

MELOXICAM, meloxicam tablet
Davao Pharma, Inc. (DA) Northford Pharmaceuticals

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MELOXICAM TABLETS USP safely and effectively. See full prescribing information for MELOXICAM TABLETS USP.

MELOXICAM Tablet USP, for oral use
United States Approved 2008

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)** can increase risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1).
- **Meloxicam tablets are contraindicated in the setting of coronary artery bypass graft (CABG) surgery (6.2).**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur with or without warning, and may occur without symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2).**

RECENT MAJOR CHANGES
Boxed Warning (2.0)
Indications and Usage, Juvenile Rheumatoid Arthritis (RA) Pauciarticular and Polyarticular Course (1.3)(9)(2016)
Dosage and Administration, General Dosing Instructions (1.2)(10/2016)
Dosage and Administration, Juvenile Rheumatoid Arthritis (RA) Pauciarticular and Polyarticular Course (1.2)(9)(2016)
Warnings and Precautions, Cardiovascular Thrombotic Events (5.1)(5/2016)
Warnings and Precautions, Heart Failure and Edema (5.4)(5/2016)

INDICATIONS AND USAGE
Meloxicam tablets are a non-steroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1)
- Rheumatoid Arthritis (RA) (1, 2)
- Juvenile Rheumatoid Arthritis (RA) in patients who weigh ≥ 60 kg (1, 3)

DOSE AND ADMINISTRATION
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1)

- **OA (2)(4)(6)(7)**
- Starting dose: 7.5 mg once daily
- Dose may be increased to 15 mg once daily
- **RA (1, 2, 4)**
- 7.5 mg once daily in children ≥ 6 kg
- Meloxicam Tablets are not interchangeable with approved formulations of oral meloxicam. Even the total milligram strength is not the same (5.6)

DOSE FORMS AND STRENGTHS
Meloxicam Tablets USP 7.5 mg and 15 mg (3)

CONTRAINDICATIONS
• Known hypersensitivity to meloxicam or any components of the drug product (4)- History of asthma, urticaria, or other drug-type reactions involving aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS
• **Boxed Warning:** Refer to general warning regarding serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal, and to general warning regarding serious gastrointestinal adverse events involving ulceration and perforation (5.1, 5.2)- **Myocardial Infarction and Stroke:** Refer to Warnings and Precautions (5.1)
- **GI Bleeding, Ulceration, and Perforation:** Avoid use in patients with severe heart failure unless benefits are expected to outweigh risk of bleeding and/or ulceration (5.2)
- **Renal Impairment:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypotension. Avoid use in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.4)
- **Hepatic Impairment:** Use with caution in patients with hepatic impairment (5.4)
- **Heart Failure and Edema:** Monitor patients with preexisting edema (without signs or symptoms) (5.4)
- **Aspirin-Salicylate:** Avoid use in patients with aspirin or aspirin-containing products (5.1)
- **Aspirin-Salicylate:** Monitor patients for bleeding or bruising in patients with any signs or symptoms of anemia (5.1, 7)

ADVERSE REACTIONS
• Most common (10% and above) have typically observed adverse events include: headache, upper respiratory tract infection, dyspepsia, and influenza-like symptoms (6.1)- Adverse events observed in clinical studies were similar in nature to the adult clinical trial experience (6.1)

TO REPORT SUSPECTED ADVERSE REACTIONS, contact Davao Pharma Pharmaceuticals (DPP), Inc. at 1-866-562-4104 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• **Drugs that Interact with Meloxicam (See Table 1):** Monitor patients for bleeding who are concomitantly taking meloxicam with drugs that interfere with hemostasis. Concomitant use of meloxicam and analgesic drugs of aspirin has been generally recommended (7).- **Aspirin:** Monitor patients for bleeding or bruising (5.1)
- **Aspirin-Salicylate:** Monitor patients for bleeding or bruising (5.1)
- **Aspirin-Salicylate:** Monitor patients for bleeding or bruising (5.1)
- **Aspirin-Salicylate:** Monitor patients for bleeding or bruising (5.1)
- **Aspirin-Salicylate:** Monitor patients for bleeding or bruising (5.1)

