CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-530

Medical Review(s)

Clinical Team Leader's Memorandum:

Reviewer: James Witter MD, PhD (HFD-550)

Date: May 26, 2004

NDA: **21-530 (7.5 mg/5 ml oral suspension)**

Sponsor: Boehringer Ingelheim Pharmaceuticals Inc.
Mobic® (meloxicam) suspension

Summary:
This supplement was to support a new formulation of meloxicam, 7.5 mg/5 ml oral suspension; it was submitted August 18, 2003. Mobic, as 7.5 and 15 mg tablets, is currently approved for the treatment of osteoarthritis (NDA 20-938; submitted December 15, 1998 with approval on April 13, 2000).

The supplement included two PK studies (107.172 and 107.74) which were re-analyzed at the request of the PK reviewers (Drs. Chaurasia and Bashaw) to establish bioequivalency to the tablet via a capsule formulation. The NDA also contained a 6-week, active-control study (107.179) in 286 patients (142 received the 7.5 mg/5ml suspension, 144 received 7.5 mg tablets) patients with osteoarthritis to support the safety and efficacy of this new formulation. The clinical review, by Dr. Oussova, concluded that study 107.179 did support the efficacy and safety of the suspension although robust conclusions (for both safety and efficacy) are not possible owing to the nature and duration of the trial. Nonetheless, no new safety issues were evident upon review of the clinical data in this NDA.

Regulatory Action:
Dr. Oussova has recommended that meloxicam oral suspension 7.5 mg/5ml be approved for the use in patients with osteoarthritis; I concur with this decision.

The revisions to the MOBIC labeling, as included in the clinical review of Dr. Oussova (DFS 5/24/2004), include additions to the Heading, Prescribing Information, Clinical Pharmacology, and HOW SUPPLIED section. Therefore, the action for the sponsor will be **APPROVED** as they have already agreed on the proposed labeling.

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/s/

James Witter
5/28/04 02:57:37 PM
MEDICAL OFFICER
Team Leader Memo

Clinical Review Cover Sheet

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Product (HFD-550)

NDA 21-530 Mobic (Meloxicam) 7.5 mg/5 ml oral suspension

Date of Submission:	**August 18, 2003**
Date received:	**August 19, 2003**
Review Date:	**May 3, 2004**
Drug Name:	**Mobic**
Generic Name:	**Meloxicam**
Chemical Name:	**4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide1,1 dioxide**
Applicant:	**Boehringer Ingelheim Pharmaceuticals, Inc.**
Related Reviews:	**Biopharm- Dr. Chaurasia, Chandra** **Chemistry- Dr. Lin, Sue -Ching**
Pharmacologic category:	**NSAID**
Proposed Indication:	**Relief of the signs and symptoms of osteoarthritis**
Dosage forms and route:	**Oral suspension 7.5 mg/5 ml**
Medical reviewer:	**Tatiana Oussova, MD, MPH**
Project Manager:	**Barbara Gould**

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Clinical Review for NDA 21-530

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approval is recommended for Meloxicam oral suspension 7.5 mg/5 ml,for the indication of the relief of the signs and symptoms of osteoarthritis (OA) in adults.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not applicable

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The use of Mobic (meloxicam) 7.5 and 15 mg tablets in treating the signs and symptoms of osteoarthritis has been established through NDA 20-938, submitted on December 15, 1998 and approved on April 13, 2000.

This current application focuses on the data to establish the bioequivalence of meloxicam oral suspension with tablets and therefore, to establish the safe and effective use of Mobic (meloxicam) oral suspension 7.5 mg/5 ml. The primary focus of this NDA submission is to establish the bioequivalence of the oral suspension formulation of meloxicam to the solid oral dosage forms, particularly the 7.5 mg and 15 mg tablets. Additional clinical evidence is provided to support the oral suspension's comparable efficacy to the tablet formulation. It was the Sponsor intent, supported by the FDA, to submit a supportive efficacy trial and not a full clinical program to support the efficacy of meloxicam oral suspension 7.5 mg.

In the current submission the Sponsor has established indirect bioequivalence of the suspension to the approved tablet dosage form (via the capsules). A direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. Since the Cmax and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulation were comparable, the Sponsor was asked to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% confidence interval (CI) for a comparison of the tablets to suspension. Based on the results of this analysis, 90% CI for AUCss and Cmax,ss measures of

meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved product meloxicam tablets, 15 mg. The formulation for the 7.5 mg and 15 mg meloxicam tablets marketed in the US is identical to the 7.5 mg and 15 mg meloxicam tablets used in the comparative bioavailability studies 107.74 and 107.82, respectively. Also, in NDA 20-938, dose proportionality has been established between the 7.5 mg and 15 mg tablets. In the current submission, dose proportionality has been demonstrated for meloxicam suspension over the range of 7.5 mg, 15 mg and 22.5 mg. Thus, although there is no direct comparison between meloxicam 7.5 mg/5 mL suspension and meloxicam 7.5 mg tablet, based on the data available, meloxicam suspension 7.5 mg/5mL is comparable to meloxicam 7.5 mg tablet with respect to safety and exposure. Thus, the meloxicam suspension 7.5 mg/5 mL is deemed bioèquivalent to meloxicam 7.5 mg tablet.

