TREPOXICAM-7.5 - meloxicam, histidine
Physician Therapeutics LLC

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

HIGHLIGHTS OF PRESCRIBING INFORMATION
Meloxicam 7.5 mg These highlights do not include all the information needed to use MOBIC safely and effectively. See full prescribing information for MOBIC. Mobic (meloxicam) tablets Mobic (meloxicam) oral suspension Initial U.S. Approval: 2000

WARNING:

CARDIOVASCULAR and GASTROINTESTINAL RISKS

See full prescribing information for complete boxed warning. Cardiovascular Risk NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1) MOBIC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (4.2, 5.1) Gastrointestinal Risk NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (5.2)

INDICATIONS AND USAGE

MOBIC is a non-steroidal anti-inflammatory drug indicated for: Osteoarthritis (OA) (1.1) Rheumatoid Arthritis (RA) (1.2) Juvenile Rheumatoid Arthritis (JRA) in patients 2 years of age or older (1.3)

DOSAGE AND ADMINISTRATION

Use the lowest effective dose for the shortest duration consistent with individual treatment goals for the individual patient.
OA (2.2) and RA (2.3): Starting dose: 7.5 mg once daily Dose may be increased to 15 mg once daily (2)
JRA (2.4): 0.125 mg/kg once daily up to a maximum of 7.5 mg. JRA dosing using the oral suspension should be individualized based on the weight of the child. (2.4) (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 7.5 mg, 15 mg (3) Oral Suspension: 7.5 mg/5 mL (3)

CONTRAINDICATIONS

Known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to meloxicam (4.1) History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4.1) Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery (4.2)

WARNINGS AND PRECAUTIONS

Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease/risk factors may be at greater risk. (5.1) Serious gastrointestinal (GI) adverse events which can be fatal. The risk is greater in patients with a prior history of ulcer disease or GI bleeding, and in patients at higher risk for GI events, especially the elderly. (5.2) Elevated liver enzymes, and rarely, severe hepatic reactions. Discontinue use immediately if abnormal liver enzymes persist or worsen. (5.3) New onset or worsening of hypertension. Blood pressure should be monitored closely during treatment. (5.4) Fluid retention and edema. Should be used with caution in patients with fluid retention or heart failure. (5.5) Renal papillary necrosis and other renal injury with long-term use. Use with caution in the elderly, those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics, ACE-inhibitors, or angiotensin II antagonists. The use of MOBIC in patients with severe renal impairment is not recommended. (5.6) Serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal and can occur without warning. Discontinue MOBIC at first appearance of rash or skin reactions. (5.8)

ADVERSE REACTIONS

Most common (Greater than or equal to 5% and greater than placebo) adverse events in adults are diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (6.1) Adverse events observed in pediatric studies were similar in nature to the adult clinical trial experience (6.1) To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. (6)

DRUG INTERACTIONS

Concomitant use of MOBIC and warfarin may result in increased risk of bleeding complications (7.7) Concomitant use of MOBIC and aspirin is not generally recommended because of the potential of increased adverse effect including increased

GI bleeding (7.2) Concomitant use with MOBIC increases lithium plasma levels (7.4) Concomitant use with NSAIDs may reduce the antihypertensive effect of ACE-inhibitors (7.1)

USE IN SPECIFIC POPULATIONS

Based on animal data, may cause fetal harm. Starting at 30 weeks gestation, MOBIC should be avoided as premature closure of the ductus arteriosus in the fetus may occur. (5.9, 8.1) Nursing Mothers: Use with caution, as meloxicam may be excreted in human milk (8.3) See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

DOSAGE AND ADMINISTRATION

Enter highlights text here (10)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING:

RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS

Cardiovascular Risk Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk [see Warnings and Precautions (5.1)]. MOBIC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see Contraindications (4.2) and Warnings and Precautions (5.1)]. Gastrointestinal Risk NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse reactions including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events [see Warnings and Precautions (5.2)].

1.1 Osteoarthritis (OA) 1.2 Rheumatoid Arthritis (RA) 1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

1 INDICATIONS AND USAGE

1.1 Osteoarthritis (OA) MOBIC is indicated for relief of the signs and symptoms of osteoarthritis [see Clinical Studies (14.1)].

1.2 Rheumatoid Arthritis (RA) MOBIC is indicated for relief of the signs and symptoms of rheumatoid arthritis [see Clinical Studies (14.1)].

1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course MOBIC is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older [see Clinical Studies (14.2)].

2.1 General Instructions 2.3 Rheumatoid Arthritis

2 DOSAGE AND ADMINISTRATION

2.1 General Instructions Carefully consider the potential benefits and risks of MOBIC and other treatment options before deciding to use MOBIC. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5.4)]. After observing the response to initial therapy with MOBIC, adjust the dose to suit an individual patient's needs. In adults, the maximum recommended daily oral dose of MOBIC is 15 mg regardless of formulation. In patients with hemodialysis, a maximum daily dosage of 7.5 mg is recommended [see Warnings and Precautions (5.6), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]. MOBIC oral suspension 7.5 mg/5 mL or 15 mg/10 mL may be substituted for MOBIC tablets 7.5 mg or 15 mg, respectively. Shake the oral suspension gently before using. MOBIC may be taken without regard to timing of meals.

2.2 Osteoarthritis For the relief of the signs and symptoms of osteoarthritis the recommended starting and maintenance oral dose of MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

2.3 Rheumatoid Arthritis For the relief of the signs and symptoms of rheumatoid arthritis, the recommended starting and maintenance oral dose of MOBIC is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course To improve dosing accuracy in smaller weight children, the use of the MOBIC oral suspension is recommended. MOBIC oral suspension is available in the strength of 7.5 mg/5 mL. For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of MOBIC is 0.125 mg/kg once daily up to a maximum of 7.5 mg. There was no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in

these clinical trials. Juvenile Rheumatoid Arthritis dosing using the oral suspension should be individualized based on the weight of the child:

0.125 mg/kg

Weight	Dose (1.5 mg/mL)	Delivered dose
12 kg (26 lb)	1.0 mL	1.5 mg
24 kg (54 lb)	2.0 mL	3.0 mg
36 kg (80 lb)	3.0 mL	4.5 mg
48 kg (106 lb	4.0 mL	6.0 mg
≥60 kg (132 lb)	5.0 mL	7.5 mg

3 DOSAGE FORMS AND STRENGTHS

3 DOSAGE FORMS AND STRENGTHS Tablets: 7.5 mg: pastel yellow, round, biconvex, uncoated tablet containing meloxicam 7.5 mg. Impressed with the Boehringer Ingelheim logo on one side and the letter “M” on the other. 15 mg: pastel yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. Impressed with the tablet code “15” on one side and the letter “M” on the other. Oral Suspension: yellowish green tinged viscous suspension containing 7.5 mg meloxicam in 5 mL.