USE IN SPECIFIC POPULATIONS
• **Renal Impairment:** Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation (5.1)(8, 9)- **Aspirin:** NSAIDs are associated with overall morbidity. Consider withdrawal of meloxicam in women who have bleeding tendency (6.3)

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4 CONTRAINDICATIONS

Meloxicam is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any component of the drug product [see Warnings and Precautions (2.7, 5.9)]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Warnings and Precautions (2.7, 5.9)]
- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three-year duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on relative dose, 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 among users 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 serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began early as the first weeks 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 such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the signs to take if they occur.

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, such as meloxicam, increases the risk of serious gastrointestinal (GI) event [see Warnings and Precautions (5.2)].

5.2 Postoperative Acute Myocardial Infarction (AMI) Syndrome

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

5.3 MI Patients

Observational 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 case cohort, the incidence of death in the first-year post-MI was 20 per 100 persons/year in NSAID-treated patients compared to 12 per 100 persons/year 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. 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 bleed 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 gastrointestinal events 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 Risks 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.
- Remains 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 (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, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Meloxicam immediately, and perform a clinical evaluation of the patient [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].

5.4 Hypertension

NSAIDs, including Meloxicam, can lead to a new onset or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, diuretic 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 Cardiovascular and Endothelial Collaborative meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalization 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 effect of several therapeutic agents used to treat these medical conditions (e.g., 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 Hypokalemia

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 prostaglandin 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, which can result in renal blood flow. This may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, 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 mask 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)].

Hypokalemia

Increases in serum potassium concentration, including hypokalemia, 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-hypoaldosteronism 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 (5.9)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subgroup of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps, 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 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 Prevention 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 (8.1)].

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 decrease in erythropoiesis. If a patient treated with Meloxicam has any sign 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 concurrent use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (NRNIs) 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 diminish the utility of diagnostic signs in detecting infection.

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 Banned Warning and Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration, and Perforation [see Banned Warning and Warnings and Precautions (5.2)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hypokalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.9)]
- 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

Dose-toxicity 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, 1505 OA patients and 151 RA patients treated with Meloxicam 15 mg/day. Meloxicam dose-toxicity was observed in these patients in at least one study and in 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo- and/or active-controlled observational trials, and 283 of these patients were treated in placebo- and/or active-controlled observational 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 to compare the efficacy and safety of Meloxicam 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 Meloxicam with placebo.

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

| | Placebo | Meloxicam 7.5 mg daily | Meloxicam 15 mg daily | Diclofenac 100 mg daily |
|--------------------------------------------|---------|------------------------|-----------------------|-------------------------|
| No. of Patients | 157 | 154 | 158 | 153 |
| Gastrointestinal | 17.2 | 20.1 | 17.3 | 20.1 |
| Abdominal pain | 2.5 | 3.9 | 2.6 | 3.9 |
| Dyspepsia | 3.8 | 3.9 | 3.2 | 9.2 |
| Dysphagia | 4.5 | 4.5 | 4.5 | 6.5 |
| Flatulence | 4.5 | 3.2 | 3.2 | 5.5 |
| Nausea | 3.2 | 3.9 | 3.8 | 7.2 |
| Body as a Whole | | | | |
| Accident/injury | 1.9 | 4.5 | 3.2 | 2.6 |
| Edema* | 2.5 | 1.9 | 4.5 | 3.3 |
| Fall | 0.6 | 0.6 | 0.6 | 1.3 |
| Headache | 5.1 | 4.5 | 5.8 | 2.6 |
| Cranial and Peripheral Nerve System | | | | |
| Dizziness | 3.2 | 3.6 | 3.8 | 2.6 |
| Headache | 10.2 | 7.8 | 8.3 | 5.9 |
| Respiratory | | | | |
| Pharyngitis | 1.3 | 0.6 | 3.2 | 1.3 |
| Upper respiratory tract infection | 0.9 | 3.2 | 1.9 | 3.3 |
| Skin | | | | |
| Rash | 2.5 | 2.6 | 0.6 | 1.0 |