See review by Dr. Chandra S. Chaurasia for more detailed information.

B. Efficacy

There was one 6-week active control study (107.179) in patients with osteoarthritis (OA) submitted as supportive evidence of efficacy of meloxicam oral suspension. Study results suggested that effectiveness of meloxicam oral suspension is comparable to that of meloxicam tablets in equal doses. However because of inadequacy of the study design (duration of only 6 weeks, lack of placebo control and lack of acceptable primary endpoints) the results cannot be viewed as robust.

C. Safety

There were no additional safety studies performed at the date of this submission. Additional data from phase I and phase III studies and postmarketing surveillance do not raise additional safety concerns.

D. Dosing

The dose will remain the same as the originally approved dose of 7.5 mg (as 7.5 mg/5 ml) with a maximum daily dose of 15 mg.

E. Special Populations

The preliminary safety data regarding pediatric usage is provided with this submission but will not be reviewed in detail. No other special groups have been studied with meloxicam oral suspension. Pediatric studies using the oral suspension formulation have been addressed in separate proposals in conjunction with the rheumatoid arthritis (RA) supplement (NDA 20-938/S004). Because the pediatric suspension and the oral suspension formulation under this review are identical, the requirement to provide pediatric information for the present NDA is waived.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

The use of Mobic (meloxicam) 7.5 and 15 mg tablets in treating signs and symptoms of osteoarthritis in adults has been established through NDA 20-938, which was submitted on December 15, 1998 and approved on April 13, 2000.

An oral suspension has been developed in order to provide a non-solid oral dosage form.

This application focuses on the information to establish the safe and effective use of Mobic (meloxicam) oral suspension 7.5 mg/5 ml in adult population (dose strength is identical to the approved solid oral dosage form, Mobic 7.5 mg tablets). It contains the data on bio-equivalence to the solid oral formulation at steady-state. The proposed maximum recommended daily dose of meloxicam oral suspension is 15 mg/day (10 ml).

Meloxicam, an oxicam derivative, is a member of the enolic acid group of non-steroidal anti-inflammatory drugs (NSAIDs). It is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1 dioxide.

Meloxicam is an NSAID that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of meloxicam may be related to prostaglandin synthetase (cyclooxygenase) inhibition.

The use of the meloxicam oral suspension formulation in treating the signs and symptoms of OA is not expected to expose patients to any new risks or increase the frequency of known risk associated with the use of Mobic 7.5 mg and 15 mg tablets, as fully described in the currently approved label.

B. Important Milestones in Product Development and Other Relevant Information

The clinical development program for use of meloxicam in osteoarthritis and rheumatoid arthritis (RA) began in 1982. Early human use included doses up to 60mg/d but the clinical findings of an excess of serious GI adverse events lead to the discontinuation of the development program for the 60mg dose in January, 1988, and for the 30mg dose in June, 1990. Trial 35 results lead to the development program for the 7.5mg dose, and in 1993 the program for the 22.5mg dose for RA was begun. The NDA for OA, filed in December, 1998, contained supporting evidence for efficacy at 7.5mg and 15mg/d in OA (one large successful trial which used placebo and active

control arms, and ten active control trials with a large degree of internal consistency), and so was approved on April 13, 2000.

There was inadequate evidence for the efficacy of meloxicam 7.5-mg and 15-mg for the treatment of RA. In addition, safety data from studies of both osteoarthritis and rheumatoid arthritis suggested a dose response from 15 to 22.5 mg in multiple adverse event categories including:

a. mortality
b. perforations, ulcers and bleeds
c. overall serious adverse events
d. overall adverse events leading to withdrawal as well as cardiovascular and gastrointestinal events leading to withdrawal
e. overall adverse events
f. laboratory adverse events: decreases in hematocrit, anemia, hepatic adverse events, renal dysfunction, hypertension.

Meloxicam is currently available on the US market as 7.5 mg and 15 mg oral tablets only, as approved under NDA 20-938. An oral suspension is considered useful in patients who have difficulties swallowing solid formulations or who have an individual preference for such a formulation (e.g., elderly). A further advantage of an oral liquid might be the possibility to individualize the dose for each patient, for example in the case of a low or high body weight or in case of dose related adverse events.

This submission focuses on the bioequivalence of the oral suspension formulation of meloxicam to the approved and marketed solid oral form.

The Division agreed that the primary source of efficacy information on meloxicam in treating the signs and symptoms of OA is NDA 20-938, and no separate ISE is required. Division agreed that no additional clinical studies are necessary provided that there is bioequivalence to the clinically studied formulation.