4.1 Allergic Reactions 4.2 Coronary Surgery

4 CONTRAINDICATIONS

4.1 Allergic Reactions MOBIC is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to meloxicam. MOBIC 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 and Precautions (5.7, 5.13)].

4.2 Coronary Surgery MOBIC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)].

5.1 Cardiovascular Thrombotic Events 5.2 Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation 5.3 Hepatic Effects 5.4 Hypertension 5.5 Congestive Heart Failure and Edema 5.6 Renal Effects 5.7 Anaphylactoid Reactions 5.8 Adverse Skin Reactions 5.9 Pregnancy 5.12 Hematological Effects 5.13 Use in Patients with Pre-existing Asthma

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years’ duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur. Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke [see Contraindications (4.2)]. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events [see Warnings and Precautions (5.2)].

5.2 Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation NSAIDs, including

MOBIC, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs, occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue with longer duration of use, 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. Prescribe NSAIDs, including MOBIC, with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. 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 in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during MOBIC therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of MOBIC until a serious GI adverse event is ruled out. For high-risk patients, consider alternate therapies that do not involve NSAIDs.

5.3 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 [see Adverse Reactions (6.1)]. A patient with symptoms and/or signs 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.), discontinue MOBIC [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

5.4 Hypertension NSAIDs, including MOBIC, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. NSAIDs, including MOBIC, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy. Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema Fluid retention and edema have been observed in some patients taking NSAIDs. Use MOBIC with caution in patients with fluid retention, hypertension, or heart failure.

5.6 Renal Effects Long-term administration of NSAIDs, including MOBIC, can result in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury. 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 a nonsteroidal anti-inflammatory drug may cause a 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, ACE-inhibitors, and angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. A pharmacokinetic study in patients with mild and moderate renal

impairment revealed that no dosage adjustments in these patient populations are required. Patients with severe renal impairment have not been studied. The use of MOBIC in patients with severe renal impairment with CrCl less than 20 mL/min is not recommended. A study performed in patients on hemodialysis revealed that although overall Cmax was diminished in this population, the proportion of free drug not bound to plasma was increased. Therefore it is recommended that meloxicam dosage in this population not exceed 7.5 mg per day. Closely monitor the renal function of patients with impaired renal function who are taking MOBIC [see Dosage and Administration (2.1), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]. Use caution 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. The extent to which metabolites may accumulate in patients with renal impairment has not been studied with MOBIC. Because some MOBIC metabolites are excreted by the kidney, monitor patients with significant renal impairment closely.

5.7 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 (4.1) and Warnings and Precautions (5.12)]. Seek emergency help in cases where an anaphylactoid reaction occurs.

5.8 Adverse Skin Reactions NSAIDs, including MOBIC, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin manifestations and discontinue use of the drug at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy Starting at 30 weeks gestation, avoid the use of MOBIC because it may cause premature closure of the ductus arteriosus [see Use in Specific Populations (8.1) and Patient Counseling Information (17.8)].

5.10 Corticosteroid Treatment MOBIC cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Slowly taper patients on prolonged corticosteroid therapy if a decision is made to discontinue corticosteroids.

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

5.12 Hematological Effects Anemia may occur in patients receiving NSAIDs, including MOBIC. This may be due to fluid retention, occult or gross 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. 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. Carefully monitor patients treated with MOBIC who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants.

5.13 Use in Patients with 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 NSAIDs 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.

5.14 Monitoring Because serious GI tract ulcerations and bleeding can occur without warning

symptoms, physicians should monitor for signs or symptoms of GI bleeding. 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.

6.1 Clinical Trials Experience

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following serious adverse reactions are discussed elsewhere in the labeling: Cardiovascular thrombotic events [see Boxed Warning and Warnings and Precautions (5.1)] Gastrointestinal effects – risk of GI ulceration, bleeding, and perforation [see Boxed Warning and Warnings and Precautions (5.2)] Hepatic effects [see Warnings and Precautions (5.3)] Hypertension [see Warnings and Precautions (5.4)] Congestive heart failure and edema [see Warnings and Precautions (5.5)] Renal effects [see Warnings and Precautions (5.6)] Anaphylactoid reactions [see Warnings and Precautions (5.7)] Adverse skin reactions [see Warnings and Precautions (5.8)] 6.1 Clinical Trials Experience Adults Osteoarthritis and Rheumatoid Arthritis 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. Table 1a depicts adverse events that occurred in greater than or equal to 2% of the MOBIC treatment groups in a 12-week placebo- and active-controlled osteoarthritis trial. Table 1b depicts adverse events that occurred in greater than or equal to 2% of the MOBIC treatment groups in two 12-week placebo-controlled rheumatoid arthritis trials.

