacy of Meloxicam in the treatment of dysmenorrhea corroborates previous descriptions in the literature, which had already described the benefit of using non-steroid anti-inflammatory drugs for this indication. The methodology adopted for this study to assess pain and other symptoms using a Visual Analogue Scale (VAS) has been validated by previous studies and support the validity of the described results. A known weakness of the present work is related to the absence of a placebo arm. If present, the comparison between active treatment – both Meloxicam and Mefenamic Acid – and placebo would have enabled us to adequately assess differences between time intervals to the onset of drug action. Additionally, it would have powered the analysis of what corresponds to drug effect and what is actually spontaneous reduction of dysmenorrhea related symptoms. In spite of that, the study findings showed comparable efficacy between the active comparator (Mefenamic Acid) and Meloxicam. Therefore, giving the previous reports demonstrating the therapeutic effect of Mefenamic Acid to the treatment of Dysmenorrhea, it is valid to say that Meloxicam is effective to the treatment of Dysmenorrhea related symptoms.