Meloxicam has been registered for the treatment of the signs and symptoms of osteoarthritis in more than 60 countries. The oral suspension formulation was recently approved for adults in France and the EU member states. Currently, the oral suspension is marketed in Mexico (60 mL bottles) and some other Latin American countries (Colombia, Ecuador, Chile).

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

There is no new information on animal pharmacology, toxicology, or statistics submitted under this NDA.

III. Human Pharmacokinetics and Pharmacodynamics

Complete review is performed by Chandra S. Chaurasia, Ph.D.

In the current submission the Sponsor has established indirect bioequivalence of the suspension to the approved tablet dosage form (via the capsules). A direct bioequivalence measurement comparing the meloxicam suspension to the tablet formulation has not been done. Since the C max and AUC levels between the meloxicam suspension and capsule, and those between the capsule and tablet formulation were comparable, the Sponsor was recommended to reanalyze the combined results of studies 107.172 and 107.74 using the capsule legs which are in both studies as a scaling factor and construct a 90% confidence interval (CI) for a comparison of the tablets to suspension. Based on the results of this analysis, 90% CI for AUCss and Cmax,ss measures of meloxicam suspension 15 mg are within the acceptable range of 80-125% when compared to the approved product meloxicam tablets, 15 mg. The formulation for the 7.5 mg and 15 mg meloxicam tablets marketed in the US is identical to the 7.5 mg and 15 mg meloxicam tablets used in the comparative bioavailability studies 107.74 and 107.82, respectively. Also, in the NDA 20-938 dose proportionality has been established between the 7.5 mg and 15 mg tablets. In the current submission, dose proportionality has been demonstrated for meloxicam suspension over the range of 7.5 mg, 15 mg and 22.5 mg. Thus, although there is no direct comparison between meloxicam 7.5 mg/5 mL suspension and meloxicam 7.5 mg tablet, based on the data available, meloxicam suspension 7.5 mg/5mL is comparable to meloxicam 7.5 mg tablet with respect to safety and exposure. Thus, the meloxicam suspension 7.5 mg/5 mL is deemed bioequivalent to meloxicam 7.5 mg tablet.

IV. Description of Clinical Data and Sources

A. Overall Data

As stated earlier in this review, efficacy of meloxicam in treating the signs and symptoms of OA has been established through the review of NDA 20-938. The primary focus of this submission is to establish the bioequivalence of meloxicam oral suspension to meloxicam solid dosage form. Efficacy information from one trial with meloxicam oral suspension and meloxicam tablets is provided as supportive information only (Trial 107.179). Data from this trial submitted in paper format only. It was agreed that the Sponsor did not need to provide separate electronic CRT data sets from the study 107.179. It was also agreed that it would not provide an integrated analysis of efficacy or safety in this NDA. However, per FDA request, BIPI is providing a safety summary including all safety data on completed and preliminary studies not included in the original tablet NDA (20-938) or supplements.

B. Postmarketing Experience

Meloxicam is currently approved in over 100 countries for the treatment of OA, RA, and ankylosing spondylitis. It is currently marketed outside of the US in tablets, capsules, ampule (for injection), suppository, and oral suspension formulations. As of January 15, 2003, meloxicam oral suspension is approved in twenty five countries and marketed in four countries. Four cases of spontaneous adverse events reported with meloxicam oral suspension are reviewed under safety section.

V. Clinical Review Methods

A. Overview of Materials Consulted in Review

- Data from clinical trial 107.179 (non-pivotal)
- Original reviews of the NDA 20-938
- Meeting minutes between the FDA and the Sponsor
- Biopharm review
- Postmarking safety data

B. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI inspections were conducted for 107.179 trial sites.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The protocol, the patient information and informed consent were submitted to their respective IRB or the relevant Ethics Committees. The trial was not started before approval by the respective IRB/Ethics Committee was available. The trial was performed according to the requirements of the Declaration of Helsinki as well as in accordance with local guidelines defining the protection of human subjects.

D. Evaluation of Financial Disclosure

Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) is a subsidiary of Boehringer Ingelheim GmbH, a privately-held company. It is not publicly traded, and has no equity available to investigators. No investigators can have or own a proprietary interest in a product owned by the company.

Of the studies described in this current submission, only one supportive study 107.179 requires financial disclosure. The sponsor certified that each of the study investigators do not have a proprietary interest in this product or a significant equity in the Sponsor. No investigator was the recipient of significant payments of other sorts.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

There were no pivotal trials submitted by the Sponsor in support of the efficacy of the product in the treatment of the signs and symptoms of OA. Trial 107.179 provides limited information on effectiveness of the suspension compared to the tablet formulation. There is no placebo arm and therefore the actual effect size of both active treatments is unknown. The trial is of short duration and there is no information on sustainability of treatment effect. The only primary end-point was the patient's assessment of pain in a target joint on movements which is not adequate to support a finding of substantial evidence of efficacy of this product. However, reassuring is the fact that both treatment groups seem to be similar with respect to trial endpoints.

