DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Jeffrey R. Snyder
Associate Director
Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

RE: NDA 20-938
Mobic (meloxicam) Tablets, 7.5 mg and 15 mg
MACMIS ID #10563

Dear Mr. Snyder:

This letter notifies Boehringer Ingelheim Pharmaceuticals Inc. (BI) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has identified promotional activities that are in violation of the Federal Food, Drug, and Cosmetic Act (Act) and its implementing regulations. Specifically, false or misleading statements about Mobic (meloxicam) Tablets have been disseminated in a direct-to-consumer (DTC) print advertisement (ad) appearing in daily newspapers including *The Washington Post* and *The New York Times*. Our specific objections follow.

Misleading Comparative Claim

Attention Vioxx®

and Celebrex® Users:

ARE YOU

DISSATISFIED?

If so, ask your doctor about MOBIC.

It's the osteoarthritis medicine with proven safety and efficacy used

by 45 million patients in 100 countries for over five years.

The print ad is misleading because it suggests that Mobic is safer and more effective for the treatment of the signs and symptoms of osteoarthritis than has been demonstrated by substantial evidence. See 21 CFR § 202.1(e)(6)(ii). The ad, with the above headlines dominating almost half of the full-page newspaper piece, is targeted to Vioxx and Celebrex users, and seeks to direct them to Mobic if they are dissatisfied with these other prescription non-steroidal anti-inflammatory drug products (NSAIDs). In the context of this presentation, the rhetorical question "Are You Dissatisfied?" implies clinical superiority of Mobic compared with Vioxx or Celebrex in osteoarthritis. In addition, the above call-out headlines followed by the broad "used by 45 million patients" safety and efficacy claim implies that Mobic is superior to other prescription NSAIDs. FDA is not aware of any studies comparing Mobic to other prescription NSAIDs for osteoarthritis. Therefore, this ad presentation is in violation of the Act because it makes unsubstantiated and hence misleading comparative safety and efficacy claims.

Furthermore, the claim "It's the osteoarthritis medicine with proven safety and efficacy used by 45 million patients...." contains unsubstantiated statistics and consequently misleading claims about the international use of Mobic for osteoarthritis. See 21 CFR § 202.1(e)(6)(x). BI has advised us that the reference in the advertisement to "data on file" ("Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.") is an editorial in a supplement to the journal *Inflammation Research* (*Inflamm Res* 2001; 50 Suppl 1:S3-4.). Also in response to our request, BI provided [ ] data from the Mobic Supplemental Application to NDA 20-938 (dated [ ] For several reasons, the editorial does not substantiate the claim. First, although BI relies on the editorial's reference to global sales of meloxicam for its claim of use in "45 million patients," the editorial itself does not cite the source of the sales data for the number of patients treated with Mobic. Second, although the Mobic ad refers to the only indication approved for use in the United States—osteoarthritis—the editorial refers to numerous other conditions for which meloxicam is used internationally (i.e., an "estimated **cumulative** exposure to meloxicam globally)" (emphasis added). Third, although the Mobic claim refers to "Mobic® (meloxicam) **tablets**" (emphasis added), the editorial references other marketed dosage forms of meloxicam, e.g., ampoules, capsules, and suppositories, such that the print ad claim misleadingly inflates the actual number of Mobic 7.5 mg and 15 mg tablets used globally for osteoarthritis. For the same reason, BI's reliance upon the [ ] data for different dosage forms of meloxicam from the Mobic Supplemental Application to NDA 20-938 (dated [ ] is not sufficient to support the [ ] claim.

Minimization of Risk Information

Promotional materials for prescription drugs may be false or misleading, and lacking in fair balance if they fail to present information relating to the risks associated with the use of the drug with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug (21 CFR §202.1(e)(7)(viii)). The efficacy claims in the Mobic ad are presented in terminology that can be understood by the typical consumer, which encourages readability by a wide audience. However, the risk information is presented in such a manner that it may be comprehensible only to healthcare professionals, which causes the ad to be misleading because consumers are the target audience.

Specifically, the benefit information in the ad is in the prominent subheading that states, "It's the osteoarthritis medicine with proven safety and efficacy used by 45 million patients in 100 countries for over five years." As discussed in the previous section, this statement is not substantiated. The information is presented in consumer-friendly terms.

The risk information in the ad is as follows:

> "Important NSAID risk information: Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3-6 months, and in about 2-4% of patients treated for one year."

This statement fails to adequately present significant risks associated with Mobic use because the statement neither defines the term "NSAID," nor does it identify Mobic as an NSAID. The headline "Important NSAID risk information" misleadingly distinguishes Mobic to appear to be in a different and safer drug class, when in fact it is a prescription NSAID just as Vioxx and Celebrex. Further, the information discussed under the heading "Important NSAID risk information" is not presented in consumer-friendly language, particularly the terms "serious GI toxicity", "upper GI ulcers", and "gross bleeding or perforation." Because the risk presentation is not presented in consumer-friendly terms when compared to the benefit information, the ad minimizes important risk information, and is therefore misleading.