Table 1b Adverse Events (%) Occurring in ≥2% of Meloxicam Patients in two 12-Week Rheumatoid Arthritis Placebo- Controlled Trials

| | Placebo | Meloxicam 7.5 mg daily | Meloxicam 15 mg daily |
|-------------------------------------------------------------|---------|------------------------|-----------------------|
| No. of Patients | 465 | 461 | 477 |
| Gastrointestinal Disorders | 14.1 | 13.9 | 16.8 |
| Abdominal pain NCI | 0.6 | 2.6 | 3.3 |
| Dyspepsia, pain and symptoms* | 3.9 | 3.9 | 4.6 |
| Nausea† | 2.6 | 3.3 | 3.8 |
| General Disorders and Administration Site Conditions | | | |
| Influenza-like illness | 2.1 | 2.9 | 2.3 |
| Infections and Infestations | | | |
| Upper respiratory tract infection | 4.1 | 7.0 | 6.5 |
| Musculoskeletal and Connective Tissue Disorders | | | |
| Arthralgia | 3.9 | 3.5 | 2.3 |
| Neuropathy Systemic | 6.4 | 6.4 | 5.5 |
| Skin and Subcutaneous Tissue Disorders | | | |
| Rash NCI | 1.7 | 1.0 | 2.1 |

* Most commonly reported were nausea, abdominal pain NCI, influenza like illness, headache NCI, and rash NCI.
 † Includes high level (severe) dyspepsia, pain and symptoms (dyspepsia, dyspepsia aggravated, constipation, gastrointestinal transit, upper respiratory tract infections, pain-related dyspepsia NCI, nausea NCI, nausea NCI), pain related signs and symptoms (abdominal, atrophic, aggravated, pain, constipation, pain, reflux, joint swelling)
 ‡ Includes events that occurred with Meloxicam in ≥2% of patients treated short-term (4 to 6 weeks) and long-term (months) in active-controlled osteoarthritis trials (see previous Table 2)

Table 2 Adverse Events (%) Occurring in ≥2% of Meloxicam Patients in a 6-Week and 6-Month Active-Controlled Osteoarthritis Trial

| | 6 Weeks Controlled Trial | 6 Month Controlled Trial |
|-------------------------------------------------------------|--------------------------|--------------------------|
| No. of Patients | Meloxicam 7.5 mg daily | Meloxicam 15 mg daily |
| No. of Patients | 465 | 461 |
| Gastrointestinal Disorders | 14.1 | 13.9 |
| Abdominal pain NCI | 0.6 | 2.6 |
| Dyspepsia, pain and symptoms* | 3.9 | 3.9 |
| Nausea† | 2.6 | 3.3 |
| General Disorders and Administration Site Conditions | | |
| Influenza-like illness | 2.1 | 2.9 |
| Infections and Infestations | | |
| Upper respiratory tract infection | 4.1 | 7.0 |
| Musculoskeletal and Connective Tissue Disorders | | |
| Arthralgia | 3.9 | 3.5 |
| Neuropathy Systemic | 6.4 | 6.4 |
| Skin and Subcutaneous Tissue Disorders | | |
| Rash NCI | 1.7 | 1.0 |

* Most commonly reported were nausea, abdominal pain NCI, influenza like illness, headache NCI, and rash NCI.
 † Includes high level (severe) dyspepsia, pain and symptoms (dyspepsia, dyspepsia aggravated, constipation, gastrointestinal transit, upper respiratory tract infections, pain-related dyspepsia NCI, nausea NCI, nausea NCI), pain related signs and symptoms (abdominal, atrophic, aggravated, pain, constipation, pain, reflux, joint swelling)
 ‡ Includes events that occurred with Meloxicam in ≥2% of patients treated short-term (4 to 6 weeks) and long-term (months) in active-controlled osteoarthritis trials (see previous Table 2)

Higher doses of Meloxicam (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore, the daily dose of Meloxicam should not exceed 15 mg.

