

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:* 20-938**

**FINAL PRINTED LABELING**

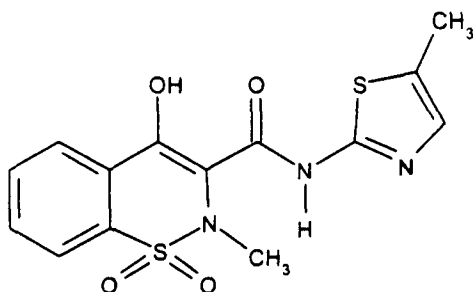
# FINAL DRAFT LABELING

MOBIC<sup>®</sup> (meloxicam) Tablets 7.5 mg

## Prescribing Information

### DESCRIPTION

MOBIC<sup>®</sup> (meloxicam), an oxicam derivative, is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each yellow tablet contains meloxicam 7.5 mg for oral administration. It is chemically designated as 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. The molecular weight is 351.4. Its empirical formula is  $C_{14}H_{13}N_3O_4S_2$  and it has the following structural formula.



Meloxicam is a yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient ( $\log P_{app}$ ) = 0.1 in *n*-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.

MOBIC is available as a tablet for oral administration containing 7.5 mg meloxicam.

The inactive ingredients in MOBIC include colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium citrate dihydrate.

### CLINICAL PHARMACOLOGY

#### Mechanism of Action

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

#### Pharmacokinetics

##### Absorption

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Meloxicam capsules have been shown to be bioequivalent to MOBIC tablets. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean  $C_{max}$  was achieved within four to five hours after a 7.5 mg meloxicam

tablet was taken under fasted conditions, indicating a prolonged drug absorption. The rate or extent of absorption was not affected by multiple dose administration, suggesting linear pharmacokinetics. With multiple dosing, steady state conditions were reached by day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting gastrointestinal recirculation.

**Table 1** Single Dose and Steady State Pharmacokinetic Parameters for Oral 7.5 and 15 mg Meloxicam (Mean and % CV)<sup>1</sup>

Pharmacokinetic Parameters (% CV)	Steady State			Single Dose	
	Healthy male adults (Fed) <sup>2</sup>	Elderly males (Fed) <sup>2</sup>	Elderly females (Fed) <sup>2</sup>	Renal failure (Fasted)	Hepatic insufficiency (Fasted)
	7.5 mg <sup>3</sup> tablets	15 mg capsules	15 mg capsules	15 mg capsules	15 mg capsules
N	18	5	8	12	12
C <sub>max</sub> [µg/mL]	1.05 (20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)
t <sub>max</sub> [h]	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)
t <sub>1/2</sub> [h]	20.1 (29)	21 (34)	24 (34)	18 (46)	16 (29)
CL/f [mL/min]	8.8 (29)	9.9 (76)	5.1 (22)	19 (43)	11 (44)
V <sub>Z</sub> /f <sup>4</sup> [L]	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)

<sup>1</sup>The parameter values in the Table are from various studies; <sup>2</sup>not under high fat conditions; <sup>3</sup>MOBIC tablets;

<sup>4</sup> V<sub>Z</sub>/f = Dose/(AUC·K<sub>e</sub>)

#### Food and Antacid Effects

Drug intake after a high fat breakfast (75 g of fat) did not affect extent of absorption of meloxicam capsules, but led to 22% higher C<sub>max</sub> values. Mean C<sub>max</sub> values were achieved between five and six hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. MOBIC tablets can be administered without regard to timing of meals and antacids.

#### Distribution

The mean volume of distribution (V<sub>ss</sub>) of meloxicam is approximately 10 L. Meloxicam is ~ 99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to ~ 99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam.

Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40 % to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown.

#### Metabolism

Meloxicam is almost completely metabolized to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism was formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). *In vitro* studies indicate that cytochrome P-450 2C9 plays an important role in this metabolic pathway with a

minor contribution of the CYP 3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively.

### **Excretion**

Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6% and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean elimination half-life ( $t_{1/2}$ ) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 mL/min.

### **Special Populations**

#### **Pediatric**

The pharmacokinetics of MOBIC in pediatric patients under 18 years of age have not been investigated.

