

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, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of events in trials of CV thrombotic events, due to their increased baseline risk. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first week of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of symptoms that might indicate an adverse CV event, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as meloxicam, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

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. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Pain in Patients

Other national studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of Meloxicam in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If Meloxicam is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including meloxicam, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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 occurred in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risk in NSAID-treated patients.

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Monitor alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue Meloxicam until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including meloxicam.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, itching, dark urine, pruritus, jaundice, loss of appetite, loss of weight, and flu-like symptoms). If clinical signs and symptoms consistent with liver disease develop, or if abnormal laboratory test results (e.g., elevations of ALT, AST, bilirubin, and/or transaminases) are observed, discontinue Meloxicam immediately, and perform a clinical evaluation of the patient [see Use in Specific Populations (5.6) and Clinical Pharmacology (12.3)].

5.4 Hypertension

NSAIDs, including Meloxicam, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Cereb and national NSAID Toxicity Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of meloxicam may blunt the CV effects of several therapeutic agents used to treat these medical conditions (i.e., diuretics, ACE-inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid the use of Meloxicam in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If Meloxicam is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hyperkalemia

Renal Toxicity

Long-term administration of NSAIDs, including Meloxicam, has resulted 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 an NSAID 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, dehydration, hypotension, heart failure, liver dysfunction, those taking diuretics and ACE-inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The renal effects of Meloxicam may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some Meloxicam metabolites are excreted by the kidney, monitor patients for signs of worsening renal function.

Correct volume status in dehydrated or hypovolemic patients prior to initiating Meloxicam. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Meloxicam [see Drug Interactions (7)].

No information is available from controlled clinical studies regarding the use of Meloxicam in patients with advanced renal disease. Avoid the use of Meloxicam in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Meloxicam is used in patients with advanced renal disease, monitor patients for signs of worsening renal function [see Clinical Pharmacology (12.3)].

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic/hypoaldosteronemic state.

5.7 Anaphylactic Reactions

Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinitis, conjunctivitis or nasal dryness, severe, potentially fatal bronchospasm, and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, Meloxicam is contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When Meloxicam is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including meloxicam, can cause serious skin adverse reactions 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 reactions, and to discontinue the use of Meloxicam at the first appearance of skin rash or any other sign of hypersensitivity. Meloxicam is contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus

Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including Meloxicam, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (6.2)].

5.11 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an idiosyncratic effect on erythropoiesis. If a patient treated with Meloxicam has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including Meloxicam, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.12 Masking of Inflammation and Fever

The pharmacological activity of Meloxicam in reducing inflammation, and possibly fever, may obscure signs of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [see Boxed Warnings and Warnings (5.1)]
- GI Bleeding, Ulceration, and Perforation [see Boxed Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.8)]
- Hematologic Toxicity [see Warnings and Precautions (5.11)]

6.1 Clinical Trial Experience

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.

Adults

Osteoarthritis and Rheumatoid Arthritis

The Meloxicam Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with Meloxicam 7.5 mg/day, 3555 OA patients and 1351 RA patients treated with Meloxicam 15 mg/day. Meloxicam 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 two placebo- and/or active-controlled trials; the remaining 28,622 of these patients were treated in the placebo- and/or active-controlled trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across Meloxicam 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 Meloxicam with placebo and with celecoxib. In this trial, 12-week meloxicam, celecoxib, and placebo trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of Meloxicam with placebo.

Table 1a depicts adverse events that occurred in ≥2% of the Meloxicam treatment groups in a 12-week placebo- and active-controlled osteoarthritis trial.

Table 1b depicts adverse events that occurred in ≥2% of the Meloxicam treatment groups in two 12-week placebo-controlled rheumatoid arthritis trials.

Table 1a Adverse Events (%) Occurring in ≥2% of Meloxicam Patients in a 12-Week Osteoarthritis Placebo- and Active-Controlled Trial

	Placebo	Meloxicam 7.5 mg/day	Meloxicam 15 mg/day	Active-Controlled, Celecoxib 100 mg/day
Overall	19.1	19.1	19.1	19.1
Gastrointestinal	17.2	20.1	17.3	28.1
Dyspepsia	2.1	2.1	2.1	2.1
Dysphagia	3.9	7.9	3.9	0.7
Flatulence	4.5	4.5	4.5	0.7
Furunculosis	4.5	4.5	4.5	3.9
Gastritis	3.9	3.9	3.9	7.2
Stomatitis	1.9	4.5	1.9	2.6
Vaginitis	2.6	3.9	4.5	3.9
Vulvitis	0.6	2.6	0.6	1.7

of NSAIDs, including Meloxicam, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

The safety and effectiveness of meloxicam in pediatric (RA patients from 17 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).