B. Detailed Review of Trial 107.179

Data from clinical trial 107.179, " A Multicenter, Double-Blind, Double-Dummy, Randomized, Parallel-Group Trial to Compare the Efficacy and Safety of 7.5 mg Meloxicam Oral Suspension with 7.5 mg Meloxicam Tablets Administered Orally Once Daily over a Period of 6 Weeks in Patients with Osteoarthritis", was submitted as supportive evidence of efficacy. The trial was conducted in five countries with a total of 25 centers. A total of 286 patients were randomized into the trial and received study treatment, 142 received meloxicam oral suspension 7.5 mg and 144 received meloxicam tablets 7.5 mg over a period of 6 weeks. The most affected joint (target joint) had to be evaluated throughout the trial. There was no difference between treatment groups in the number of patients prematurely discontinued from the trial (175 in both groups), or in the reasons for discontinuation from the trial. Twenty six (26) patients were excluded from the analysis due to major protocol violations, leaving 260 patients included in the explanatory analysis.

1. Primary Endpoints

- Patient's assessment of pain on active movement in the target joint

2. Secondary Endpoints

2.1 Efficacy:

- Patient's assessment of pain at rest in the target joint
- Lequesne Index
- Patient global assessment of disease activity
- Investigator's global assessment of disease activity
- Range of motion
- Tenderness on palpation
- Redness
- Swelling

- Final global assessment of efficacy by patient
- Final global assessment of efficacy by investigator
- Withdrawal due to inadequate efficacy
- Patient status with regard to change of arthritic condition assessed by patient

2.2 Safety:

- Incidence and intensity of adverse events (AE's)
- Incidence of laboratory adverse events (liver, kidney, hematology)
- Withdrawal due to adverse event
- Final global tolerability by patient
- Final global tolerability by investigator
- Duration of hospital stay due to gastrointestinal serious adverse events (GI-SAE)
- Duration of hospital stay due to adverse events related to trial drug administration
- Additional visits to physician due to gastrointestinal adverse event (GI-AE)

- Acceptability of oral suspension

Reviewer's comments:

- ***Study primary endpoints are limited to one single endpoint of pain on active motion in a target joint. This would not be sufficient for a pivotal trial since it provides information on pain only and not on physical function and overall patient improvement (those are required by the Division of pivotal OA trials as co-primary endpoints).***

3. Study Population

3.1 Inclusion Criteria

- Male or female aged 40 years or above
- Patients who were suffering from acute and painful exacerbation of osteoarthritis of the hip or knee
- The diagnosis had to be based on
  - ✓ X-ray diagnosis (at least two of the following criteria: joint space narrowing, sclerosis, formation of osteophytes, or subchondral cysts)

and

  - ✓ Clinical signs and symptoms according to trial protocol

If radiographic findings characteristic for OA were present on old radiographs new radiographs were not required.

- Clinical signs and symptoms had to be present since at least three months
- Assessment of pain on active movement (by the patient) of the most affected joint had to **exceed 35 mm** on a 100 mm visual analogue scale (VAS; 0-no pain and 100-inbearable pain)

- Symptoms of OA had to require administration of NSAIDs
- Patient's informed consent in accordance with local legislation and ICH GCP

Reviewer's comments:

- ***Study allowed including patienst with VAS pain level above 35 mm. Most trials evaluating pain of OA would allow patients into the trial with a level of pain above 40 and even 50 mm on VAS scale. Thus inclusion criteria allowed patients with less severe pain into the trial.***

3.2 Exclusion Criteria

- Known or suspected hypersensitivity to the trial drugs or their excipients, analgesics, antipyretics or NSAIDs
- Active peptic ulcer within the last 6 months before the trial
- History of recurrent peptic (gastric or duodenal) ulcer
- Pregnancy or breastfeeding
  Precaution: attention had to be drawn to reports that NSAIDs were reported to decrease the effectiveness of intrauterine devices (R95-0164)
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- Concomitant treatment with anti-coagulants (including heparin, ticlopidine)
- Concomitant treatment with lithium
- Concomitant administration of other NSAIDs (including aspirin >150 gm) or analgesic agents (except paracetamol up to 4 g per day)
- Administration of any NSAID during the wash-out period prior to entry to the trial
- Treatment with diarcerheine and chondroitin sulphate initiated or not kept stable within the past three months prior to entry to the trial
- Confinement to bed rest