Warnings

Paraneoplastic and Psychiatric Events Associated with Rheumatoid Arthritis (RA)
 Three hundred and eighty-seven patients with paraneoplastic and polyarthritic course RA were exposed to Meloxicam 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 48-week extension) and one 1-year open-label PK study. The adverse events observed in these pediatric studies with Meloxicam were similar to those in 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 pruritus, were more common in the pediatric than in the adult trials. Rash was reported in seven (<2%) patients receiving Meloxicam. 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 ≥2% of patients receiving Meloxicam in clinical trials involving approximately 16,200 patients.

| Body as a Whole | allergic reactions, face edema, fatigue, fever, hot flashes, malaise, syncope, weight decrease, weight increase |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cardiovascular | angina pectoris, cardiac failure, edema, hypertension, myocardial infarction, syncope |
| Cranial and Peripheral Nervous System | convulsions, dizziness, headache, vertigo |
| General Disorders | asthenia, fatigue, malaise, weakness |
| Gastrointestinal | colitis, dry mouth, duodenal ulcer, enteritis, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastroenteritis, hemorrhage, hematemesis, hemorrhagic shock, hemorrhagic gastritis, ulcers, intestinal perforation, nausea, constipation, perforated duodenal ulcer, perforated gastric ulcer, stomatitis, ulceration |
| Heart Rate and Rhythm | bradycardia, palpitations, tachycardia |
| Hematologic | hemiparesis, purpura, thrombocytopenia |
| Immune and Allergic System | anaphylaxis, anaphylactoid reaction, allergic reaction |
| Musculoskeletal and Neuronal | dehiscence |
| Psychiatric | delirium, depression, insomnia, agitation, increased confusion, depression, nervousness, somnolence |
| Respiratory | asthma, bronchospasm, dyspnea |
| Skin and Appendages | alopecia, angiodema, bullous eruption, photosensitivity reaction, pruritus, swelling, increased, urticaria |
| Special Senses | abnormal vision, conjunctivitis, eye irritation, tearing |
| 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 Meloxicam. 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. Decision about whether to include an adverse event from spontaneous reports is based on the number of reports, the severity of the event, (2) whether the event is specifically based on one or more of the following factors: (1) seriousness of the event; (2) whether the event is new or unexpected; (3) whether the event is likely to affect the benefit-risk balance of the drug. Adverse reaction reported in worldwide post marketing experience or in the literature include acute urinary reaction, angitis, thrombocytopenia, meningitis, rash, anaphylaxis, anaphylactoid reaction, including, shock, erythema multiforme, exfoliative dermatitis, impetigo, allergic, purpura; liver failure, Steven-Johnson syndrome, toxic epidermal necrolysis, and interstitial keratitis.

7 DRUG INTERACTIONS

See Table 3 for clinically significant drug interactions with meloxicam. See also Warnings and Precautions (5.2, 5.6, 5.11) and Clinical Pharmacology (12.3).