Table 1a Adverse Events (%) Occurring in greater than or equal to 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
No. of Patients	157	154	156	153
Gastrointestinal	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
Body as a Whole				
Accident household	1.9	4.5	3.2	2.6
Edema1	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

Central and Peripheral Nervous System				
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Respiratory				
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3
Skin				
Rash2	2.5	2.6	0.6	2.0

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

Table 1b Adverse Events (%) Occurring in greater than or equal to 2% of MOBIC Patients in two 12-Week Rheumatoid Arthritis Placebo-Controlled Trials

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily
No. of Patients	469	481	477
Gastrointestinal Disorders	14.1	18.9	16.8
Abdominal pain NOS2	0.6	2.9	2.3
Dyspeptic signs and symptoms1	3.8	5.8	4.0
Nausea2	2.6	3.3	3.8
General Disorders and Administration Site Conditions			
Influenza-like illness2	2.1	2.9	2.3
Infection and Infestations			
Upper respiratory tract infections-pathogen class unspecified1	4.1	7.0	6.5
Musculoskeletal and Connective Tissue Disorders			
Joint related signs and symptoms1	1.9	1.5	2.3
Nervous System Disorders			
Headaches NOS2	6.4	6.4	5.5
Skin and Subcutaneous Tissue Disorders			
Rash NOS2	1.7	1.0	2.1

1 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) 2 MedDRA preferred term: nausea, abdominal pain NOS, influenza-like illness, headaches NOS, and rash NOS The adverse events that occurred with MOBIC in greater than or equal to 2% of patients treated short-term (4 to 6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 2.

Table 2 Adverse Events (%) Occurring in greater than or equal to 2% of MOBIC Patients in 4 to 6 Weeks and 6 Month Active-Controlled Osteoarthritis Trials

	4 to 6 Weeks Controlled Trials	4 to 6 Weeks Controlled Trials	6 Month Controlled	6 Month Controlled

	Controlled Trials	Controlled Trials	Trials	Trials
	MOBIC 7.5 mg daily	MOBIC 15 mg daily	MOBIC 7.5 mg daily	MOBIC 15 mg daily
No. of Patients	8955	256	169	306
Gastrointestinal	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
Body as a Whole				
Accident household	0.0	0.0	0.6	2.9
Edema1	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
Central and Peripheral Nervous System				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
Hematologic				
Anemia	0.1	0.0	4.1	2.9
Musculoskeletal				
Arthralgia	0.5	0.0	5.3	1.3
Back pain	0.5	0.4	3.0	0.7
Psychiatric				
Insomnia	0.4	0.0	3.6	1.6
Respiratory				
Coughing	0.2	0.8	2.4	1.0
Upper respiratory tract infection	0.2	0.0	8.3	7.5
Skin				
Pruritus	0.4	1.2	2.4	0.0
Rash2	0.3	1.2	3.0	1.3
Urinary				
Micturition frequency	0.1	0.4	2.4	1.3
Urinary tract infection	0.3	0.4	4.7	6.9

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 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. Pediatrics Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA) Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to MOBIC with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12-week multicenter, double-blind, randomized trials (one with a 12-week open-label extension and one with a 40-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with MOBIC were

similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events, abdominal pain, vomiting, diarrhea, headache, and pyrexia, were more common in the pediatric than in the adult trials. Rash was reported in seven (less than 2%) patients receiving MOBIC. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect. The following is a list of adverse drug reactions occurring in less than 2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients.

Body as a Whole	allergic reaction, 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	leukopenia, purpura, thrombocytopenia
Liver and Biliary System	ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis
Metabolic a nd Nutritional	dehydration
Psychiatric	abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence
Respiratory	asthma, bronchospasm, dyspnea
Skin and Appendages	alopecia, angioedema, bullous eruption, photosensitivity reaction, pruritus, sweating increased, urticaria
Special Senses	abnormal vision, conjunctivitis, taste perversion, tinnitus
Urinary System	albuminuria, BUN increased, creatinine increased, hematuria, renal failure

6.2 Post Marketing Experience The following adverse reactions have been identified during post approval use of MOBIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. Adverse reactions reported in worldwide post marketing experience or the literature include: acute urinary retention; agranulocytosis; alterations in mood (such as mood elevation); anaphylactoid reactions including shock; erythema multiforme; exfoliative dermatitis; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome, and toxic epidermal necrolysis.

7.1 ACE-inhibitors 7.2 Aspirin 7.4 Lithium 7.5 Methotrexate 7.7 Warfarin

7 DRUG INTERACTIONS See also Clinical Pharmacology (12.3).

7.1 ACE-inhibitors NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking MOBIC concomitantly with ACE-inhibitors.

7.2 Aspirin When MOBIC is administered with aspirin (1000 mg three times daily) to healthy volunteers, an increase in the AUC (10%) and Cmax (24%) of meloxicam was noted. 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.

7.3 Diuretics Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. However, 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 MOBIC, patients should be observed closely for signs of renal failure [see Warnings and Precautions (5.6)], as well as to ensure diuretic efficacy.

7.4 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 twice daily with meloxicam 15 mg every day as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by MOBIC. Closely monitor patients on lithium treatment for signs of lithium toxicity when MOBIC is introduced, adjusted, or withdrawn.

7.5 Methotrexate NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Therefore, NSAIDs may reduce the elimination of methotrexate, thereby enhancing the toxicity of methotrexate. Use caution when MOBIC is administered concomitantly with methotrexate [see Clinical Pharmacology (12.3)].

7.6 Cyclosporine MOBIC, like other NSAIDs, may affect renal prostaglandins, thereby altering the renal toxicity of certain drugs. Therefore, concomitant therapy with MOBIC may increase cyclosporine's nephrotoxicity. Use caution when MOBIC is administered concomitantly with cyclosporine.

7.7 Warfarin The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone. Monitor anticoagulant activity, 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 than with the use of either drug alone. Use caution 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 [see Clinical Pharmacology (12.3)].

8.1 Pregnancy 8.7 Renal Impairment

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C; Category D starting 30 weeks gestation There are no adequate and well-controlled studies in pregnant women. Meloxicam crosses the placental barrier. Prior to 30 weeks gestation, use MOBIC during pregnancy only if the potential benefit justifies the potential risk to the fetus. Starting at 30 weeks gestation, avoid MOBIC and other NSAIDs, in pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, inform the patient of the potential hazard to a fetus [see Warnings and Precautions (5.9) and Patient Counseling Information (17.8)]. Teratogenic Effects Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the maximum recommended human daily dose [MRHD] based on body surface area [BSA] comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an

increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day. The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion) . Nonteratogenic Effects In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65- and 6.5- fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

8.2 Labor and Delivery The effects of MOBIC on labor and delivery of pregnant women are unknown. Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (at least 12.5 times lower than the maximum recommended human daily dose based on body surface area comparison).

