

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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DATE: July 12, 2006

TO: Lisa L. Mathis, M.D., OND Associate Director
Pediatric and Maternal Health Team
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Gita Akhavan-Toyserkani, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
for
Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Mobic[®] (meloxicam, NDA# 20-938, 21-530)
Pediatric Exclusivity Approval Date: April 12, 2005

1. Executive Summary

The Adverse Event Reporting System (AERS) database was searched for reports of adverse events (serious and non-serious) occurring with the use of meloxicam in pediatric patients. From the date of FDA approval, 4/13/2000, to the "data lock" date of 5/12/2006, AERS contained 1416 cases for meloxicam (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric cases represent approximately 0.5% of the total (7/1416).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, April 12, 2005 to May 12, 2006. We used an AERS data lock date of 5/12/2006, to allow time for reports received up to 4/12/2006, to be entered into AERS. During the first 13 months after pediatric exclusivity was granted, AERS received a total of 297 cases (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). We will refer to this 13-month interval as the

pediatric exclusivity period in the remainder of this review. The AERS search did not retrieve any pediatric cases reported during the one year pediatric exclusivity. Given that there were no pediatric cases reported during the pediatric exclusivity period, we reviewed all pediatric cases reported from time of marketing approval.

Between the marketing approval date (4/13/2000) and the data lock date of May 12, 2006, AERS contained seven pediatric cases associated with meloxicam, including two duplicate cases. There were no pediatric deaths associated with meloxicam reported during this period. Of the five unduplicated reports, three were serious non-fatal reports to include one report of disability and two reports of hospitalization.

The first of the three serious cases reported Bell's palsy involving a 15-year-old male patient who ingested one dose of meloxicam for hip pain secondary to sport injury. The second case reported gastroesophageal reflux and sleep apnea involving an infant (approximately 2-months-old) with a history of in utero exposure during the third trimester. Meloxicam is a Pregnancy Category C drug. The third serious report is a foreign case and involves a suicide attempt of a 15-year-old with multiple medications, including meloxicam. The two remaining cases reported non-serious labeled adverse events, including dizziness and urticaria. In the case of urticaria, it is very likely that the adverse event was related to meloxicam. In the other four cases, it is not clear if the adverse event is directly related to meloxicam, but an association between meloxicam and these adverse events cannot be excluded.

In conclusion, there were no reports of adverse events associated with meloxicam in pediatric patients occurring during the pediatric exclusivity period. Since drug approval, there were five pediatric adverse event reports in the AERS database for Mobic, but no safety signals unique to the pediatric population were identified in the review of these cases. The Division of Drug Risk Evaluation (DDRE) will continue to routinely monitor reports of adverse events with the use of meloxicam in pediatric patients.

2. Products, Indications, Pediatric Labeling, and Pediatric Filing History

2.1 Meloxicam Products

Meloxicam is supplied in the U.S. as:

Tablet for oral administration containing 7.5 mg or 15 mg meloxicam and as an oral suspension containing 7.5 mg meloxicam per 5 ml

2.2 Meloxicam Approved indication

Meloxicam is approved for the following indications:

MOBIC is indicated for relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

MOBIC is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course of Juvenile Rheumatoid Arthritis in patients 2 years of age and older.

2.3 Meloxicam Pediatric Labeling

The labeling for meloxicam includes the following information concerning pediatric patients:

Special Populations, *Pediatric:*

After single (0.25 mg/kg) dose administration and after achieving steady-state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2-6 years old) as compared to the older patients (7-16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg (see DOSAGE AND ADMINISTRATION). The meloxicam mean (SD) elimination half-life was 15.2 (10.1) and 13.0 hours (3.0) for the 2-6 year old patients, and 7-16 year old patients, respectively. The pharmacokinetics of MOBIC in pediatric patients under 2 years of age have not been investigated.

Clinical Trials:

The use of MOBIC for the treatment of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older was evaluated in two 12-week, double-blind, parallel-arm, active-controlled trials. Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam dosing began at 0.125 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and naproxen dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 mg/kg/day (22.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR Pediatric 30 responder definition, a composite of parent and investigator assessments, counts of active joints and joints with limited range of motion, and erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

Indications and usage:

MOBIC is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course of Juvenile Rheumatoid Arthritis in patients 2 years of age and older.