Table 3 Clinically Significant Drug Interactions with Meloxicam

| Drug Class | Interaction with Meloxicam |
|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anticoagulants | Meloxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Meloxicam reduces the plasma levels and antiplatelet activity of aspirin. Close clinical and laboratory monitoring of patients should be conducted when the concomitant use of drugs that interfere with serotonin receptors and NSAIDs may potentiate the risk of bleeding more than an NSAID alone. Monitor patients with concurrent use of Meloxicam with anti-coagulants (e.g., warfarin, antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin reuptake inhibitors (SRIIs) for signs of bleeding (see Warnings and Precautions (5.1)). |
| Aspirin | Concomitant use of Meloxicam and low-dose aspirin or analgesic doses of aspirin do not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone (see Warnings and Precautions (5.2)). Concomitant use of Meloxicam and low-dose aspirin or analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding (see Warnings and Precautions (5.1)). Meloxicam is not a substitute for low dose aspirin for cardiovascular protection. |
| ACE Inhibitors, Angiotensin Receptor Blockers, or Beta-Blockers | NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or beta-blockers (see Indications, Proprietary). Patients who are already receiving treatment for hypertension should be monitored for any reduction in blood pressure when concomitant use of NSAIDs with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. During concomitant use of Meloxicam and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of Meloxicam and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function (see Warnings and Precautions (5.6)). When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter. |
| Diuretics | Diuretics, as well as loop diuretics, may increase the risk of renal impairment when used concomitantly with NSAIDs. During concomitant use of Meloxicam with diuretics, observe patients for signs of worsening renal function, in addition to assessing diuretic efficacy including antihypertensive effects (see Warnings and Precautions (5.6)). |
| Lithium | NSAIDs have reduced elevation of plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis (see Clinical Pharmacology (12.3)). During concomitant use of Meloxicam and lithium, monitor patients for signs of lithium toxicity. |
| Meloxicam | Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., myelosuppression, thrombocytopenia, renal dysfunction). During concomitant use of Meloxicam and methotrexate, monitor patients for methotrexate toxicity. |
| Cyclosporin | Concomitant use of Meloxicam and cyclosporin may increase cyclosporin's nephrotoxicity. During concomitant use of Meloxicam and cyclosporin, monitor patients for signs of worsening renal function. |
| NSAIDs and Salicylates | Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salicylates) increases the risk of GI toxicity, with little or no increase in efficacy (see Warnings and Precautions (5.2)). Concomitant use of meloxicam with other NSAIDs or salicylates is not recommended. |
| Penicillins | Concomitant use of Meloxicam and penicillins may increase the risk of penicillin-associated myelosuppression, renal, and GI toxicity (see the penicillin prescribing information). During concomitant use of Meloxicam and penicillin, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following penicillin administration. Patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with penicillin is not recommended. |

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary:
 Use of NSAIDs, including Meloxicam, during the third trimester of pregnancy increases the risk of 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 Warnings and Precautions (5.1)).

There are no adequate and well-controlled studies of Meloxicam in pregnant women. Data from observational studies regarding potential embryofetal risk of NSAID use in women in the first or second trimester of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformation, and 15-20% for pregnancy loss.
 In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 5.5-fold the maximum recommended human dose (MRHD) of Meloxicam. Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at oral doses equivalent to 7.5-fold the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and stillbirths in mice given meloxicam at oral doses equivalent to 2.5- and 20-fold the MRHD (see Data).
 Based on animal data, prostaglandin have been shown to have an important role in embryofetal vascular permeability, placental implantation, and decidualization. In animal studies, administration of prostaglandin synthase inhibitors, such as meloxicam, resulted in increased pre- and post-implantation

NSAID.

Pharmacokinetics

-

Labor or Delivery

There are no studies on the effects of Meloxicam during labor or delivery. In animal studies, NSAIDs, including meloxicam, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

-

Animal Data

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 MRHD of 15 mg of meloxicam based on 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 (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA comparison). In rats and rabbits, embryofetality occurred at oral meloxicam doses of 1 mg/kg/day and 1 mg/kg/day, respectively (0.6-fold greater, respectively, than the MRHD based on BSA comparison when administered throughout organogenesis).

Oral administration of meloxicam to pregnant rats during 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 (0.08-times MRHD based on BSA comparison).

2.1 Lactation

Risk Summary

There are no human data available on whether meloxicam is present in human milk, or on the effects on breastfed infants, or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Meloxicam and any potential adverse effects on the breastfed infant from the Meloxicam from the underlying maternal condition.

Data

Animal Data

Meloxicam was present in the milk of lactating rats at concentrations higher than those in plasma.

2.2 Fertility and Male of Reproductive Potential

Female

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Meloxicam, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthase inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including Meloxicam, in women who have difficulties conceiving or who are undergoing investigation of infertility.

2.3 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 (4.1) and Clinical Studies (4.2.1)).

2.4 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, 7.1)).

2.5 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)).

2.6 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 overdosage have been typically limited to headache, dizziness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare (see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)).