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects (see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.6, 5.13)).

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 and hepatotoxicity may occur, use meloxicam with caution in patients with hepatic impairment (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 Meloxicam in subjects with severe renal impairment is not recommended. In patients on hemodialysis, meloxicam should not exceed 7.5 mg per day. Meloxicam is not dialyzable (see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)).

10 OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, renal failure, respiratory depression, and coma have occurred, but were rare (see Warnings and Precautions (5.3, 5.2, 5.4, 5.6)).

Manage patients with symptomatic and supportive care following an NSAID overdose. There is no specific antidote. Consider gastric decontamination with activated charcoal (500 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or emetic cathartics in symptomatic patients given within four hours of exposure in a patient with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, dialysis, or hemodialysis, or hemoperfusion may not be useful due to high protein binding.

There is limited experience with meloxicam overdose. Cholestyramine is known to accelerate the clearance of meloxicam. Accelerated removal of meloxicam by 4 g oral dose of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

Meloxicam Tablets USP are a nonsteroidal anti-inflammatory drug (NSAID). Each tablet contains 7.5 mg or 15 mg meloxicam for oral administration. Meloxicam is chemically designated as 4-hydroxy-2-methyl-6-(5-methyl-2-thiazolyl)-2-h-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C₁₆H₁₄N₂O₅S₂ and it has the following structural formula:



Chemical Structure

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*_{ow}) = -1.1 in octanol/water at 7.4. Meloxicam has pKa values of 1.1 and 4.2.

Meloxicam is available as a tablet for oral administration containing 15 mg meloxicam. The inactive ingredients in Meloxicam tablets USP include colloidal silicon dioxide, croscarmellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium citrate dihydrate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meloxicam has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of Meloxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis *in vitro*. Meloxicam concentrations reached during therapy have produced *in vivo* effects. Prostaglandins are synthesized from arachidonic acid by the enzyme cyclooxygenase. Prostaglandins are animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacokinetics

Absorption

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 80 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 oral administration, pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. 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 capsules have been shown to be bioequivalent to Meloxicam tablets.

Table 4 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and % CV) *					
Pharmacokinetic Parameters (N/CV)	Steady State				
	7.5 mg Tablets	15 mg Capsules	15 mg Capsules	15 mg Capsules	15 mg Capsules
N	18	18	18	18	18
<i>t</i> _{max}	1.0 (1.0)	2.7 (2.0)	3.7 (2.4)	3.5 (2.0)	0.8 (1.0)
C _{max}	4.4 (1.8)	5.1 (2.2)	6.2 (2.7)	4.0 (2.5)	10.8 (2.7)
AUC	10	20.1 (2.0)	41.1 (2.4)	21.1 (2.0)	41.1 (2.0)
C _{trough}	8.8 (2.0)	9.9 (1.9)	5.1 (1.2)	10.1 (1.3)	11.1 (1.4)
<i>t</i> _{1/2}	11.1	15.1 (1.2)	15.1 (1.2)	10.1 (1.0)	11.1 (1.0)

* The parameter values in the table are from various studies.

† *t*_{max} = 10 min

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multiple doses of meloxicam on the pharmacokinetics of meloxicam taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of meloxicam. In vitro, meloxicam did not displace meloxicam from its human serum binding sites. [see Drug Interactions (7)]

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 Meloxicam 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)]

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 2.5 times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day Meloxicam based on body surface area [BSA] 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 8 mg/kg/day in males and 5 mg/kg/day in females up to 5.8- and 1.2-fold greater, respectively, than the MRHD based on BSA comparison.

14 CLINICAL STUDIES

14.1 Osteoarthritis and Rheumatoid Arthritis

The use of Meloxicam 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. Meloxicam (7.5 mg, 15 mg, and 15 mg daily) was compared to placebo. The four primary endpoints were investigator global assessment, patient global assessment, patient pain assessment, and total WOMAC score (a self-administered questionnaire addressing pain, function, and stiffness). Patients on Meloxicam 7.5 mg daily and Meloxicam 15 mg daily showed significant improvement in each of these endpoints compared with placebo.

The use of Meloxicam 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 16 months' duration. In these trials, the efficacy of Meloxicam, in doses of 7.5 mg/day and 15 mg/day, was comparable to piroxicam 20 mg/day and diclofenac 50-100 mg/day and consistent with the efficacy seen in the U.S. trial.