Precautions, *Pediatric use:*

The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials (see CLINICAL TRIALS, ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION sections).

Adverse Reactions, *Pediatrics*:

Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to MOBIC with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12-week multicenter, double-blind, randomized trials (one with a 12-week open-label extension and one with a 40-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with MOBIC were similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events, abdominal pain, vomiting, diarrhea, headache, and pyrexia, were more common in the pediatric than in the adult trials. Rash was reported in seven (<2%) patients receiving MOBIC. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect.

2.4 Pediatric Filing History

A formal Written Request (WR) for pediatric studies of meloxicam was issued to Boehringer Ingelheim Pharmaceutical, Inc. on November 22, 2004. The sponsor completed the following studies:

- Pharmacokinetic studies of meloxicam in patients with Juvenile Rheumatoid Arthritis (JRA)
- Clinical safety and efficacy studies of meloxicam in patient with JRA

These studies fulfilled the requirements of the WR and the pediatric exclusivity was granted on April 12, 2005. A supplemental new drug application was submitted on February 18, 2005 to provide for the use of meloxicam tablets and oral suspension for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patient 2 years of age and older. This application was approved on August 11, 2005.

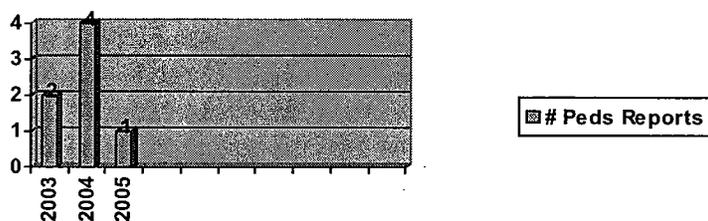
3. AERS Search Results: Meloxicam

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts ¹ of AERS Reports for All Sources from Marketing Approval Date (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	1095 (437)	867 (236)	138 (23)
Pediatrics (0-16 yrs.)	7 ³ (4)	4 (1)	0 (0)
Age unknown (Null values)	314 (212)	191 (91)	36 (7)
Total	1416 (653)	1062 (328)	174 (30)

¹ May include duplicates.
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.
³ Crude counts. Actual number after removing duplicates is 5.

Figure 1: Reporting trend for pediatric reports from approval date



3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts ¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	213 (92)	201 (81)	26 (5)
Pediatrics (0-16 yrs)	0	0	0
Age unknown (Null Values)	84 (38)	80 (34)	16 (0)
Total	297 (130)	281 (115)	42 (5)

¹ May include duplicates
² Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

4. Postmarketing Review of All Pediatric Adverse Event Reports received during the one-year after a drug receives pediatric market exclusivity.

There were no pediatric reports received during the 1 year post-pediatric exclusivity period.

5. Postmarketing Review of All Pediatric Adverse Event Reports received between the drug approval and May 12, 2006.

Between the marketing approval date (4/13/2000) and the data lock date of May 12, 2006, AERS contained seven pediatric cases associated with meloxicam, including two duplicate cases. There were no pediatric deaths associated with meloxicam reported during this period.

Of the five unduplicated reports, three were serious non-fatal reports to include one report of disability and two reports of hospitalization. The first of the three serious cases reported Bell's palsy involving a 15-year-old male patient who ingested one dose of meloxicam for hip pain secondary to sport injury. The second case reported gastroesophageal reflux and sleep apnea involving an infant (approximately 2-months old) with a history of in utero exposure during the third trimester. Meloxicam is a Pregnancy Category C drug. The third serious report is a foreign case and involves a suicide attempt of a 15-year-old with multiple medications, including meloxicam. The

two remaining cases reported non-serious labeled adverse events, including dizziness and urticaria. In the case of urticaria, it is very likely that the adverse event was related to meloxicam. In the other four cases, it is not clear if the adverse event is directly related to meloxicam, but an association between meloxicam and these adverse events cannot be excluded.

5.1 Case Characteristics¹:

Table 3 describes the characteristics of 5 pediatric cases reported between time of approval and May 12, 2006.