Monitor patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (50 to 100 g in adults, 1 to 2 g per kg of body weight in pediatric patients under 16 years of age) in symptomatic patients more than four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

For additional information about overdosage treatment, call a poison control center (1-800-222-1232).

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 cholesteryl-2-(methyl-*N*-(5-oxo-5H-tetrahydro-2H-pyridin-2-ylidene)-2H-1,2,4-oxadiazol-3-yl)carbamate-1,1-dioxide. The molecular weight is 321.4. Its empirical formula is C₁₈H₁₈N₂O₅ and it has the following structural formula:



Meloxicam is a pale 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}) of 1.1 in octanol-buffer (pH 7.4). Meloxicam has *p*K_a values of 1.1 and 4.2.

Meloxicam is available as a tablet for oral administration containing 7.5 mg or 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 vivo*. Meloxicam concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in 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 prostaglandin in peripheral tissues.

12.2 Pharmacokinetics

Absorption

The absolute bioavailability of meloxicam capsules was 99% 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 to 15 mg. After multiple oral doses, the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean *C*_{max} was achieved within 1 to 2 hours after a 7.5 mg meloxicam tablet was administered under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 3. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose, suggesting biliary recirculation.

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 (% CV) | Steady State | | Single Dose | |
|-----------------------------------|----------------------------|----------------|------------------------|----------------|
| | Healthy male adults (n=12) | | Elderly females (n=12) | |
| | 7.5 mg tablets | 15 mg capsules | 15 mg capsules | 15 mg capsules |
| <i>C</i> _{max} | 1.0 (20) | 2.1 (24) | 0.9 (18) | 0.84 (20) |
| <i>t</i> _{max} | 0.5 | 0.7 | 0.6 | 0.7 |
| <i>t</i> _{1/2} | 20.1 (29) | 21.1 (43) | 18 (46) | 16 (29) |
| <i>t</i> _{1/2} (fast) | 8.8 (20) | 8.5 (75) | 5.1 (22) | 10 (44) |
| <i>t</i> _{1/2} (slow) | 11.7 (42) | 10 (30) | 25 (44) | 14 (22) |

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

† = acute high fat condition

‡ Meloxicam tablets

§ *N*-(2-(5-oxo-5H-tetrahydro-2H-pyridin-2-ylidene)-2-methyl-1,2,4-oxadiazol-3-yl)carbamate-1,1-dioxide

¶ Food and Absorption Effects

Administration of meloxicam capsules following a high fat breakfast (75% of fat) resulted in mean peak drug levels (i.e., *C*_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (*T*_{max}) was achieved between 1 and 5 hours. No pharmacokinetic interaction was detected with concurrent administration of antacids. Based on these results, Meloxicam can be administered without regard to timing of meals or concurrent administration of antacids.

Distribution

The mean volume of distribution (V_d) 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.

Elimination

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 7-carboxy meloxicam (60% of dose), from *P*-450 mediated metabolism formed by oxidation of an intermediate metabolite 5-hydroxymethyl meloxicam which also undergoes 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' peroxisome activity is probably responsible for the other two metabolites which account for 16% and 6% of the administered dose, respectively. All the four metabolites are not known to have any *in vitro* pharmacological activity.

Excretion

Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extent in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The route of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 52%, 5%, and 12% of the dose were found in urine in the form of meloxicam, and the 5-hydroxymethyl and 7-carboxy metabolites, respectively. There is significant biliary and/or renal excretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean elimination half-life (*t*_{1/2}) ranges from 13 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.

Specific 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 by a dose of 0.25 mg/kg (see Dosage and Administration (2.4)). The meloxicam mean (SD) elimination half-life was 15.2 (10.1) and 13.0 hours (1.0) 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 plasma clearance. The body weight normalized apparent oral clearance values were adequate predictors of meloxicam exposure in pediatric patients.

The pharmacokinetics of Meloxicam in pediatric patients under 2 years of age have not been investigated.

Geriatric

Elderly males (≥65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (≥65 years of age) had a 47% higher AUC_{0-∞} and 32% higher *C*_{max} as compared to younger females (≤55 years of age) after body weight normalization. Despite the increased oral 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.