- Present treatment or treatment within the last two months prior to entry to the trial with conticosteroids (systemic, intra-articular)
- Planned surgical intervention of the affected joint during the trial
- Infectious arthritis of the affected joint
- Prior total replacement of the anatomic area of interest
- Past history of trauma of the affected joint requiring any compensation
- Non-dialyzed severe renal failure
- Severe hepatic failure
- Hematological disorder (platelet count <100,000/mm3, leukocyte count <3,000/mm3)
- Abnormal baseline laboratory results which were deemed clinically relevant by the investigator
- Participation in another clinical trial during this study or during the previous month prior to entry into study
- Previous participation in this trial
- Any other rheumatologic or non-rheumatologic disease that could interfere with the evaluation of efficacy and safety (e.g. rheumatoid arthritis, ankylosing spondylitis, severe osteoporosis)
- Patient unable to comply with the protocol
- Patient with known drug abuse
- Patient with known alcohol abuse

4. Withdrawals

- The patient withdrew consent
- The patient failed to comply with the protocol requirements and the specified dosage regimen according
- The patient was no longer able to participate in the trial (e.g. adverse events, insufficient efficacy of the trial drug, surgery, concomitant disease, concomitant therapies or administrative reasons).
- Eligibility criteria, i.e. inclusion and exclusion criteria were violated

5. Treatments

Meloxicam oral suspension 7.5 mg once daily was compared with meloxicam 7.5 mg tablets once daily.

6. Concomitant Therapy

The intake of other NSAIDs (except low-dose aspirin up to 150 mg per day) and those drugs listed in the exclusion criteria during the trail was not allowed. A wash-out phase of at least two days (three days for oxicams) had to be observed prior to the first administration of the trial drug. Patients who had not taken NSAIDs during at least 3 days prior to the trial were not required to perform a wash out.

Patients who experienced an increase in symptoms to an unacceptable level for more than 24 hours during the treatment were allowed to use **paracetamol** (acetaminophen) as rescue medication (**not to exceed 4 g/day**) for a **maximum of 5 days per flare**. The use of paracetamol had to be discontinued for at least 12 hours prior to the trial –required evaluations or assessments.

The intake of paracetamol (not to exceed 4 g/day) during the wash out was allowed up to 2 hours before baseline examination. Paracetamol (not to exceed 4 g/day) was allowed to treat pain of origin other than patient's OA up to 12 hours before the trial-required baseline evaluations or assessments. Use of paracetamol had to be documented in the CRF.

The consumption of analgesics other than paracetamol during the wash-out period and during treatment period was not allowed.

Any concomitant therapies that were not listed as exclusion criteria were allowed. Physiotherapy of the target joint had to be kept stable during the duration of the trial.

7. Adverse events

Adverse events were, by definition, any reaction, side effect or untoward event that occurred during the course of clinical trial, whether or not the event is considered drug related.

7.1 Serious adverse events

Serious adverse events (SAE) are those events where one or more of the following criteria were fulfilled:

- Fatal
- Immediately life-threatening (clinical experience)
- Permanently or severely disabling
- Requiring or prolonging inpatient hospitalization
- Congenital anomaly
- Overdose (leading to an adverse event)
- Any other reason representing a significant hazard comparable to the criteria mentioned before

All serious adverse events had to be reported within 24 hours of their occurrence to the clinical Monitor.

7.2 Significant adverse events

Significant adverse events are those events which may fulfill the seriousness criteria, but because of their type are significant for this trial. The following events were deemed significant:

- Thrombocyte count below 50.000/µl
- Perforation, ulceration, bleeding (PUB) verified by endoscopy, x-ray or surgery

8. Trial Flow Chart

Visit	1	2	3	4	5	EOT	FU
Week	Week -1	Day 0	Week 2	Week 4	Week 6	Week 6 or Early Termination	Follow-up[1]
Procedure							
Informed Consent	x						
Medical history		x					
Medication history	x						
Physical examination		x				x	
Height, Weight	x						
Clinical lab tests	x					x	x[2]
x-ray	x (if needed)						
In-/Exclusion	x						
Randomization		x					
Investigator's global assessment of disease activity		x	x	x	x		
Patient's global assessment of disease activity		x	x	x	x		
Lequesne Index		x	x	x	x		
Patient's assessment of pain on active movement		x	x	x	x		
Patient's assessment of pain at rest		x	x	x	x		
Investigator's assessment of tenderness, redness, and swelling		x	x	x	x		
Range of motion		x	x	x	x		
Patient's final assessment of global efficacy						x	
Investigator's final assessment of global efficacy						x	
Patient's assessment of status with regard to change of arthritic condition						x	
Patient's final assessment						x	

of global tolerability							
Investigator's final assessment of global tolerability						x	
Duration of hospital stay due to GI-SAE or drug-related AE			x	x	x		x
Additional visit at physician due to GI-AE			x	x	x		x
Acceptability of suspension						x	
Review adverse events		x	x	x	x		x
Review concomitant therapies/medications		x	x	x	x		x
Dispense medications		x	x	x			
First intake of trial drug		x[3]					
Collect one suspension bottle			x	x			
Collect medications						x	
Check compliance			x	x	x		
Blood sample for compliance check	x		x	x	x		
Conclusion of participation						x	

1 necessary if AE not yet recovered at conclusion visit or new AE within 14 days after completion of the trial
2 if clinically required
3 either in the evening of day 0 (with dinner) or in the morning of day 1 (with breakfast)

9. Disposition of Subjects

A total of 311 patients were enrolled by 25 centers in 5 countries. Two hundred and eighty six patients were randomized and treated.