Table 3 : Characteristics of pediatric cases reported from time of approval (April 13, 2000 through May 12, 2006) n=5	
Gender [n=5]	Male: 3 Female: 2
Age [n=4]	6-11 yrs:1 12-16 yrs:3 Mean: 13.5; Median: 14.5; Range: 10-15
Origin [n=5]	US: 3 Foreign: 2
Event date (n=4)	2002: 1 2003: 2 2004: 1
Daily dose [n=3]	7.5mg once daily
Indications [n= 5]	Shoulder pain: 1 Back pain: 1 Hip pain secondary to sport injury: 1 Pauciarticular JRA: 1 Suicide intent: 1
Outcomes [n=5]	Hospitalization: 2 Disability: 1 Other: 2

6. Summary/Recommendations

In summary, there were no reports of adverse events associated with meloxicam in pediatric patients occurring during the pediatric exclusivity period. Our search of the AERS database did not identify any pediatric death reports. Our search did identify five unduplicated pediatric meloxicam cases reported to the Agency since drug marketing in 2000. The five cases reported Bell's palsy, suicide attempt, gastroesophageal reflux/sleep apnea, urticaria, and dizziness. Given the limited number and clinical information of these cases, we could not identify safety signals specific for the pediatric population. DDRE will continue to routinely monitor reports of adverse events with the use of meloxicam in pediatric patients.

¹ See Appendix 1 for narratives of the five cases.

Gita Akhavan-Toyserkani, Pharm.D.
Safety Evaluator

Concur:

Lauren Lee, Pharm.D.
Team Leader

Appendix 1

AERS ISR # 4364128-7, U.S., 2004

A physician reported a 15-year-old male patient began a sample of Mobic 7.5 mg (lot number 242185N) daily on February 26, 2004 for right groin, hip pain, and back contusion, all secondary to sports. On _____ after one dose of Mobic, the patient developed Bell's palsy on the left side of his face. He presented to the emergency room where he was observed and treated with antivirals and steroids. A nerve conduction velocity (NCV) test and an MRI were completed. The patient has not yet recovered. The patient was not on any other medications and has no history of allergies or any other medical problems.

AERS ISR # 4490016-1, Mexico, 2004

A report was received October 14, 2004 from an unspecified reporter concerning a male patient born in August 2004 who was exposed to Mobic during pregnancy. The patient's mother was on Mobic during her last trimester for back pain (dosage was not reported). After birth, the newborn was diagnosed with gastroesophageal reflux that needed treatment. On an unspecified date, the newborn experienced sleep apnea that required hospitalization. The patient recovered after one week and was discharged from the hospital.

AERS ISR # 4281869-0, Germany, 2004

A report received from a physician regarding a 15-year-old female who was hospitalized on _____ for attempted suicide by ingesting unknown quantities of glyburide, reserpine, flunitrazepam, biperiden, tramadol, digoxin, levothyroxine, and Mobic. The patient received medicinal coal and sodium sulfate for treatment of drug intoxication. The patient completely recovered from the events of suicide intent. It was not reported if any of the drugs in the report were regularly prescribed for the patient. It was not reported if the patient had a history of prior psychiatric disease or history of suicide.

AERS ISR # 4111724-8, U.S., 2003

A report was received from a physician regarding a 10-year-old female patient who was initiated Mobic 7.5 mg daily on January 9, 2003 for JRA. On January 17, 2003, the patient developed dizziness at school and bumped into a door. The patient's mother noted that the patient was being taken off of Dexedrine spansule, considered to be an alternate suspect drug, for ADD, at the time and that the event could have been attributed to that. Flonase was also reported as a concomitant medication. The patient did not have any known drug allergies. The patient had returned to baseline one month after the reported event. Mobic therapy was continued.

AERS ISR # 4057718-2, U.S., 2003

A report was received from a physician regarding a 14-year-old female patient who was initiated on Mobic 7.5 mg tablets daily on December 4, 2002 for the treatment of shoulder pain. On December 9, 2002, the patient developed hives on her feet. The patient was treated with topical benadryl and a topical over the counter anti-inflammatory. Mobic therapy was discontinued on 12/9/2002 and patient recovered from the event. The patient was not on any other medications at the time of the event.

Appendix 2

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

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/s/

Gita Akhavan-Toyserkani
7/18/2006 02:40:41 PM
DRUG SAFETY OFFICE REVIEWER

Rosemary Johann-Liang
7/20/2006 01:31:41 PM
MEDICAL OFFICER