8.3 Nursing Mothers

8.3 Nursing Mothers It is not known whether this drug is excreted in human milk; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because many drugs are excreted in human milk and 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.

8.4 Pediatric Use The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials [see Dosage and Administration (2.3), Adverse Reactions (6.1), and Clinical Studies (14.2)].

8.6 Hepatic Impairment 8.7 Renal Impairment

8.5 Geriatric Use As with any NSAID, caution should be exercised in treating the elderly (65 years and older). Of the total number of subjects in clinical studies, 5157 were age 65 and over (4044 in OA studies and 1113 in RA studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

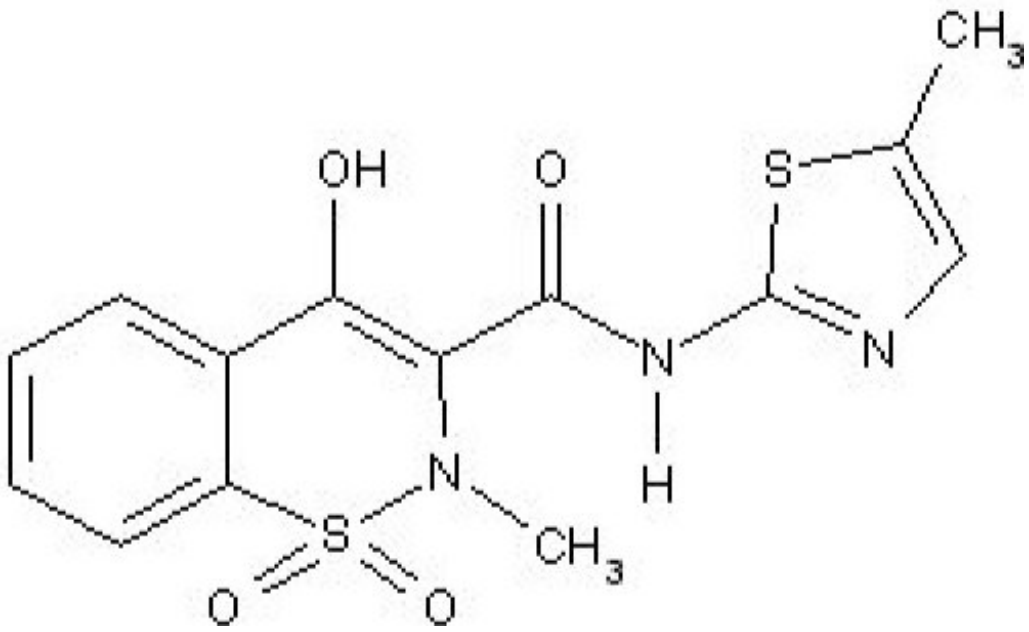
8.6 Hepatic Impairment No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been adequately studied. Since meloxicam is significantly metabolized in the liver; the use of meloxicam in these patients should be done with caution [see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

8.7 Renal Impairment No dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been studied. The use of MOBIC in subjects with severe renal impairment is not recommended. Following a single dose of meloxicam, the free Cmax plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Therefore, it is recommended that meloxicam dosage in this population not exceed 7.5 mg per day. Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable [see Dosage and Administration (2.1), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)].

10 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 include 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. Administration of activated charcoal is recommended for patients who present 1 to 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. For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION Meloxicam, an oxicam derivative, is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each pastel yellow MOBIC tablet contains 7.5 mg or 15 mg meloxicam for oral administration. Each bottle of MOBIC oral suspension contains 7.5 mg meloxicam per 5 mL. Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2- benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C14H13N3O4S2 and it has the following structural formula:



Meloxicam is a pastel 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 or 15 mg meloxicam, and as an oral suspension containing 7.5 mg meloxicam per 5 mL. The inactive ingredients in MOBIC tablets include colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium citrate dihydrate. The inactive ingredients in MOBIC oral suspension include colloidal silicon dioxide, hydroxyethylcellulose, sorbitol, glycerol, xylitol, monobasic sodium phosphate (dihydrate), saccharin sodium, sodium benzoate, citric acid (monohydrate), raspberry flavor, and purified water.

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action The mechanism of action of meloxicam, like that of other NSAIDs, may be related to prostaglandin synthetase (cyclo-oxygenase) inhibition which is involved in the initial steps of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.

12.2 Pharmacodynamics Meloxicam exhibits anti-inflammatory, analgesic, and antipyretic activities.

12.3 Pharmacokinetics

12.3 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. 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 Cmax was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

Meloxicam oral suspension doses of 7.5 mg/5 mL and 15 mg/10 mL have been found to be bioequivalent to meloxicam 7.5 mg and 15 mg capsules, respectively. Meloxicam capsules have been shown to be bioequivalent to MOBIC tablets.

Table 3 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and % CV)1

		Steady State	Steady State	Steady State	Single Dose	Single Dose
Pharmacokinetic Parameters (% CV)		Healthy male adults (Fed)2	Elderly males (Fed)2	Elderly females (Fed)2	Renal failure (Fasted)	Hepatic insufficiency (Fasted)
		7.5 mg3 tablets	15 mg capsules	15 mg capsules	15 mg capsules	15 mg capsules
N		18	5	8	12	12
Cmax	[µg/mL]	1.05(20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)
tmax	[h]	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)
t1/2	[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)
Vz/f4	[L]	14.7(32)	15 (42)	10 (30)	26 (44)	14 (29)

1The parameter values in the table are from various studies 2 not under high fat conditions 3 MOBIC tablets 4 Vz/f =Dose/(AUC-Kel) Food and Antacid Effects Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e., Cmax) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (Tmax) was achieved between 5 and 6 hours. In comparison, neither the AUC nor the Cmax values for meloxicam suspension were affected following a similar high fat meal, while mean Tmax values were increased to approximately 7 hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Based on these results, MOBIC can be administered without regard to timing of meals or concomitant administration of antacids. Distribution The mean volume of distribution (Vss) 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 extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism 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 CYP2C9

(cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. All the four metabolites are not known to have any in vivo pharmacological activity. 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 (t1/2) 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 After single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg [see Dosage and Administration (2.2)]. The meloxicam mean (SD) elimination half-life was 15.2 (10.1) and 13.0 hours (3.0) for the 2 to 6 year old patients, and 7 to 16 year old patients, respectively. In a covariate analysis, utilizing population pharmacokinetics body-weight, but not age, was the single predictive covariate for differences in the meloxicam apparent oral plasma clearance. The body-weight normalized apparent oral clearance values were adequate predictors of meloxicam exposure in pediatric patients. The pharmacokinetics of MOBIC in pediatric patients under 2 years of age have not been investigated. Geriatric Elderly males (³65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (³65 years of age) had a 47% higher AUCss and 32% higher Cmax,ss as compared to younger females (£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 Cmax or Tmax across genders. Hepatic Impairment Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in patients with mild (Child- Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]. Renal Impairment Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of MOBIC in subjects with severe renal impairment is not recommended [see Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]. Hemodialysis Following a single dose of meloxicam, the free Cmax 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 [see Dosage and Administration (2.1), Warnings and Precautions (5.6), and Use in Specific Populations (8.7)].

Drug Interactions Aspirin: When MOBIC is administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and Cmax (24%) of meloxicam. The clinical significance of this interaction is not known [see Drug Interactions (7.2)]. Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t1/2, 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 four times daily 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 b-acetyldigoxin administration for 7 days at clinical doses. In vitro testing found no protein binding drug interaction between digoxin and meloxicam. 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 twice daily with meloxicam 15 mg QD every day as compared to subjects receiving lithium alone [see Drug Interactions (7.4)]. 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 [see Drug Interactions (7.5)]. Warfarin: 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 [see Drug Interactions (7.7)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis: There was no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.5- and 2.6-fold, respectively, the maximum recommended human daily dose based on body surface area comparison). Mutagenesis: 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. Impairment of Fertility: Meloxicam did not impair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/ kg/day in females (up to 5.8- and 3.2-fold greater, respectively, than the maximum recommended human daily dose based on body surface area comparison).

14.1 Osteoarthritis and Rheumatoid Arthritis 14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

14 CLINICAL STUDIES

14.1 Osteoarthritis and Rheumatoid Arthritis The use of MOBIC for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a 12-week, double-blind, controlled trial. 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. ranging from 4 weeks’ to 6 months’ duration. In these trials, the efficacy of MOBIC, in doses of 7.5 mg/day 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. The use of MOBIC for the treatment of the signs and symptoms of

rheumatoid arthritis was evaluated in a 12-week, double-blind, controlled multinational trial. MOBIC (7.5 mg, 15 mg, and 22.5 mg daily) was compared to placebo. The primary endpoint in this study was the ACR20 response rate, a composite measure of clinical, laboratory, and functional measures of RA response. Patients receiving MOBIC 7.5 mg and 15 mg daily showed significant improvement in the primary endpoint compared with placebo. No incremental benefit was observed with the 22.5 mg dose compared to the 15 mg dose. 14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course The use of MOBIC for the treatment of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older was evaluated in two 12-week, double-blind, parallel-arm, active-controlled trials. Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam dosing began at 0.125 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and naproxen dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 mg/ kg/day (22.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen. The efficacy analysis used the ACR Pediatric 30 responder definition, a composite of parent and investigator assessments, counts of active joints and joints with limited range of motion, and erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

16 HOW SUPPLIED/STORAGE AND HANDLING MOBIC is available as a pastel yellow, round, biconvex, uncoated tablet containing meloxicam 7.5 mg or as a pastel yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. The 7.5 mg tablet is impressed with the Boehringer Ingelheim logo on one side, and on the other side, the letter “M”. The 15 mg tablet is impressed with the tablet code “15” on one side and the letter “M” on the other. MOBIC is also available as a yellowish green tinged viscous oral suspension containing 7.5 mg meloxicam in 5 mL. MOBIC tablets 7.5 mg: NDC 0597-0029-01; Bottles of 100 MOBIC tablets 15 mg: NDC 0597-0030-01; Bottles of 100 MOBIC oral suspension 7.5 mg/5 mL: NDC 0597-0034-01; Bottles of 100 mL

Storage Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Keep MOBIC tablets in a dry place. Dispense tablets in a tight container. Keep oral suspension container tightly closed. Keep this and all medications out of the reach of children.

17 PATIENT COUNSELING INFORMATION 17.8 Effects During Pregnancy

17 PATIENT COUNSELING INFORMATION See FDA-approved Medication Guide Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. 17.1 Medication Guide Inform patients of the availability of a Medication Guide for NSAIDs that accompanies each prescription dispensed, and instruct them to read the Medication Guide prior to using MOBIC.

17.2 Cardiovascular Effects NSAIDs including MOBIC may cause serious CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up [see Warnings and Precautions (5.1)].

17.3 Gastrointestinal Effects NSAIDs including MOBIC, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. 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 sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up [see Warnings and Precautions (5.2)].

17.4 Hepatotoxicity Inform patients 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, instruct patients to stop therapy and seek immediate medical therapy [see Warnings and Precautions (5.3)].

17.5 Adverse Skin Reactions NSAIDs including MOBIC, can cause serious skin side effects such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Advise patients to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible [see Warnings and Precautions (5.8)].

17.6 Weight Gain and Edema Advise patients to promptly report signs or symptoms of unexplained weight gain or edema to their physicians [see Warnings and Precautions (5.5)].

17.7 Anaphylactoid Reactions Inform patients of the signs of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients seek immediate emergency help [see Warnings and Precautions (5.7)].