Table 1. Disposition of Patients (Sponsor's Tables 1.1.2-3, Appendix 15.9.2)

	Suspension 7.5 mg		Tablets 7.5 mg		Total	
	N	%	N	%	N	%
enrolled					311	
not randomized					25	
randomized	142	100	144	100	286	100
treated	142	100	144	100	286	100
included in ITT analysis	142	100	144	100	286	100
prematurely discontinued	24	17	25	17	49	17
adverse events	8	6	12	8	20	7
lack of efficacy	12	8	7	5	19	7
admin. reasons	4	3	6	4	10	3
planned observation time reached	118	83	119	83	237	83
excluded from	12	8	14	10	26	9

explanatory analysis						
included in explanatory analysis	130	100	130	100	260	100
prematurely discontinued	24	18	24	18	48	18
adverse events	8	6	12	9	20	8
lack of efficacy	12	9	6	5	18	7
admin. reasons	4	3	6	5	10	4
Planned observation time reached	106	82	106	82	212	82

The patient disposition was homogeneous between the treatment groups. All patients randomized were included in the ITT analysis and the analysis of safety.

The two treatment groups were comparable with respect of the type and frequency of protocol violations. All the protocol violations were considered minor (pain on active movement at baseline <35 mm, time window deviations for scheduling of visits, treatment non-compliance, paracetamol intake criteria not met) without clinical importance and were supposed not to impact the assessment of efficacy and tolerability.

On-site audit was performed at center ZA 701 in South Africa. This center had 26 patients included into the trial. In addition to the ITT analysis, an exploratory analysis was performed that excluded these 26 patients of center ZA 701.

10. Demographic and Baseline Features

The two treatment groups were comparable with regard to age, weight and height. Ninety three males and 193 females were randomized and treated.

Table 2. Demographic Data of Treated Patients (ITT). (Sponsor's Tables 2.1.1-14, Appendix 15.9.2)

	Meloxicam Suspension (N=142)	Meloxicam Tablets (N=144)
Age (years)	66± 11	66± 10
Females	66± 10	66± 10
Males	65± 12	66± 10
Weight (kg)	82±17	81± 17
Height (cm)	164±10	165± 10

The patients allocated to the meloxicam suspension treatment had suffered from OA for an average of 7.65 years whereas the patients allocated to the meloxicam tablet group had OA for an average of 7.49 years.

The majority of patients (73 % in the suspension group and 72 % in the tablet group) suffered from OA of the knee. The hip alone was affected in 9 % and 10 % of patients in the suspension group and tablet group, respectively. Eighteen percent of patients in both groups had OA of both joints.

The baseline values for evaluation of disease activity were assessed at visit 2 after the washout. Regarding the primary variable "Pain on active movement", a significant

difference (p=0.029) between the treatment groups was observed which was adjusted for by means of evaluation with the ANCOVA-model.

Table 3. Baseline Values Obtained at Visit 2. Given are mean Values (Sponsor's tables 2.5.1-39, 4.2.5.6, Appendix 15.9.2)

	Meloxicam Suspension		Meloxicam Tablets	
	N	Value	N	Value
Pain on active movement	142	72.2± 16.3	144	67.9± 17.1
Pain at rest	142	41.7± 27.1	144	44.9± 26.5
Lequesne Index for hip (sum score)	17	10.2± 3.6	23	12.2± 4.9
Lequesne Index for knee (sum score)	124	13.7± 3.9	117	13.5± 3.7
Disease activity by investigator (mean score)	142	2.5± 0.7	144	2.4± 0.6
Disease activity by patient (mm)	142	67.5± 17.5	144	65.6± 19.1
Flexion of hip (degrees)	17	86.2± 16.0	23	89.3± 23.8
Extension of hip (degrees)	16	11.6± 10.6	22	6.2± 6.4
Adduction of hip (degrees)	16	15.4± 9.4	23	19.4± 10.2
Abduction of hip (degrees)	17	28.4± 9.9	23	26.5± 11.0
Flexion of knee (degrees)	124	109.2± 20.8	121	109.0± 23.0
Extension of knee (degrees)	124	-2.1± 8.5	120	-3.7± 10.7
Tenderness (positive)	142	74 %	143	74 %
Redness (positive)	142	4 %	143	1 %
Swelling (positive)	142	54 %	143	49 %

Reviewer's comments:

- ***The difference observed between treatment groups in "pain on active movement" baseline value should be accounted for during analysis***
- ***Both treatment groups were similar with regards to other baseline values***

11. Efficacy Results

All patients randomized were included in the intent-to-treat analysis for evaluation of efficacy. Out of 286 evaluable patients in the ITT population, 26 patients were excluded from the per protocol (PP) analysis. Results of the ITT and PP analyses were similar.