#### **Geriatric**

Elderly males ( $\geq 65$  years of age) exhibited meloxicam plasma concentrations and steady state pharmacokinetics similar to young males. Elderly females ( $\geq 65$  years of age) had a 47% higher  $AUC_{ss}$  and 32% higher  $C_{max,ss}$  as compared to younger females ( $\leq 55$  years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

#### **Gender**

Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg MOBIC, the mean elimination half-life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs. 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the  $C_{max}$  or  $T_{max}$  across genders.

#### **Hepatic Insufficiency**

Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic insufficiency. No dose adjustment is necessary in mild to moderate hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied.

### **Renal Insufficiency**

Meloxicam pharmacokinetics have been investigated in subjects with different degrees of renal insufficiency. Total drug plasma concentrations decreased with the degree of renal impairment while free AUC values were similar. Total clearance of meloxicam increased in these patients probably due to the increase in free fraction leading to an increased metabolic clearance. There is no need for dose adjustment in patients with mild to moderate renal failure (CrCL >15 mL/min). Patients with severe renal insufficiency have not been adequately studied. The use of MOBIC in subjects with severe renal impairment is not recommended (see WARNINGS, Advanced Renal Disease).

### **Hemodialysis**

Following a single dose of meloxicam, the free C<sub>max</sub> plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable.

### **CLINICAL TRIALS**

The use of MOBIC for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a double-blind controlled trial in the U.S. involving 464 patients treated with MOBIC for 12 weeks. MOBIC (3.75 mg, 7.5 mg and 15 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and total WOMAC score (a self-administered questionnaire addressing pain, function and stiffness). Patients on MOBIC 7.5 mg daily and MOBIC 15 mg daily showed significant improvement in each of these endpoints compared with placebo.

The use of MOBIC for the management of signs and symptoms of osteoarthritis was evaluated in six double-blind, active-controlled trials outside the U.S. in which a total of 9589 patients were treated for 4 weeks to 6 months. In these trials, the efficacy of MOBIC, in doses of 7.5 and 15 mg/day, was comparable to piroxicam 20 mg/day and diclofenac SR 100 mg/day and consistent with the efficacy seen in the U.S. trial.

### **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, or of shorter duration, and reversible. MOBIC does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). Patients receiving MOBIC who may be adversely affected by alterations 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  $\beta$ -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 1.8. 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 embryoletality at oral doses  $\geq$  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 60 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 embryoletality at oral doses  $\geq$  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  $\geq$  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.

#### ***Nonteratogenic Effects:***

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses  $\geq$  0.125 mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation 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  $\geq$  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  $\geq$  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 3,505 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. Table 2 depicts adverse events that occurred in  $\geq 2\%$  of the MOBIC treatment groups.

**Table 2** Adverse Events (%) Occurring in  $\geq 2\%$  of MOBIC Patients in a 12-Week Osteoarthritis Placebo and Active-Controlled Trial

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 100 mg daily
<b>No. of Patients</b>	<b>157</b>	<b>154</b>	<b>156</b>	<b>153</b>
<b>Gastrointestinal</b>	17.2	20.1	17.3	28.1
Abdominal Pain	2.5	1.9	2.6	1.3
Diarrhea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	3.2	3.9	3.8	7.2
<b>Body as a Whole</b>				
Accident Household	1.9	4.5	3.2	2.6
Edema <sup>1</sup>	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-Like Symptoms	5.1	4.5	5.8	2.6
<b>Central and Peripheral Nervous System</b>				
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
<b>Respiratory</b>				
Pharyngitis	1.3	0.6	3.2	1.3
Upper Respiratory Tract Infection	1.9	3.2	1.9	3.3
<b>Skin</b>				
Rash <sup>2</sup>	2.5	2.6	0.6	2.0

<sup>1</sup> WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined

<sup>2</sup> WHO preferred terms rash, rash erythematous and rash maculo-papular combined

The adverse events that occurred with MOBIC in  $\geq 2\%$  of patients treated short-term (4-6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 3.