17.8 Effects During Pregnancy Starting at 30 weeks gestation, MOBIC should be avoided as premature closure of the ductus arteriosus in the fetus may occur [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]. Please address medical inquiries to (800) 542-6257 or (800) 459-9906 TTY. Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA Licensed from: Boehringer Ingelheim International GmbH 10003990/06 OT1400GD2810 090340141-7 OT1407E

Medication Guide for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (See the end of this Medication Guide for a list of prescription NSAID medicines.) What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)? NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases: - with longer use of NSAID medicines - in people who have heart disease NSAID medicines should never be used right before or after a heart surgery called a "coronary artery bypass graft (CABG)." NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding: - can happen without warning symptoms - may cause death The chance of a person getting an ulcer or bleeding increases with: - taking medicines called "corticosteroids" and "anticoagulants" - longer use - smoking - drinking alcohol - older age - having poor health NSAID medicines should only be used: - exactly as prescribed - at the lowest dose possible for your treatment - for the shortest time needed What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)? NSAID medicines are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as: - different types of arthritis - menstrual cramps and other types of short-term pain Who should not take a Non-Steroidal Anti-Inflammatory Drug (NSAID)? Do not take an NSAID medicine: - if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine - for pain right before or after heart bypass surgery Tell your healthcare provider: - about all of your medical conditions. - about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. Keep a list of your medicines to show to your healthcare provider and pharmacist. - if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy. - if you are breastfeeding. Talk to your doctor. What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)? Serious side effects include: - heart attack - stroke - high blood pressure - heart failure from body swelling (fluid retention) - kidney problems including kidney failure - bleeding and ulcers in the stomach and intestine - low red blood cells (anemia) - life-threatening skin reactions - life-threatening allergic reactions - liver problems including liver failure - asthma attacks in people who have asthma Other side effects include: - stomach pain - constipation - diarrhea - gas - heartburn - nausea - vomiting - dizziness Get emergency help right away if you have any of the following symptoms: - shortness of breath or trouble breathing - chest pain - weakness in one part or side of your body - slurred speech - swelling of the face or throat Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms: - nausea - more tired

or weaker than usual - itching - your skin or eyes look yellow - stomach pain - flu-like symptoms - vomit blood - there is blood in your bowel movement or it is black and sticky like tar - unusual weight gain - skin rash or blisters with fever - swelling of the arms and legs, hands and feet These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Aspirin is an NSAID medicine but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines. - Some of these NSAID medicines are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

NSAID medicines that need a prescription

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Cataflam, Voltaren, Arthrotec (combined with misoprostol)
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen* (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke. This Medication Guide has been approved by the U.S. Food and Drug Administration.

NDC 0597-0029-01 ATTENTION DISPENSER: Disperse with separately provided Medication Guide. Mobic (meloxicam) tablets 7.5 mg 100 tablets Dosage: Read accompanying prescribing information. RX only Boehringer Ingelheim EXP. LOT

Store at 25 degree C (77 degree F); excursions permitted to 15 degree - 30 degree C (59 degree - 86 degree F.) Dispense in a tight container.Keep in a dry place. Keep out of reach of children. Mfd. by:

Boehringer Ingelheim (BI) Promeco, S.A de C.V. Mexico City,Mexico Lic. from: BI Int'l GmbH Mkd. by: BI Pharmaceuticals, Inc. Ridgefield, CT 06877 USA C2009 BI Int'l GmbH L1411A

Trepadone (U.S. patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids, glucosamine, chondroitin sulfate, fish oil, and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. (PD) (IC), particularly diseases associated with joint pain. Must be administered under physician supervision.

Medical Foods

Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. Trepadone has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. Trepadone must be used while the patient is under the ongoing care of a physician.

PAIN DISORDERS (PD) INFLAMMATORY CONDITIONS (IC)

PD and IC as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion." It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with pain disorders responds to a tryptophan formulation by decreasing perceived pain, a deficiency of tryptophan is assumed to exist.

Patients with pain disorders and inflammatory conditions are known to have nutritional deficiencies of tryptophan, choline, arginine, GABA, flavonoids, and certain antioxidants. Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of tryptophan and GABA and have been shown to respond to oral administration of GABA, arginine, tryptophan, or a 5-hydoxytryptophan formulation. Research has shown that tryptophan, arginine or GABA reduced diets result in a fall of circulating tryptophan, arginine, and/or GABA. Patients with pain disorders frequently exhibit activation of the degradation pathways that increases the turnover of GABA, arginine and/or tryptophan leading to a reduced level of production of serotonin, GABA or nitric oxide for a given precursor blood level. Patients with pain disorders and inflammatory conditions are known to have nutritional deficiencies of glucosamine and chondroitin sulfate. Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of glucosamine and chondroitin sulfate and have been shown to respond to oral administration of glucosamine and chondroitin sulfate formulation. Patients with pain disorders and inflammatory conditions are known to have nutritional deficiencies of prostaglandin precursors such

as omega-3 free fatty acids. Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of prostaglandin precursors and have been shown to respond to oral administration of prostaglandin precursors, such as the Omega-3 free fatty acids, particularly in the form of fish oils. Research has also shown that a genetic predisposition to accelerated degradation of prostaglandins can lead to increased precursor requirements in certain patients with pain disorders and inflammatory conditions.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Flavonoids potentiate the production of acetylcholine by the neurons thereby reducing pain. Diets deficient in flavonoid rich foods and choline result in inadequate flavonoid concentrations, impeding acetylcholine production in certain patients with pain disorders and/or inflammatory conditions. Acetylcholine in pre-synaptic ganglia is necessary for the production of serotonin and nitric oxide in post-synaptic ganglia. Provision of tryptophan, arginine, GABA, choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial serotonin, nitric oxide, and acetylcholine, thereby reducing the perception of pain and reducing inflammation. L-Histidine is known to produce brain histamine that stimulates production of ACTH.