11.1 Primary endpoint of efficacy-Pain on active movement

The degree of pain on active movement was assessed by the patient on a horizontal 100 mm visual analogue scale (VAS). Since a significant baseline difference between the treatment groups was observed for this parameter the analysis was carried out by means of

ANCOVA. This parameter improved significantly ($p<0.0001$) in both treatment groups during the course of the trial but there was no significant difference between the groups.

Additionally, the potential impact of age and gender was investigated. There were no significant influences of these covariates on the result found.

Table 4. Pain on Movement by Patient on a VAS. Given are means Values (LOCF) ±SD in mm (Sponsor's tables 4.1.1.4 and 4.1.1.6, Appendix 15.9.2)

Visit	Treatment duration	Meloxicam Suspension		Meloxicam Tablets	
		Pain on movement (mm)	N	Pain on movement (mm)	N
2	baseline	72± 16	142	68± 17	144
3	2 weeks	51± 23	142	52± 25	144
4	4 weeks	48± 26	142	47± 27	144
5	6 weeks	44± 27	142	44± 28	144
Differences from last value to baseline (adjusted LS means)		-27 (SE 2.3) 95 % CI (-32, -23)	142	- 25 (SE 2.3) 95 % CI (-29, -20)	144

11.2 Secondary Efficacy Endpoints

1. Pain at rest.

This parameter improved in both groups from baseline ($p<0.0001$), but there was no significant difference between treatment groups.

Table 5. Pain at Rest by the Patient on a Visual Analogue Scale (VAS). Given are Mean values (LOCF) ± SD in mm. SE=Standard Error (Sponsor's tables 4.1.2.4 and 4.1.2.6, Appendix 15.9.2)

Visit	Treatment duration	Meloxicam suspension		Meloxicam tablets	
		Pain at rest (mm)	N	Pain at rest (mm)	N
2	Baseline	42 ± 27	142	45 ± 27	144
3	2 weeks	31 ± 25	142	31 ± 26	144
4	4 weeks	27 ± 25	142	29 ± 25	144
5	6 weeks	26 ± 24	142	30 ± 27	144
Differences from last value to baseline (adjusted LS means)		-16 (SE 2.5) 95% CI (-21, -11)	142	-15 (SE 2.5) 95% CI (-20, -10)	144

2. Disease activity assessed by the patient

This parameter improved in both groups from baseline ($p<0.0001$), but there was no significant difference between treatment groups.

Table 6. Disease Activity by the Patient on a Visual Analog Scale (VAS). Given are Mean values (LOCF) ± SD in mm. SE=Standard Error (Sponsor's tables 4.1.6.4 and 4.1.6.5, Appendix 15.9.2)

Visit	Treatment duration	Meloxicam suspension		Meloxicam tablets	
		Disease activity (mm)	N	Disease activity (mm)	N
2	Baseline	68 ± 17	142	66 ± 19	144
3	2 weeks	52 ± 23	142	52 ± 24	144
4	4 weeks	47 ± 26	142	46 ± 26	144
5	6 weeks	44 ± 27	142	43 ± 28	144
Differences from last value to baseline		-24 ± 28	142	-22 ± 25	144

3. Disease activity assessed by the investigator

This parameter improved in both groups from baseline ($p<0.0001$), but there was no significant difference between treatment groups.

Table 6. Disease Activity by the Investigator on a Ordinal Scale. Given are Mean values (LOCF) ± SD in mm. SE=Standard Error (Sponsor's tables 4.1.5.5 and 4.1.5.6, Appendix 15.9.2)

Visit	Treatment duration	Meloxicam suspension		Meloxicam tablets	
		Disease activity	N	Disease activity	N
2	Baseline	2.5 ± 0.7	142	2.4 ± 0.6	144
3	2 weeks	2.1 ± 0.8	142	2.0 ± 0.8	144
4	4 weeks	1.9 ± 0.9	142	1.9 ± 0.8	144
5	6 weeks	1.8 ± 0.9	142	1.8 ± 0.9	144
Differences from last value to baseline		-0.7 ± 0.8	142	-0.6 ± 1.0	144

C. Efficacy Conclusions

- There were no significant differences between the two meloxicam treatments with respect to the primary efficacy endpoint: patient's assessment of pain on active movement.

- There was no significant difference between treatment groups with respect to the improvement of the secondary variables pain at rest, Lequesne index for hip and knee, disease activity assessed by the patient and the investigator, tenderness, redness and swelling of the target joint.
- Different number of patients (8.5% in suspension group and 4.9% in the tablet group) withdrew due to lack of efficacy. This difference did not reach a statistical significance.

