CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
BPCA SUMMARY REVIEW

NDA 21-530/20-938

Brand Name:	Mobic® Oral Suspension
Generic Name:	Meloxicam
Dosage Form:	Oral Suspension
Dosage Strength:	7.5 mg/5 mL
Indication:	For relief of the signs and symptoms of pauciarticular or polyarticular Juvenile Rheumatoid Arthritis in patients 2 years of age and older
NDA Type:	Efficacy Supplement Pediatric Written Request
Sponsor:	Boehringer Ingelheim
Primary Reviewer:	Chandra S. Chaurasia, Ph.D.
Pharmacometric Reviewer:	Dakshina Chilukuri, Ph.D.
Pharmacometric Team Leader:	Jogarao Gobburu, Ph.D.
Deputy Director:	Arzu Selen, Ph.D.

EXECUTIVE SUMMARY

Mobic® contains the active ingredient meloxicam, a non-steroidal, anti-inflammatory agent. It is available as a tablet for oral administration containing 7.5 mg or 15 mg meloxicam (NDA 20-938), and as an oral suspension containing 7.5 mg meloxicam per 5 mL (NDA 21-530). Mobic is approved in the U.S. for relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) in the adults.

The Sponsor has submitted this supplemental NDA in response to a Pediatric Written Request.

The JRA development program consisted of 3 clinical trials (involving 470 JRA patients) conducted using the meloxicam oral suspension formulation 7.5 mg/5 mL. The Sponsor conducted two PK studies 107.162 and 107.235 to investigate the pharmacokinetics, safety, and efficacy of meloxicam suspension in patients aged 2 to 16 years with Juvenile Rheumatoid Arthritis. Study 107.162 was a single-dose study involving administration of 0.25 mg/kg meloxicam suspension to a total of 18 patients - 7 in the age group of 2-6yrs and 11 in the age group of 7-16 yrs. Study 107.235 was a multiple dose (0.375 mg/kg daily for 12 weeks) steady-state study, in 28 patients with JRA - 5 in the age group of 2-6 yrs and 23 in the 7-16 yrs age group. A supportive clinical efficacy trial (study #107.208) in JRA patients was conducted that included the 0.125 mg/kg once daily dosing regimen.

The meloxicam PK profiles, in general, were comparable within the age groups of 2-6 and 7-16 yrs, for both the single and multiple dose studies.

Meloxicam is recommended by the sponsor to be administered once daily to pediatric JRA patients 2-17 years of age with the lowest starting dose of 0.125 mg/kg. The dose may be increased to 0.25 mg/kg for additional benefit in some patients with a maximum daily dose not to exceed 15 mg.

The 0.25 mg/kg and 0.375 mg/kg dose used in the PK trials of this submission correspond to 15 mg and 22.5 mg dose for an average normal adult population. To estimate the meloxicam exposure in pediatric population at the 0.125 mg/kg dose, the Sponsor simulated meloxicam concentrations for this dose utilizing the PK data obtained from 0.25 mg/kg and 0.375 mg/kg dosing in the pediatric patients. It is noted that the Sponsor did not collect any PK data at 0.125 mg/kg dose in the JRA patients.

A summary of the pediatric clinical pharmacology study results are provided below:

A similar trend was observed in the meloxicam plasma concentration-time profiles between the two pediatric age groups (2-6 years and 7-16 years) following the administration of 0.375 mg/kg for 12 weeks and those observed after a single dose of 0.25 mg/kg meloxicam dose. Systemic meloxicam exposures were lower in the younger patients than the older pediatric patients. The mean steady-state Cmaxss and AUCss meloxicam values were 24.2% and 37.7% lower, respectively, in younger children (2-6 years) as compared to the older children (7-16 years). A similar trend was seen with Cminss. Following the administration of a single 0.25 mg/kg of meloxicam suspension, the mean apparent oral clearance of meloxicam was 2.5 mL/min in the younger group and was 30.6% lower in comparison to the mean apparent oral plasma clearance (3.6 mL/min) in the older age group. The mean body-weight normalized meloxicam apparent oral clearance values were 0.168 mL/min/kg for the younger group and 0.117 mL/min/kg for the older group. This approximate 30% difference in body-weight normalized apparent oral clearance values is consistent with the approximate 30% difference in the meloxicam systemic exposure observed between the younger and the older pediatric patients.

The mean apparent volume of distribution was also about 29% lower in the younger age group, 2.87 L compared with 4.07 L in the older children. This may be due to the lower body-weight of the younger patients compared to the older pediatric patients with mean (range) body-weight values of 15.6 kg (12.5 to 22.0) and 34.0 kg (19.5 to 50.3), respectively.

In addition, , since there was a high correlation between the meloxicam apparent volume of distribution and apparent oral plasma clearance, further analysis of meloxicam apparent oral distribution volume was considered to be of limited value and hence, was not pursued.

During repeated dosing, the steady-state terminal elimination half-life for meloxicam was about 28% lower in the younger age group (11.3 hr) as compared to the older age group (15.7 hr).

Based on the population PK analysis, the typical meloxicam apparent oral clearance (CL/F) value of a 34 kg pediatric patient is 0.287 L/h and it increases with increasing body-weight by 2 % per kg body weight. The typical V/F value of a 34 kg pediatric patient is 6.2 L and similarly, it increases with increasing body-weight by 2.5 % per kg body weight.

In this submission, while some differences were noted in the meloxicam apparent oral clearance values, overall, meloxicam apparent oral clearance values in the younger and the older pediatric patients were comparable to those seen in adults.