PRODUCT DESCRIPTION

Primary Ingredients

Trepadone consists of a proprietary blend of amino acids, prostaglandin precursors in the form of omega-3 free fatty acids, glucosamine, chondroitin sulfate, cocoa, caffeine, cinnamon, and flavonoids in specific proportions. These ingredients fall into the category of Generally Regarded as Safe" (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

Amino Acids

Amino Acids are the building blocks of protein. All amino acids are GRAS listed as they have been ingested by humans for many thousands of years. The doses of the amino acids in Trepadone are equivalent to those found in the usual human diet. Patients with pain disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Tryptophan, for example, is an obligatory amino acid. The body cannot make tryptophan and must obtain tryptophan from the diet. Tryptophan is needed to produce serotonin. Serotonin is required to reduce pain. Patients with pain disorders and inflammatory conditions have altered serotonin metabolism. Some patients with pain disorders and inflammatory conditions have a resistance to the use of tryptophan that is similar to the mechanism found in insulin resistance. Patients with pain disorders and inflammatory conditions cannot acquire sufficient tryptophan from the diet to alter the perception of pain and the inflammatory process without ingesting a prohibitively large amount of calories, particularly calories from protein.

Chondroitin Sulfate and Glucosamine

Chondroitin sulfate and glucosamine are the building blocks of joint cartilage and are GRAS listed as

they have been ingested by humans for thousands of years. The doses of the chondroitin sulfate and glucosamine in Trepadone are equivalent to those found in the usual human diet. Patients with pain disorders, particularly of the joints, may require an increased amount of chondroitin sulfate and glucosamine that cannot be obtained from normal diet alone. Patients with pain disorders and inflammatory conditions, particularly of the joints have altered chondroitin sulfate and glucosamine metabolism. Some patients with pain disorders and inflammatory conditions of the joints have a resistance to the use of chondroitin sulfate and glucosamine. Patients with pain disorders and inflammatory conditions of the joints cannot acquire sufficient chondroitin sulfate and glucosamine from the diet to alter the pain and the inflammatory process of the joint without ingesting a prohibitively large amount of calories, particularly calories from protein.

Omega-3 Free Fatty Acids in the Form of Fish Oil

Omega-3 Free Fatty Acids in the Form of Fish Oil are the building blocks of prostaglandin precursors that control the inflammatory process. Omega-3 Free Fatty Acids in the Form of Fish Oil are GRAS listed as they have been ingested by humans for thousands of years. The doses of the Omega-3 Free Fatty Acids in the Form of Fish Oil in Trepadone are equivalent to those found in the usual human diet. Patients with pain disorders, particularly of the joints, may require an increased amount of Omega-3 Free Fatty Acids in the Form of Fish Oil that cannot be obtained from normal diet alone. Patients with pain disorders and inflammatory conditions, particularly of the joints have altered prostaglandin metabolism. Some patients with pain disorders and inflammatory conditions exhibit a resistance to the use of Omega-3 Free Fatty Acids in the Form of Fish Oil. Patients with pain disorders and inflammatory conditions of the joints cannot acquire sufficient Omega-3 Free Fatty Acids in the Form of Fish Oil from the diet to alter the pain and the inflammatory process of the joint without ingesting a prohibitively large amount of calories.

Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in Trepadone cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

Other Ingredients
Trepadone contains the following inactive or other ingredients, as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material).

Physical Description
Trepadone is a yellow to light brown powder. Trepadone contains L-Glutamine, L-Arginine, L-Histidine, and L-Serine, 5-Hydroxytryptophan as Griffonia Seed Extract, GABA, Choline Bitartrate, Cinnamon, Cocoa, Hydrolyzed Whey Protein, and Grape Seed Extract.

CLINICAL PHARMACOLOGY
Mechanism of Action
Trepadone acts by restoring and maintaining the balance of the neurotransmitters; GABA, nitric oxide, serotonin, and acetylcholine that are associated with pain disorders and inflammatory conditions. Trepadone stimulates the production ACTH to reduce inflammation. Trepadone stimulates the production prostaglandins to reduce inflammation. Trepadone stimulates the production joint cartilage.

Metabolism
The amino acids in Trepadone are primarily absorbed by the stomach and small intestines. All cells

metabolize the amino acids in Trepadone. Circulating tryptophan, arginine and choline blood levels determine the production of serotonin, nitric oxide, and acetylcholine. The Omega-3 free fatty acids in Trepadone are primarily absorbed by the stomach and small intestines. Inflammatory cells metabolize the free fatty acids in Trepadone.

Excretion
Trepadone is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes. Free fatty acids, glucosamine, and chondroitin sulfate do not appear to have an effect on drug metabolizing enzymes

INDICATIONS FOR USE
Trepadone is intended for the clinical dietary management of the metabolic processes of pain disorders and inflammatory conditions, particularly those associated with joint pain.

CLINICAL EXPERIENCE
Administration of Trepadone has demonstrated significant reduction in symptoms of pain and inflammation in patients with acute and chronic pain when used for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Administration of Trepadone results in the induction and maintenance of pain relief in patients with pain disorders and inflammatory conditions associated with joint pain.

PRECAUTIONS AND CONTRAINDICATIONS
Trepadone is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of Trepadone.

ADVERSE REACTIONS
Oral supplementation with L-tryptophan, L-arginine or choline at high doses up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each Trepadone capsule does not exceed 400 mg. The doses of chondroitin sulfate, glucosamine, and omega-3 free fatty acids are well tolerated. Large doses of free fatty acids can be associated with bleeding disorders.

DRUG INTERACTIONS
Trepadone does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of Trepadone may allow for lowering the dose of coadministered drugs under physician supervision.

OVERDOSE
There is a negligible risk of overdose with Trepadone as the total dosage of amino acids in a one month supply (90 capsules) is less than 36 grams. Overdose symptoms may include diarrhea, weakness, and nausea. There is a negligible risk of overdose with Trepadone as the total dosage of glucosamine, chondroitin sulfate, and omega-3 free fatty acids in a one month supply (90 capsules) is less than 10 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

POST-MARKETING SURVEILLANCE
Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to Trepadone flavonoid ingredients, including cinnamon, cocoa, and chocolate. These reactions were transient in nature and subsided within 24 hours.

DOSAGE AND ADMINISTRATION

Recommended Administration

For the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions, particularly joint pain. Take (2) capsules up to four times per day times daily or as directed by physician. As with most amino acid formulations Trepadone should be taken without food to increase the absorption of key ingredients.

How Supplied
Trepadone is supplied in green and yellow, size 0 capsules in bottles of 90 capsules.