Conclusions and Requested Actions

BI should immediately cease publication and distribution of this and other similar promotional materials for Mobic that contain the same or similar claims or presentations. BI should submit a written response to DDMAC on or before November 7, 2002, describing its intent and plans to comply with the above. In its letter to DDMAC, BI should include the date on which this and other similarly violative materials were discontinued.

BI should direct its response to the undersigned by facsimile at (301) 594-6759, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications HFD-42, Rm. 8B-45, 5600 Fishers Lane, Rockville, Maryland 20857. In all future correspondence on this matter, please refer to MACMIS ID# 10563 as well as the NDA number. DDMAC reminds BI that only written communications are considered official.

Sincerely,

{See appended electronic signature page}

Christine Hemler Smith, Pharm.D.
Consumer Promotion Analyst
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christine Smith
10/24/02 02:56:57 PM

Attention Vioxx® and Celebrex® Users:

ARE YOU DISSATISFIED?

If so, ask your doctor about MOBIC.

It's the osteoarthritis medicine with proven safety and efficacy used by 45 million patients in 100 countries for over five years.[1]

mobic®

[meloxicam] tablets

Please see adjacent page for important safety information.

1-888-355-7550

www.mobictablet.com

Vioxx is a registered trademark of Merck & Co., Inc. Celebrex is a registered trademark of Pharmacia Corporation.

Important NSAID risk information: Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Reference: 1. Data on file, Boehringer Ingelheim Pharmaceuticals, Inc.

Ask your doctor if MOBIC is right for you.

Osteoarthritis Sufferers

15 DAYS FREE

mobic® [meloxicam] tablets

Prescription Required

In the Clinic: MOBIC (meloxicam) is available by prescription only. When this certificate, accompanied by a prescription from your physician, is presented at a participating pharmacy, you are entitled to up to 15 days of MOBIC 7.5 mg or 15 mg tablets.

In the Pharmacy: When this certificate is accompanied by a prescription for MOBIC (meloxicam) 7.5 mg or 15 mg tablets, it is redeemable for up to 15 tablets, one time only. No substitutions permitted. Fax copy not valid. A claim for this prescription for reimbursement under Medicaid, Medicare, or similar federal or state healthcare programs. Submit claim only to Pharmaceutical Partners Group (PPG—formerly NDS) using BIN # 610500. For pharmacy processing questions, please call 1-800-750-9825.

Important Note: Certificate valid until 12/31/02. Void where prohibited by law. Not valid if reproduced or submitted to other payers. Limit one certificate per patient. Prescription ID # required on prescription. Offer valid at participating pharmacies only. Boehringer Ingelheim Pharmaceuticals, Inc. reserves the right to rescind, revoke, or amend this offer without notice.

Boehringer Ingelheim

Issued: 6/02

Group # N152-4000 ID # MVT698664 Expiration Date: 12/31/02

mobic (meloxicam) tablets

MOBIC® (meloxicam) Tablets 7.5 mg and 15 mg
Brief Summary of Prescribing Information

INDICATIONS AND USAGE
MOBIC is indicated for relief of the signs and symptoms of osteoarthritis.

CONTRAINDICATIONS
MOBIC is contraindicated in patients with known hypersensitivity to meloxicam. It should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions, and PRECAUTIONS, Pre-existing Asthma).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation:
Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of the patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration.** For high-risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions have occurred in patients without known prior exposure to MOBIC. MOBIC should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease
In cases with advanced kidney disease, treatment with MOBIC is not recommended. If NSAID therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).

Pregnancy
In late pregnancy, as with other NSAIDs, MOBIC should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General
MOBIC cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of MOBIC in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including MOBIC. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Patients with signs and/or symptoms suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MOBIC. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), MOBIC should be discontinued.

Renal Effects
Caution should be used when initiating treatment with MOBIC in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with MOBIC. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, Advanced Renal Disease).

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of NSAIDs may cause dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The extent to which metabolites may accumulate in patients with renal failure has not been studied with MOBIC. Because some MOBIC metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including MOBIC. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including MOBIC, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

Drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving MOBIC who may be affected by this quantitative platelet dysfunction, such as those with coagulation disorders or patients in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Fluid Retention and Edema
Fluid retention and edema have been observed in some patients taking NSAIDs, including MOBIC. Therefore, as with other NSAIDs, MOBIC should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, MOBIC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Information for Patients
MOBIC, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be made aware of the importance of this follow-up (see WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation).

Patients should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS, Anaphylactoid Reactions).

In late pregnancy, as with other NSAIDs, MOBIC should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests
Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, MOBIC should be discontinued.

Drug Interactions
ACE inhibitors Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin-converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE inhibitors.

Aspirin Concomitant administration of aspirin (1000 mg TID) to healthy volunteers tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects. Concomitant administration of low-dose aspirin with MOBIC may result in an increased rate of GI ulceration or other complications, compared to use of MOBIC alone. MOBIC is not a substitute for aspirin for cardiovascular prophylaxis.

Cholestyramine Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{1/2}$ from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine Concomitant administration of 200 mg cimetidine QID did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Digoxin Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Furosemide Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with furosemide and MOBIC, patients should be observed closely for signs of declining renal function (see PRECAUTIONS, Renal Effects), as well as to assure diuretic efficacy.

