BPCA SUMMARY OF MEDICAL REVIEW

PRODUCT: Mobic (meloxicam Tablets) 7.5 mg and 15 mg
Mobic (meloxicam) Oral Suspension 7.5 mg/5 mL

NDA: 20-938 (S-013)
21-530 (S-001)

SPONSOR: Boerhinger Ingelheim Pharmaceuticals, Inc.

INDICATION: Relief of the Signs and Symptoms of Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis in Patients 2 Years of Age and Older

SUBMISSION DATE: February 18, 2005

1 SUMMARY

1.1 Recommendation on Regulatory Action

With this submission, Boehringer Ingelheim is seeking approval for Mobic (meloxicam) Tablets 7.5 mg and 15 mg and Oral Suspension 7.5 mg/5 mL administered once daily for the treatment of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis (JRA) in pediatric patients ages 2 and older. Mobic is approved in the U.S. for the relief of the signs and symptoms of osteoarthritis (OA) and adult rheumatoid arthritis (RA). Establishing efficacy in JRA for meloxicam is based on having demonstrated efficacy in adult RA with confirmatory evidence in active-controlled clinical trials of JRA. The Sponsor has submitted this supplemental NDA in response to a Pediatric Written Request (WPR) dated Nov 22, 2004. The studies in the pediatric program were performed in response to and in accordance with the WR.

In this submission, the Sponsor provided adequate evidence of efficacy of meloxicam 0.125 mg/kg/day for the treatment of the signs and symptoms of JRA. Meloxicam 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.

The higher meloxicam doses, 0.250 mg/kg/day and 0.375 mg/kg/day, did not demonstrate any additional efficacy. Experience with NSAIDs, and though this particular dataset from JRA trials did not raise safety concerns, previous safety concerns raised during reviews of adult OA and RA trials cannot be disregarded.

There were no unexpected findings in the safety database. There were also no dose-related differences in the frequency of adverse events across the meloxicam doses. following exposure in a larger number of patients with JRA. Experience with NSAIDs informs us that there are generally dose-related increases in toxicity. Taking this into consideration, along with the failure to demonstrate any consistent trend favoring efficacy in doses of meloxicam greater than 0.125 mg/kg/day, the logical conclusion is that 0.125 mg/kg/day, up to a maximum of 7.5 mg, is the appropriate dose

1.2 Recommendation on Postmarketing Actions

The Sponsor should to continue to report postmarketing safety data including use in the pediatric population.

1.3.1 Brief Overview of Clinical Program

Two clinical efficacy studies were submitted in support of the JRA indication. Both studies were double blind, three-arm active controlled (two dosages of meloxicam and one dosage of naproxen) of three or more months duration evaluating the efficacy, safety and dose response of meloxicam oral suspension in pauci- and polyarticular JRA patients. In addition, PK study 107.168 was also included with this submission to provide additional data on safety.

1.3.2 Efficacy

In Trial 107.235, meloxicam, at doses of 0.125 titrated to 0.25 mg/kg/d (meloxicam L) and 0.25 titrated to 0.375 mg/kg/d (meloxicam H), was comparable to treatment with the active comparator naproxen, administered 5 mg/kg twice daily titrated to 7.5 mg/kg twice daily, based on the primary efficacy endpoint, the ACR Pediatric 30 responder rate. The ACR Pediatric 30 responder rates at Week 12 (%, 90% confidence interval) were 73.6% (63.4, 83.8) for the meloxicam H treatment group, 69.4% (57.9, 80.8) for the meloxicam L treatment group, and 68.0% (57.4, 78.6) for the naproxen treatment group. The efficacy response demonstrated during the 12-week, double-blind phase was sustained during the 12-week open-label extension.

Subgroup analyses did not demonstrate any effects on the response to treatment for type of arthritis course, age, gender, nor MTX usage.

Assessment of the individual components of the ACR core set parameters revealed that the number of joints with active arthritis and investigator's global assessment of overall

disease activity had the highest proportion of responders for each of the treatment groups. The only core set parameter that did not change substantially over the 12-week course of treatment for each of the groups was the ESR. All other individual core set parameters demonstrated improvement over the 12 weeks of therapy for all groups.

Additional secondary endpoints assessed showed improvement for all treatment groups without significant difference between the meloxicam groups and naproxen group.

In Trial 107.208, meloxicam 0.125 mg/kg/d and 0.25 mg/kg/d were comparable to treatment with naproxen 10 mg/kg/d after 12 weeks of treatment based on the primary efficacy endpoint of the ACR Pediatric 30 responder rate. The Pediatric ACR responder rate (%, 90% confidence interval) for the two meloxicam doses was 63.0% (51.9, 74.1) and 58.1% (46.9, 69.4) for 0.125 mg/kg/d and 0.25 mg/kg/d, respectively, compared to 64.1% (53.5, 74.8) for the naproxen group. The efficacy response demonstrated during the first 12 weeks was sustained during the 40-week, double-blind extension for all three treatment groups.

1.3.3 Safety

The meloxicam JRA development program included an overall total of 378 patients with pauci- and polyarticular course JRA treated with meloxicam in the three clinical trials: 107.235, 107.208, and 107.162.

The safety profile of meloxicam was comparable to that of naproxen over the course of these trials. Adverse events were representative of those expected in a pediatric JRA population. Analysis of AEs by subgroup including age, gender, concomitant use of methotrexate, race, and disease course (pauci- and polyarticular), did not reveal any differences between the meloxicam- and naproxen-treated groups.

Analysis of the safety profile for those patients treated in the trials (either double-blinded or open-labeled) for up to 1 year did not suggest any duration–associated qualitative differences in the AE profile (compared to the short-term data). Assessment for possible growth and development-related adverse events or weight change over time for up to 1 year of treatment did not suggest that meloxicam or naproxen has a significant negative effect on growth and development.

1.3.4 Dosing Regimen and Administration

The meloxicam doses selected for study in the JRA clinical program were derived from the experience with adult doses (7.5 mg, 15 mg and 22.5 mg per day) which had been shown to be effective in rheumatoid arthritis in two 12-week, placebo-controlled trials. Based on a 60 kilogram adult, the adult doses discussed above translate on a mg/kg basis to the following pediatric doses: 0.125 mg/kg/d (7.5 mg/d), 0.25 mg/kg/d (15 mg/d), and 0.375 mg/kg/d (22.5 mg/d)

Based on the PK data, meloxicam oral suspension exposure with 0.125 mg/kg/d, 0.25 mg/kg/d, and 0.375 mg/kg/d in children are comparable to the exposure seen in adults dosed once a day with 7.5 mg, 15 mg, and 22.5 mg meloxicam.

Bioequivalence of the oral suspension to the tablets was established during the adult development program. Therefore, both tablets and oral suspension are approved for use under this application.

The recommended dosing of meloxicam for relief of the signs and symptoms of pauciarticular and polyarticular juvenile rheumatoid arthritis in patients 2 years of age and older is 0.125 mg/kg/d up to a maximum of 7.5 mg.

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Sharon Hertz

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