Physician Supervision
Trepadone is a Medical Food product available by prescription only and must be used while the patient is under ongoing physician supervision.

U.S. patents pending.

Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225

Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. www.ptlcentral.com

NDC # 68405-1003-02

NDC: 68405-1016-03

Storage
Store at room temperature, 59-86oF (15-30oC) Protect from light and moisture. Trepadone is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

PHYSICIAN THERAPEUTICS TREPADONE Medical Food Rx only 90 Capsules Directions for use: Must be administered under medical supervision. For adults only. As a Medical Food, take two (2) capsules four times daily in between meals. For the dietary management of osteoarthritis, tendonitis, and joint pain. Contains no added sugar, starch, wheat, yeast, preservatives, or flavor. Storage: Keep tightly closed in a cool dry place 8-32 Degree Centigrade (45-90 Degree F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC#68405-1016-03 Ingredients: Each serving (per 2 capsules) contains: Proprietary Amino Acid Blend L-Histadine, GABA, Hydrolyzed Whey Protein Glucosamine Omega - 3 FFA from Tuna Oil Chondroitin Sulfate Grape Seed Extract Cocoa (6% Theobromine) (fruit) Other indgredients: Gelatin. tricalcium phosphate, magnesium stearate, silicon dioxide, microcrystalline cellulose, FD and C yello #5, FD and C yellow #6, chlorophyllin copper complex, titanium dioxide. Distributed by: Physician Therapeutics LLC, Los Angeles, CA 90077 www.ptlcentral.com Patent Pending

For the Dietary Management of Joint Disorder.

Two capsules up to four times daily or as directed by physician. See product label and insert.

Trepadone Medical Food

PHYSICIAN THERAPEUTICS

Trepadone Meloxicam 7.5 mg

A Convenience Packed Medical Food and Drug

Trepoxicam - 7.5

PHYSICIAN THERAPEUTICS

Trepadone 90 Capsules

Meloxicam 7.5 mg 30 Tablets

No Refills Without Physician Authorization

Rx only

NDC# 68405-036-36 of this co-pack

As prescribed by physician. See product label and product information insert.

Meloxicam 7.5 mg

Rx Drug

Manufactured and Distributed by Physician Therapeutics, A Division of Targeted Medical Pharma Inc. Los Angeles, CA 90077 www.ptlcentral.com
B-NDC# 68405-8036-36

68405-1016-03

Directions for use:
Must be administered under medical supervision.

For adults only. As a Medical Food, take two (2) capsules four times daily in between meals.

For the dietary management of osteoarthritis, tendonitis, and joint pain.

Contains no added sugar, starch, wheat, yeast, preservatives, or flavor.

Storage:
Keep tightly closed in a cool dry place 8-32˚C (45-90˚F), relative humidity, below 50%.

Warning: Keep this product out of the reach of children.

NDC# 68405-1016-03

PHYSICIAN THERAPEUTICS™

TREPADONE™
Medical Food

℞ only
90 Capsules

Ingredients:
Each serving (per 2 capsules) contains:
Proprietary Amino Acid Blend
L-Histadine, GABA, Hydrolyzed Whey Protein
Glucosamine
Omega-3 FFA from Tuna Oil
Chondroitin Sulfate
Grape Seed Extract
Cocoa (6% Theobromine) (fruit)
Other indgredients: Gelatin, tricalcium phosphate, magnesium stearate, silicon dioxide, microcrystalline cellulose, FD&C yellow #5, FD&C yellow #6, chlorophyllin copper complex, titanium dioxide.

Distributed by:
Physician Therapeutics LLC, Los Angeles, CA 90077
www.ptlcentral.com
Patent Pending

52959-0856-30

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See outsert for addl Rx info KEEP OUT O REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

MELOXICAM 7.5mg TABLET

Lot #: MLC03IU

Mfg: UNICHEM

Exp: 08/11

#30

Compare to: Mobic

Mfg. NDC: 29300-0124-10

Take as directed by your Doctor or
See outsert for usual dosage information

MELOXICAM 7.5mg TABLET
52959-0856-30 Qty #30
08/11 Lot MLC03IU
Mobic 29300-0124-10

MELOXICAM 7.5mg TABLET
52959-0856-30 Qty #30
08/11 Lot MLC03IU
Mobic 29300-0124-10

MELOXICAM 7.5mg TABLET
52959-0856-30 Qty #30
08/11 Lot MLC03IU
Mobic 29300-0124-10

MELOXICAM 7.5mg TABLET
52959-0856-30 Qty #30
08/11 Lot MLC03IU
Mobic 29300-0124-10

Repack: HJ Harkins Co., Inc. Nipomo, CA 9344

TREPOXICAM-7.5

meloxicam, histidine kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68405-036

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68405-036-36	1 in 1 KIT		

Quantity of Parts		
Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	30
Part 2	1 BOTTLE	90

Part 1 of 2

MOBIC

meloxicam tablet

Product Information	
Item Code (Source)	NDC:52959-856(NDC:0597-0029)
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
MELOXICAM (UNII: VG2QF83CGL) (SILICON DIOXIDE - UNII:ETJ7Z6XBU4)	MELOXICAM	7.5 mg

Inactive Ingredients	
Ingredient Name	Strength
CROSPOVIDONE (UNII: 68401960MK)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
POVIDONE (UNII: FZ989GH94E)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	

Product Characteristics			
Color	yellow (YELLOW)	Score	no score
Shape	ROUND	Size	8mm
Flavor		Imprint Code	Company;symbol;M
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-856-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA020938	01/31/2011	

Part 2 of 2

TREPADONE 90

histidine capsule

Product Information

Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
HISTIDINE (UNII: 4QD397987E) (HISTIDINE - UNII:4QD397987E)	HISTIDINE	50 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	green (GREEN YELLOW)	**Score**	no score
Shape	CAPSULE	**Size**	21mm
Flavor		**Imprint Code**	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		90 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		02/02/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		01/31/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Boehringer Ingelheim Pharma GmbH and Co. KG		551147440	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc.		147681894	repack

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma Inc.		126962740	manufacture

Revised: 8/2011 Physician Therapeutics LLC