Sex

Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg Meloxicam, the mean elimination half-life was 19.5 hours for the female group as compared to 22.4 hours for the male group. At steady state, the data were similar (17.6 hours vs. 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C_{max} or T_{max} across genders.

Hepatic 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 (6.6)].

Renal Impairment

Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and renal 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 fractions of unbound meloxicam which is available for renal elimination 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 Meloxicam in subjects with severe renal impairment is not recommended [see Dosage and Administration (2.5), Warnings and Precautions (5.6) and Use in Specific Populations (6.7)].

Hemodialysis

Following a single dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic hemodialysis (7% free fraction) in comparison to healthy volunteers (93% 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) and Use in Specific Populations (6.7)].

Drug Interactions/Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. When Meloxicam is administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [see Drug Interactions (7)].

Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicamly 50%. This results in decrease in t_{1/2} from 19.5 hours to 12.5 hours, and a 30% 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: Concurrent 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 intravenous administration for 7 days at clinical doses. In vivo testing found no protein binding displacement 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)].

Mefenamic Acid: A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of mefenamic acid once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of mefenamic acid. In vivo, mefenamic acid 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 (93 weeks) administered meloxicam oral doses up to 0.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 5.5- and 2.2-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 impact 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-times 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 22.5 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and 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 6 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 SR 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) Pastericoides and Polyarticular Course

The use of Meloxicam for the treatment of the signs and symptoms of pastericoides 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 0.25 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 reduction 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 responses 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 responses 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

Meloxicam tablets USP are available as a light yellow, round, flat, uncoated tablet containing meloxicam 7.5 mg or a light yellow, oblong, biconvex, uncoated tablet containing meloxicam 15 mg. The 7.5 mg tablet is impressed with letter U and L on one side and tablet code 7.5 on the other side. The 15 mg tablet is impressed with letter U and L on one side and tablet code 15 on the other side.

Meloxicam Tablets USP 7.5 mg are available as follows:

NDC 29300-124-13, Bottles of 30

NDC 29300-124-01, Bottles of 100

NDC 29300-124-10, Bottles of 1,000

NDC 29300-124-50, Bottles of 5,000

Meloxicam Tablets USP 15 mg are available as follows:

NDC 29300-125-13, Bottles of 30

NDC 29300-125-01, Bottles of 100

NDC 29300-125-10, Bottles of 1,000

NDC 29300-125-50, Bottles of 5,000

Store at 20° to 25° (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.

Additional Medication Guides can be obtained by calling Unichem at 1-866-562-4616.

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 health-care provider immediately [see Warnings and Precautions (5.1)].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulceration and bleeding, including epigastric pain, dyspepsia, nausea, and hematemesis to their health-care 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)].

Hepatotoxicity

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 (5.3)].

Heart Failure and Edema

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 health-care provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions

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)].

Severe Skin Reactions

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

Fertility Evaluation

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 (6.3)].

Fetal Toxicity

Inform pregnant women to avoid use of Meloxicam tablets and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (6.3)].

Avoid Concurrent Use of NSAIDs

Inform patients that the concurrent use of Meloxicam tablets with other NSAIDs or salicylates (e.g., difflucan, ibuprofen) is not recommended due to the increased risk of gastrointestinal toxicity, and this may also increase the risk of bleeding [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Advise patients that NSAIDs may be present in "over the counter" medications for treatment of cold, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

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

For current prescribing information, call Unichem at 1-866-562-4616.

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Pilanesberg, Randburg, Gauteng, 2091, South Africa

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Medication Guide for Non-steroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Non-steroidal 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:
 • with increasing doses of NSAIDs
 • with longer use of NSAIDs.
 Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."
 Avoid 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:
 • aspirin during use
 • without warning symptoms
 • that may cause death
 The risk of getting an ulcer or bleeding increases with:
 • past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
 • taking medicines called "corticosteroids", "anti-coagulants", "SSRIs", or "SNRIs"
 • increasing doses of NSAIDs
 • longer use of NSAIDs
 • smoking
 • drinking alcohol
 • older age
 • poor health
 • advanced liver disease
 • bleeding problems
 NSAIDs should only be used:
 • exactly as prescribed
 • at the lowest dose possible for your treatment
 • for the shortest time needed

What are NSAIDs?
 NSAIDs 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.