The trial design itself, with only a single primary endpoint, its short duration and lack of placebo arm, precludes the reviewer from making a definite conclusion about the efficacy of meloxicam suspension. However, the fact that both treatment groups seem to be similar with respect to trial endpoints is reassuring and support the oral suspension's comparable efficacy to the tablet formulation.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

The safety of meloxicam in treating patients with the signs and symptoms of OA has been evaluated during the review of NDA 20-938 (Mobic 7.5 mg and 15 mg tablets, April 2000). Additionally, the sponsor has provided a safety summary including all safety data on completed and preliminary studies not included in the original tablet NDA 20-938 or supplements.

Three adult pharmacokinetic trials (107.172, 107.243, 107.254), one phase III adult trial (107.179), one pediatric Phase I/II trial (107.162) and two Phase III pediatric trials (107.208, 107.235) have been or are currently being conducted using the oral suspension. The overall safety profile seen in the trials with meloxicam oral suspension is comparable to that of meloxicam tablets. The types of events seen were also comparable to those seen in trials with meloxicam tablets.

C. Description of Patient Exposure

There have been three Phase I pharmacokinetic trials in healthy adult volunteers conducted to date with Mobic oral suspension (107.172, 107.243, 107.254). These trials included a total of 66 subjects exposed to Mobic oral suspension with doses ranging from 7.5 to 22.5 mg of meloxicam. The mean duration of exposure in these trials was 4 days, with a minimum of one and a maximum of 14 days.

The Phase III adult trial (107.179) included 286 patients, 142 treated with meloxicam suspension 7.5 mg once daily and 144 patients treated with meloxicam tablets 7.5 mg once daily. The mean time on drug was 38 days for the suspension and 39 days for the tablets with a median of 42 days for both drugs.

D. Methods and Specific Findings of Safety Review

There were no studies specifically conducted to assess safety.

Overall adverse events were combined and summarized for the adult Phase I trials (107.172-meloxicam oral suspension 15 mg or meloxocam tablets 15 mg; 107.243-meloxicam oral suspension 7.5-22.5 mg; 107.254- meloxicam oral suspension 7.5-22.5 mg). The most common types of events reported by system organ class were gastrointestinal disorders (19.7%), nervous system disorders (18.8%), and general disorders (9.1%). There was no difference across the dose groups in the incidence of these events.

In the adult OA trial 107.179 (meloxicam oral suspension 7.5 mg and meloxicam tablets 7.5 mg), the most common classes of adverse events reported were gastrointestinal disorders (28.5% tablet, 35.9% suspension), body as a whole disorders (16.0% tablet, 17.6% suspension) and central and peripheral nervous system disorders (16.7% tablet, 15.5% suspension). The majority of adverse events were reported to be mild or moderate. No GI perforation, ulcers, or bleeding were reported in either group.

In trial 107.179 elderly patients (>65 years of age) constituted the major proportion of patients in both treatment groups (suspension 54%, tablets 55%). The incidence of overall AEs and GI AEs was comparable for both the subpopulation of elderly patients and the younger subpopulation (<65 years). No effect of gender on the adverse event profile was observed.

No serious adverse events (SAE) were reported in Phase I adult trials with meloxicam oral suspension. One SAE leading to death (exacerbation of cardiac failure) occurred nine weeks after trial discontinuation in the Phase III adult OA trial 107.179. The event appeared to be unrelated to trial medication.

In adult trial 107.179 there were 4 cases of AST or ALT elevations >1.2 but <2 x ULN in meloxicam suspension group (where baseline values were above ULN) and 3 cases of ALT elevation >1.2 but <2 x ULN in tablets group (with 2 cases of baseline values above ULN).

E. Postmarketing data on meloxicam suspension

Mobic oral suspension has received an approval in twenty five countries as of January 15, 2003. Four cases of spontaneous adverse events were reported and included with the current submission. Those narratives were reviewed and seemed not to be related to study medication.

VIII. Use in Special Populations

There were no additional studies done in special population

C. Evaluation of Pediatric Program

The pediatric data included with this submission is preliminary and will not be reviewed here. Pediatric studies using the oral suspension formulation have been addressed in separate proposals in conjunction with the rheumatoid arthritis (RA) supplement (NDA 20-938/S004). Because the pediatric suspension and the oral suspension formulation under this review are identical, the requirement to provide pediatric information for the present NDA is waived.

IX. Conclusions and Recommendations

A. Conclusions

The Sponsor established the bioequivalence of meloxicam oral suspension 7.5 mg/5 ml to meloxicam tablets 7.5 mg and 15 mg (approved formulation). Data from trial 107.179 was submitted as supportive and suggested that meloxicam oral suspension 7.5 mg once daily was equally effective to meloxicam tablets 7.5 mg once daily in patients with osteoarthritis of the knee and hip. The safety data did not produce additional safety concerns.

B. Recommendations

This reviewer recommends an approval of meloxicam oral suspension 7.5 mg/5 ml for the treatment of the signs and symptoms of osteoarthritis.

The label has been agreed to with the Sponsor and included in Appendix #1.

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