

# Factor Fracture Risk Detail Into BMD Reports

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NEW ORLEANS — Giving primary care physicians quantitative information about fracture risk can help them make more judicious use of preventive drug therapy for postmenopausal women at below-average risk for osteoporosis, Joan M. Neuner, M.D., said at the annual meeting of the Society of General Internal Medicine.

In a national survey targeting a random

sample of primary care physicians, those who received lifetime and 5-year quantitative fracture risk estimates along with bone mineral density (BMD) reports were less likely than those given standard BMD reports to recommend preventive prescription drugs for a 70-year-old, average-weight woman with a T score of -1.01, Dr. Neuner reported.

The survey included nationally representative proportions of general internists, family physicians, general practitioners,

and ob.gyns. The physicians were asked to respond to four clinical vignettes that varied with regard to patient age, weight, and hip BMD. The survey also included Likert-scaled items to measure osteoporosis knowledge, attitudes, and screening preferences.

Of the respondents, 141 randomly received standard hip BMD measures for each vignette (reported as g/cm<sup>2</sup> with T score and z score), and 138 received augmented BMD reports, which included

quantitative lifetime and 5-year risk fracture estimates derived from the Study of Osteoporotic Fractures. For each vignette, the physicians were asked to estimate the patient's hip fracture risk, compared with average-risk women of the same age and race.

Dr. Neuner and her colleagues at the Medical College of Wisconsin in Milwaukee developed a logistic regression model to adjust the results for physician specialty, physician demographics, and physician



## 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 and rheumatoid arthritis.

### 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, anaphylactoid-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

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

MOBIC should be avoided in late pregnancy 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 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 MOBIC. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with 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 MOBIC. Therefore, 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 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).

MOBIC should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

### Laboratory Tests

Patients on long-term treatment with MOBIC 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<sub>max</sub> (24%) of meloxicam. The clinical significance of this interaction is not known; however, 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<sub>1/2</sub>, 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 8-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 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, adjusted, 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.

# United States Not Yet Ready For Gender-Blind T Scores

BY SHERRY BOSCHERT  
San Francisco Bureau

SAN FRANCISCO — A trend toward using one set of parameters to diagnose osteoporosis in both men and women hasn't caught on in the United States, where sex-specific bone density scores are the norm, Eric S. Orwoll, M.D., said at a meeting on osteoporosis sponsored by the University of California, San Francisco.

Yet despite the ease of a gender-blind system and some persuasive data, using a sex-specific method is the way to go, at least until more data accumulate on bone loss and fracture risk in men, suggested Dr. Orwoll, professor of medicine at Oregon Health and Science University, Portland.

The evidence supporting the use of one set of parameters is mounting. Studies in recent years have shown, for example, that the 1-year risk for hip fracture overlaps in men and women with the same hip bone mineral densities. As the density gets lower, the risk for fracture increases at essentially the same rate in both sexes.

Such findings have led some bone experts to suggest that it would be easier and logical for clinicians to use just one reference range for diagnosing osteoporosis instead of using separate T scores for men and women. Bone densitometry machines in the United States currently calculate a sex-specific T score.

**‘There’s a little bit of incongruity in the application of the [international] recommendations, despite the fact that they’re scientifically reasonable.’**

The International Osteoporosis Foundation in 2000 noted that the same absolute values of bone density in men and women yield the same absolute risk of vertebral or hip fracture, suggesting that using one threshold for calculating risk makes sense. The data on men are scanty, according to the statement.

Those who favor using one set of parameters usually propose using T scores that report the number of standard deviations between current bone density and the mean peak density of a 30-year-old female.

But the problem with using such a strategy, Dr. Orwoll said, is that only about 3% of older men would be identified as osteoporotic, in comparison with a young female reference population, while 19% of older men would be deemed osteoporotic if their T scores came from reference to young male norms.

About 25%-30% of older men will have a fragility fracture, but if the female reference range were used, only a small percentage of them would be identified as osteoporotic.

“So there’s a little bit of incongruity in the application of the International Osteoporosis Foundation recommendations, despite the fact that they’re scientifically reasonable,” he said.

Dr. Orwoll encouraged clinicians to keep using the current system of sex-specific T scores from densitometry machines until better, long-term, prospective data on fracture risk in men become available.

He added that it’s also critical to include other clinical criteria besides T scores in identifying fracture risk in men.

estimates of relative fracture risk for a patient with below-average risk.

“In the unadjusted analysis, physicians who received augmented BMD reports were no more or less likely to recommend prescription medications for any of the vignettes,” Dr. Neuner said. In the adjusted model, however, 25% of the physicians who received the augmented BMD would have prescribed drug therapy for the below-average-risk 70-year-old, compared with 36% of the physicians who received the standard BMD report only—a statistically significant difference, she said.

Physicians in the standard BMD

group who correctly identified the woman as having a below-average risk of hip fracture based on age, weight, and hip BMD also were less likely to recommend drug therapy, she added.

The findings suggest that adding quantitative fracture risk estimates to BMD reports “has the potential to change physician prescribing behavior” for women at low risk for osteoporosis. Similarly, educating primary care providers about risk classification could change their perceptions about who should get preventive drug therapy, Dr. Neuner said.

**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  $\geq 1$  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 embryolethality 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**

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 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3505 OA patients and 1351 RA 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 and 2363 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis 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. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo.

The following adverse events (%) occurred in  $\geq 2\%$  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<sup>1</sup>, 1.9%, 4.5%; fall, 2.6%, 0.0%; influenza-like symptoms, 4.5%, 5.8%; dizziness, 2.6%, 3.8%; headache, 7.8%, 8.3%; pharyngitis, 0.6%, 3.2%; upper respiratory tract infection, 3.2%, 1.9%; rash<sup>2</sup>, 2.6%, 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in  $\geq 2\%$  of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.7%, 4.7%; 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, 0.6%, 1.8%; edema<sup>1</sup>, 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<sup>2</sup>, 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  $\geq 2\%$  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, 0.8%, 2.6%; edema<sup>1</sup>, 2.0%, 1.6%; pain, 2.0%, 5.2%; dizziness, 1.8%, 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<sup>2</sup>, 1.2%, 1.3%; micturition frequency, 0.4%, 1.3%; urinary tract infection, 0.4%, 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.

The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in  $\geq 2\%$  of patients treated in two 12-week rheumatoid arthritis placebo controlled trials: abdominal pain NOS<sup>3</sup>, 2.9%, 2.3%; diarrhea NOS<sup>3</sup>, 4.8%, 3.4%; dyspeptic signs and symptoms<sup>1</sup>, 5.8%, 4.0%; nausea<sup>2</sup>, 3.3%, 3.8%; influenza like illness<sup>3</sup>, 2.9%, 2.3%; upper respiratory tract infections-pathogen class unspecified<sup>1</sup>, 7.0%, 6.5%; joint related signs and symptoms<sup>1</sup>, 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC<sup>1</sup>, 1.7%, 2.9%; headaches NOS<sup>2</sup>, 6.4%, 5.5%; dizziness (excl vertigo)<sup>2</sup>, 2.3%, 0.4%; rash NOS<sup>2</sup>, 1.0%, 2.1%.

<sup>1</sup>MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

<sup>2</sup>MedDRA preferred term: diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (excl vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been 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 16,200 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. **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. **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 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.

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