When 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, or if you have ever had heart failure surgery
 • before taking NSAIDs, if your healthcare provider about all of your medical conditions, including if you:
 • have liver or kidney problems
 • have high blood pressure
 • have asthma
 • 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 medicine, 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 Non-steroidal Anti-inflammatory Drugs (NSAIDs)?"
 • new or worse high blood pressure
 • heart failure
 • liver problems including liver failure
 • kidney problems including kidney failure
 • low red blood cells (anemia)
 • low platelets (which may cause bleeding)
 • life-threatening allergic reaction
 • Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, headache, and dizziness.
 Get emergency help right away if you get any of the following symptoms:
 • chest pain or trouble breathing
 • dizziness
 • chest pain
 • weakness in one part or side of your body
 • blurred speech
 • swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:
 • Nausea and/or weaker than usual
 • diarrhea
 • dizziness
 • feeling
 • your skin or eyes look yellow
 • indigestion or stomach pain
 In the following symptoms:
 • vomit blood
 • there is blood in your bowel movement or it is black and sticky like tar
 • unusual weight gain
 • skin rash or hives with fever
 • swelling of the arms, legs, hands and feet

You take too much of your NSAID, call your healthcare provider or get medical help right away.
 There are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs:
 • Aspirin is an NSAID 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 NSAIDs 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.

General information about the safe and effective use of NSAIDs:
 Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.
 If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

Additional Medication Guides can be obtained by calling Unichem at 1-866-562-4616.
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 1-800-562-4616

This Medication Guide has been approved by the U.S. Food and Drug Administration.
 Revised: September 2017

Principal Display Panel

NDC: 79934-611-30



| MELOXICAM | | | |
|----------------------------------------|-----------------------------------------------------|-----------------------------------------------------------|----------------------------|
| meloxicam tablet | | | |
| Product Information | | | |
| Product Type | HUMAN PRESCRIPTION DRUG | Item Code (Package) | NDC 79934-611-30 (30) (30) |
| Route of Administration | ORAL | | |
| Active Ingredient/Active Moiety | | | |
| | Ingredient Name | Strength | |
| | MELOXICAM (SHE VEGANIC) (MELOXICAM - UNICHEM) (C12) | MELOXICAM | 15 mg |
| Inactive Ingredients | | | |
| | Ingredient Name | Strength | |
| | CELLULOSE, MICROCRYSTALLINE (SHE OPERATIONS) | | |
| | CROSCARROLLON (SHE OPERATIONS) | | |
| | LACTOSE MONOHYDRATE (SHE OPERATIONS) | | |
| | MAGNESIUM HYDROXIDE (SHE OPERATIONS) | | |
| | POLYBOND 838 (SHE OPERATIONS) | | |
| | PLAQUE BARRIER (SHE OPERATIONS) | | |
| | TETRAHYDROFURAN DIMETHYLACRYLATE (SHE OPERATIONS) | | |
| Product Characteristics | | | |
| Color | White | Shape | 15 mg oval |
| Shape | OVAL | Size | 15 mg |
| Marking | | Impression Code | 15 mg |
| Packaging | | | |
| # | Item Code | Package Description | Marketing Start Date |
| 1 | NDC 79934-611-30 | 30 in BOTTLE (PLASTIC, Type 0, Not a Combination Product) | 1/11/2017 |
| Marketing Information | | | |
| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
| NDA | ANDA487927 | 2009-04-27 | |

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Registrant: Unichem Pharmaceuticals, Inc. (DIA Northford Pharmaceuticals) (8855246)

| Establishment | | | |
|---------------|-------------------------------|----------|--------------------|
| | Name | Address | Business Operation |
| | Unichem Pharmaceuticals, Inc. | 18410100 | 79934-611-30 (30) |