As evident in the results of the exposure-efficacy and exposure-safety evaluations carried out in OCPB for this review, although there is a 30% decrease in exposure in the pediatric patients 2-6 years of age compared to the patients 7-16 years, there is no need to adjust meloxicam dose based on age. This is also consistent with the information from literature. The concentrations observed in this study are well above the 50% inhibitory concentration (IC50) reported for basal and stimulated COX activity in human synovial cells 11.8 ng/mL and 0.7 ng/mL, respectively ***(F. Lapicque et al. Clin. Pharmacokinet. 2000 Nov. 39(5): 369-382)***. In addition, even in adult patients (18 to 80 year old) with RA where age and gender effects were noted as covariates affecting clearance, gender differences were attributed to differences in body-weight and age related dose-adjustment of less than 10% was deemed unnecessary ***(I. Meineke and D. Turck, Br. J. Clin. Pharmacol. 2003, 55: 32-38)***. The advanced age and female gender were associated with a decrease in meloxicam clearance and increased body-weight with increasing meloxicam clearance.

Meloxicam dosing for pediatric patients as proposed in the label (0.125 mg/kg - 0.25 mg/kg once daily) will result in comparable steady-state exposure as obtained in adults at dose levels of 7.5 and 15 mg. The concentration-time profiles generated by the sponsor for the 0.125 mg/kg dose using population PK modeling and subsequent simulation are acceptable.

Meloxicam is recommended by the sponsor to be administered to pediatric patients 2-17 years of age with the lowest starting dose of 0.125 mg/kg. The dose may be increased to 0.25 mg/kg for additional benefit in some patients. Based on the effectiveness analysis conducted by the Pharmacometrics Reviewer, it appears that the response is at the plateau of the dose-response curve (Figure 1). The effectiveness of meloxicam appears to improve as time progresses and increased effectiveness is seen in patients who receive the drug for 12 weeks (Figure 1). There is no evidence of a relationship between the age of the patients and the effectiveness of meloxicam (Figure 2). There is no evidence of a relationship between meloxicam dose and gastrointestinal adverse events (Figure 3).

Figure 1: Observer responder rates (ACR pediatric 30) at Week 4 (open bars) and Week 12 (closed bars) per treatment groups for integrated trials 107.235 and 107.208

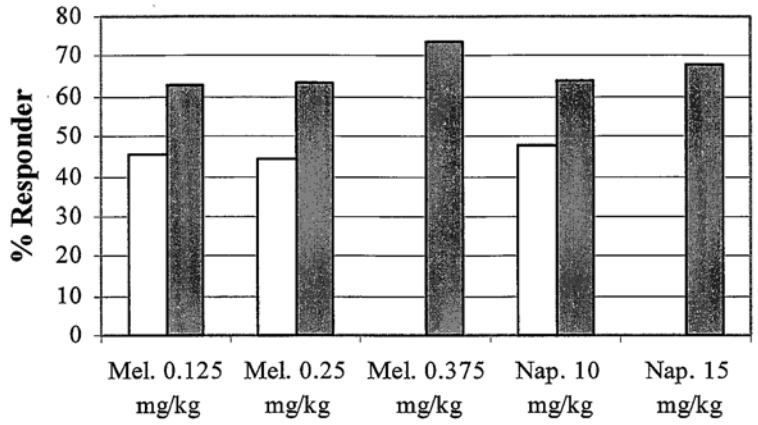


Figure 2. Relationship between ages of patients enrolled in the clinical trials and the treatment outcome

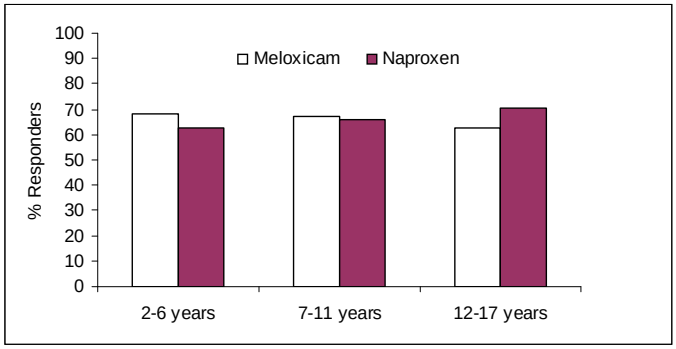
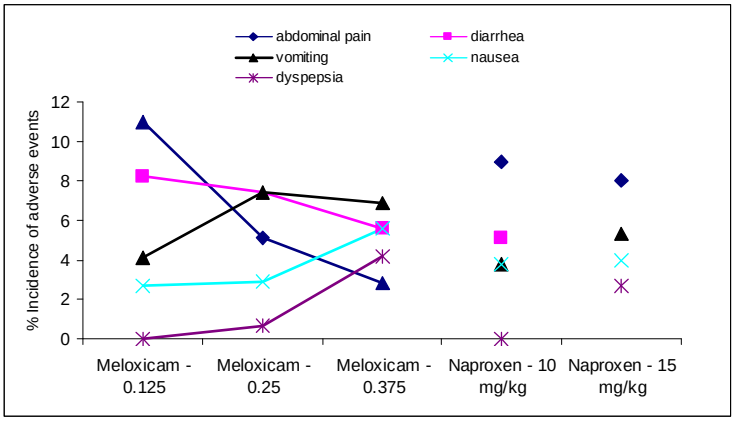


Figure 3: Incidence of GI-related adverse events across various meloxicam dose groups



Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the supplement NDAs 20-938 and 21-530. The information submitted is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

The proposed labeling recommendations in Section 3 should be communicated to the Sponsor as appropriate.

Phase IV Commitments: None requested from Clinical Pharmacology and Biopharmaceutics perspectives.

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Deputy Director
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CC: NDA 21-530/20-938, HFD-170 (C. Markos), HFD-880 (J. Lazor, A. Selen, J. Gobburu, D. Chilukuri, C. Chaurasia, A. Noory)

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/s/

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