Lithium In clinical trials, NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg BID with meloxicam 15 mg QD as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by MOBIC. Patients on lithium treatment should be closely monitored when MOBIC is introduced or withdrawn.

Methotrexate A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate; *in vitro*, methotrexate did not displace meloxicam from its human serum binding sites.

Warfarin Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing MOBIC therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding. The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.9. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the average anticoagulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering MOBIC with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryolethality at oral doses ≥ 1 mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

Pregnancy
Teratogenic Effects: Pregnancy Category C. Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 50 mg/kg/day (64.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryolethality at oral doses ≥ 5 mg/kg/day (5.4-fold the human dose, as noted above) when rabbits were treated throughout organogenesis. Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis. An increased incidence of stillbirths was observed when rats were given oral doses ≥ 1 mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. MOBIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

area conversion) when rats were treated during the [illegible] period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

Labor and Delivery
Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, increased length of delivery time, and delayed parturition at oral dosages ≥ 1 mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages ≥ 0.125 mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

Nursing Mothers
Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from MOBIC, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients under 18 years of age have not been established.

Geriatric Use
As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

ADVERSE REACTIONS
The MOBIC phase 2/3 clinical trial database includes 10,122 patients treated with MOBIC 7.5 mg/day and 3,595 patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control.

The following adverse events (%) occurred in ≥ 2% of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=156) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial: abdominal pain, 1.9%, 2.6%; diarrhea, 7.8%, 3.2%; dyspepsia, 4.5%, 4.5%; flatulence, 3.2%, 3.2%; nausea, 3.9%, 3.8%; accident household, 4.5%, 3.2%; edema[1], 1.3%, 2.6%, 3.8%; headache, 7.6%, 3.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash[2], 2.6%, 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in ≥ 2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.7%, 4.1%; constipation, 0.8%, 1.8%; diarrhea, 1.9%, 5.9%; dyspepsia, 3.8%, 8.9%; flatulence, 0.5%, 3.0%; nausea, 2.4%, 4.7%; vomiting, 1.6%, 3.8%; edema[1], 0.6%, 2.4%; pain, 0.9%, 3.6%; dizziness, 1.1%, 2.4%; headache, 2.4%, 3.6%; anemia, 0.1%, 4.1%; arthralgia, 0.5%, 5.3%; back pain, 0.5%, 3.0%; insomnia, 0.4%, 3.6%; coughing, 0.2%, 2.4%; upper respiratory tract infection, 0.2%, 8.3%; pruritus, 0.4%, 2.4%; rash[2], 0.3%, 3.0%; micturition frequency, 0.1%, 2.4%; urinary tract infection, 0.3%, 4.7%.

The following adverse events (%) occurred with MOBIC 15 mg daily in ≥ 2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.3%, 2.9%; constipation, 1.2%, 2.6%; diarrhea, 2.7%, 2.6%; dyspepsia, 7.4%, 9.5%; flatulence, 0.4%, 2.6%; nausea, 4.7%, 7.2%; vomiting, 0.9%, 2.6%; edema[1], 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.6%, 2.6%; headache, 2.7%, 2.6%; anemia, 0.0%, 2.9%; arthralgia, 0.0%, 1.3%; back pain, 0.4%, 0.7%; insomnia, 0.0%, 1.6%; coughing, 0.8%, 1.0%; upper respiratory tract infection, 0.0%, 7.5%; pruritus, 1.2%, 0.0%; rash[2], 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 8.9%.

[1]WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined

[2]WHO preferred terms rash, rash erythematous and rash maculo-papular combined

As with other NSAIDs, higher doses of MOBIC (e.g., chronic daily 30 mg dose) were associated with an increased risk of serious GI events, therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse drug reactions occurring in < 2% of patients receiving MOBIC in clinical trials involving approximately 15,400 patients. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare (< 0.1%).

Body as a Whole: allergic reaction, *anaphylactoid reactions including shock*, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase **Cardiovascular:** angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis **Central and Peripheral Nervous System:** convulsions, paresthesia, tremor, vertigo **Gastrointestinal:** colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative **Heart Rate and Rhythm:** arrhythmia, palpitation, tachycardia **Hematologic:** *agranulocytosis*, leukopenia, purpura, thrombocytopenia **Liver and Biliary System:** ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, *jaundice, liver failure* **Metabolic and Nutritional:** dehydration **Psychiatric Disorders:** abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence **Respiratory:** asthma, bronchospasm, dyspnea **Skin and Appendages:** alopecia, angioedema, bullous eruption, *erythema multiforme*, photosensitivity reaction, pruritus, *Stevens-Johnson syndrome*, sweating increased, *toxic epidermal necrolysis*, urticaria **Special Senses:** abnormal vision, conjunctivitis, taste perversion, tinnitus **Urinary System:** albuminuria, BUN increased, creatinine increased, hematuria, *interstitial nephritis*, renal failure.

OVERDOSAGE
There is limited experience with meloxicam overdose. Four cases have taken 8 to 11 times the highest recommended dose; all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

Rx only

MB-BS-(04/01)4057500/US/B

Boehringer Ingelheim