The use of Meloxicam for the treatment of the signs and symptoms of rheumatoid arthritis was evaluated in a 12-week, double-blind, controlled multinational trial. Meloxicam (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 Meloxicam 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 Meloxicam for the treatment of the signs and symptoms of pauciarticular or polyarticular 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 0.1 mg/kg/day. On study day 1, patients received their first dose of naproxen or meloxicam. On study day 14, patients clearly used their doses throughout the 12-week dosing period, while the other group accepted a 30% drop in doses to doses of 0.25 mg/kg/day and 0.375 mg/kg/day (0.5 mg maximum) of meloxicam and 10 mg/kg/day of naproxen.

The efficacy analyses used the ACR Pediatric 20 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 was similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

16 HOW SUPPLIED/STORAGE AND HANDLING

Meloxicam tablets USP are available as a light yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. The 15 mg tablet is imprinted with letter U and L on one side and tablet code 15 on the other side.

Meloxicam Tablets USP 15 mg are available as follows:

NDC 76420-039-07: Bottles of 7 (repackaged from NDC 29300-125-xx)

NDC 76420-039-10: Bottles of 10 (repackaged from NDC 29300-125-10)

NDC 76420-039-14: Bottles of 14 (repackaged from NDC 29300-125-xx)

NDC 76420-039-20: Bottles of 20 (repackaged from NDC 29300-125-xx)

NDC 76420-039-30: Bottles of 30 (repackaged from NDC 29300-125-10)

NDC 76420-039-60: Bottles of 60 (repackaged from NDC 29300-125-10)

NDC 76420-039-90: Bottles of 90 (repackaged from NDC 29300-125-90)

Storage/How to Use: 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature]. Keep Meloxicam Tablets USP in a dry place.

Dispense tablets in a tight container.

Keep this and all medications out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed.

Inform patients, families or their caregivers of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, nausea, and hematemesis, to their healthcare provider. In the setting of concurrent use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Headaches

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop Meloxicam tablets and seek immediate medical therapy [see Warnings and Precautions (5.8)].

Swallow Tablets and Doses

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Respiratory Function

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].

Serious Skin Reactions

Advise patients to stop Meloxicam tablets immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9)].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including Meloxicam tablets, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8.3)].

Label Claims

Inform pregnant women to avoid use of Meloxicam tablets and other NSAIDs starting at 28 weeks gestation because of the risk of premature closure of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of Meloxicam tablets with other NSAIDs or salicylates (e.g., effervescent, buffered, or rectal) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with Meloxicam tablets until they talk to their healthcare provider [see Drug Interactions (7)].

Repackaged by:

Emmecham PHARMACEUTICALS

Torrance, CA 90503

SPL MEDGUIDE

Medication Guide for Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
What is the most important information I should know about medicines called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)? NSAIDs can cause serious side effects, including: • Increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase: o with increasing doses of NSAIDs; o with longer use of NSAIDs; • Temporary artery bypass graft (CABG). • After taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack. • Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines. o anytime during use o without warning symptoms • They may cause death. The risk of getting an ulcer or bleeding increases with: o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs o taking medicines called "corticosteroids," "anti-coagulants," "SSRIs," or "SRIs" o long-term use of NSAIDs o smoking o drinking alcohol o older age o poor health o advanced liver disease • bleeding problems. NSAIDs should only be used: o exactly as prescribed o at the lowest dose possible for your treatment o for the shortest time needed.
What are NSAIDs? NSAIDs are used to treat pain and reduce, 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 NSAIDs? Do not take NSAIDs: • If you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID. • Right before or after heart bypass surgery. Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you: • Have liver or kidney problems. • Are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 weeks of pregnancy. • Are breastfeeding or plan to breast feed. Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first. What are the possible side effects of NSAIDs? NSAIDs can cause serious side effects, including: See "What is the most important information I should know about medicines called Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)?" • one or more high blood pressures • heart failure • liver problems including liver failure • kidney problems including kidney failure • low red blood cells (anemia) • life-threatening skin reactions • life-threatening allergic reactions • Other side effects of NSAIDs include stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness. Get emergency help right away if you get any of the following symptoms: • Chest pain • Shortness of breath or trouble breathing • Weakness in one part or side of your body • Slurred speech • Swelling of the face or throat.
If you take your NSAID and call your healthcare provider right away if you get any of the following symptoms: • More tired or weaker than usual • Dizziness • Fainting • Your skin or eyes look yellow • Redness or stomach pain • flu-like symptoms • Joint pain • There is blood in your bowel movement or it is black and sticky like tar • Unexplained weight gain • Skin rash or blisters with fever • Swelling of the arms, legs, hands and feet
If you take too much of your NSAID, call your healthcare provider or get