**Table 3 Adverse Events (%) Occurring in  $\geq 2\%$  of MOBIC Patients in 4 to 6 Weeks and 6 Month Active-Controlled Osteoarthritis Trials**

	4-6 Weeks Controlled Trials		6 Month Controlled Trials	
	MOBIC 7.5 mg daily	MOBIC 15 mg daily	MOBIC 7.5 mg daily	MOBIC 15 mg daily
<b>No. of Patients</b>	<b>8955</b>	<b>256</b>	<b>169</b>	<b>306</b>
<b>Gastrointestinal</b>	11.8	18.0	26.6	24.2
Abdominal Pain	2.7	2.3	4.7	2.9
Constipation	0.8	1.2	1.8	2.6
Diarrhea	1.9	2.7	5.9	2.6
Dyspepsia	3.8	7.4	8.9	9.5
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.7	4.7	7.2
Vomiting	0.6	0.8	1.8	2.6
<b>Body as a Whole</b>				
Edema <sup>1</sup>	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
<b>Central and Peripheral Nervous System</b>				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
<b>Hematologic</b>				
Anemia	0.1	0.0	4.1	2.9
<b>Musculo-Skeletal</b>				
Arthralgia	0.5	0.0	5.3	1.3
Back Pain	0.5	0.4	3.0	0.7
<b>Psychiatric</b>				
Insomnia	0.4	0.0	3.6	1.6
<b>Respiratory</b>				
Coughing	0.2	0.8	2.4	1.0
Upper Respiratory Tract Infection	0.2	0.0	8.3	7.5
<b>Skin</b>				
Pruritus	0.4	1.2	2.4	0.0
Rash <sup>2</sup>	0.3	1.2	3.0	1.3
<b>Urinary</b>				
Micturition Frequency	0.1	0.4	2.4	1.3
Urinary Tract Infection	0.3	0.4	4.7	6.9

<sup>1</sup> WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined

<sup>2</sup> 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%).

<b>Body as a Whole:</b>	allergic reaction, <i>anaphylactoid reactions including shock</i> , face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase
<b>Cardiovascular:</b>	angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis
<b>Central and Peripheral Nervous System:</b>	convulsions, paresthesia, tremor, vertigo
<b>Gastrointestinal:</b>	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
<b>Heart Rate and Rhythm:</b>	arrhythmia, palpitation, tachycardia
<b>Hematologic:</b>	<i>agranulocytosis</i> , leukopenia, purpura, thrombocytopenia
<b>Liver and Biliary System:</b>	ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, <i>jaundice, liver failure</i> ,
<b>Metabolic and Nutritional:</b>	dehydration
<b>Psychiatric Disorders:</b>	abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence
<b>Respiratory:</b>	asthma, bronchospasm, dyspnea
<b>Skin and Appendages:</b>	alopecia, angioedema, bullous eruption, <i>erythema multiforme</i> , photosensitivity reaction, pruritus, <i>Stevens-Johnson syndrome</i> , sweating increased, <i>toxic epidermal necrolysis</i> , urticaria
<b>Special Senses:</b>	abnormal vision, conjunctivitis, taste perversion, tinnitus
<b>Urinary System:</b>	albuminuria, BUN increased, creatinine increased, hematuria, <i>interstitial nephritis</i> , renal failure

## OVERDOSAGE

There is limited experience with meloxicam overdose. Four cases have taken 6 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, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

#### **DOSAGE AND ADMINISTRATION**

The lowest dose of MOBIC should be sought for each patient. For the treatment of osteoarthritis the recommended starting and maintenance dose of MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily. The maximum recommended daily dose of MOBIC is 15 mg.

MOBIC may be taken without regard to timing of meals.

#### **HOW SUPPLIED**

MOBIC is available as a yellow, round, biconvex, uncoated tablet containing meloxicam 7.5 mg. The tablet is impressed with the Boehringer Ingelheim logo on one side, and on the other side, the letter "M". MOBIC is available as follows:

NDC 0597-0029-30; Bottles of 30

NDC 0597-0029-01; Bottles of 100

NDC 0597-0029-61; Unit dose packages of 100 (10 blister cards of 10 tablets each)

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Keep in a dry place.

Dispense in a tight container.

#### **Rx Only**

**Manufactured by:**  
**Boehringer Ingelheim Pharma KG**  
**Ingelheim, Germany**

**Marketed by:**  
**Boehringer Ingelheim Pharmaceuticals, Inc.**  
**Ridgefield, CT 06877, USA**  
**and**

**Abbott Laboratories**  
**North Chicago, IL 60064, USA**

**Licensed from:**  
**Boehringer Ingelheim International GmbH**