

**MELOXICAM** meloxicam tablet

OPharma Inc.  
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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

MELOXICAM tablets, for oral use  
Initial U.S. Approval: 2009

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

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased 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 is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4.1).**
- **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 at any time during use and without warning symptoms. Elderly patients and patients with prior history of upper GI bleeding are at greater risk for serious GI events (5.2).**

**RECENT MAJOR CHANGES**

Revised Warnings	5/2016
Indications and Usage, Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course (1.3)	6/2016
Dosage and Administration, General Dosage Instructions (2.1)	6/2016
Dosage and Administration, Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course (2.4)	6/2016
Warnings and Precautions, Cardiovascular, Thrombotic Events (5.1)	6/2016
Warnings and Precautions, Heart Failure and Edema (5.4)	5/2016

**INDICATIONS AND USAGE**  
Meloxicam Tablets are non-steroidal anti-inflammatory drugs indicated for:

- Osteoarthritis (OA) (1)
- Rheumatoid Arthritis (RA) (2)
- Juvenile Rheumatoid Arthritis (JRA) 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) and RA (2):
  - Starting dose: 7.5 mg once daily
  - Dose may be increased to 15 mg once daily
- JRA (1.3):
  - 7.5 mg once daily in children ≥ 60 kg

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

**CONTRAINDICATIONS**

- Known hypersensitivity reactions to any component of this drug product (6)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

**WARNINGS AND PRECAUTIONS**

- **Hypotension:** Inform patients of warning signs and symptoms of hypotension. Discontinue if abnormal vital signs persist or worsen or if clinical signs and symptoms of low blood pressure develop (2.1).
- **Hypertension:** Patients taking usual analgesic/analgesic medications may have increased response to these therapies when taking NSAIDs. Monitor blood pressure (4.2).
- **Heart Failure and Edema:** Avoid use of meloxicam in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.4).
- **Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypotension. Avoid use of meloxicam in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6).
- **Anaphylactoid Reactions:** Seek emergency help for anaphylactoid reactions (5.7).
- **Exacerbation of Asthma Related to Aspirin Sensitivity:** Meloxicam is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with pre-existing asthma without aspirin sensitivity (5.8).
- **Serious Skin Reactions:** Discontinue meloxicam at first appearance of skin rash or other signs of hypersensitivity (5.9).
- **Pregnancy Class of Food/Drug Interaction:** Avoid use in pregnant women starting at 30 weeks gestation (5.10, 8.1).
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with signs or symptoms of anemia (5.11, 7).

**ADVERSE REACTIONS**

- Most common (≥5%), and greater than placebo/adverse events in adults are diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (6.1)
- Adverse events observed in pediatric studies were similar in nature to the adult clinical trial experience (6.1)

**DRUG INTERACTIONS**

- Drug-Drug Interactions with Ibuprofen (e.g., warfarin, aspirin, SSRIs, NSAIDs): Monitor patients for bleeding who are concurrently taking meloxicam with drugs that increase the risk of bleeding. Concurrent use of meloxicam and analgesic doses of aspirin are not generally recommended (7)
- ACE Inhibitors, Angiotensin Receptor Blockers (ARBs) or Beta-Blockers: Concurrent use with meloxicam may decrease antihypertensive effect of these drugs. Monitor blood pressure (7)
- ACE Inhibitors and ARBs: Concurrent use with meloxicam may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- Diuretics: NSAIDs can reduce diuretic effect of furosemide and thiazide diuretics. Monitor patients to assess diuretic efficacy including antihypertensive effect (7)

**USE IN SPECIFIC POPULATIONS**

- **Pregnancy:** 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 (5.10, 8.1).
- **Lactation:** NSAIDs are associated with reversible lactation. Consider withdrawal of meloxicam in women who have difficulty conceiving (5.12)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2018

**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

**INDICATIONS AND USAGE**  
1.1 Osteoarthritis (OA)  
1.2 Rheumatoid Arthritis (RA)  
1.3 Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course

**2 DOSE AND ADMINISTRATION**  
2.1 General Dosage Instructions  
2.2 Osteoarthritis  
2.3 Rheumatoid Arthritis  
2.4 Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course  
2.5 Renal Impairment  
2.6 Non-Interchangeability with Other Formulations of Meloxicam

**3 DOSE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**  
5.1 Cardiovascular Thrombotic Events  
5.2 Gastrointestinal Bleeding, Ulceration, and Perforation  
5.3 Hypotension  
5.4 Hypertension  
5.5 Heart Failure and Edema  
5.6 Renal Toxicity and Hypertolemia  
5.7 Anaphylactoid Reactions  
5.8 Exacerbation of Asthma Related to Aspirin Sensitivity  
5.9 Serious Skin Reactions  
5.10 Pregnancy Class of Food/Drug Interaction  
5.11 Hematologic Toxicity  
5.12 Masking of Inflammation and Fever  
5.13 Laboratory Monitoring

**6 ADVERSE REACTIONS**  
6.1 Clinical Trial Experience  
6.2 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**  
8.1 Pregnancy  
8.2 Lactation  
8.3 Females and Males of Reproductive Potential  
8.4 Pediatric Use  
8.5 Geriatric Use  
8.6 Hepatic Impairment  
8.7 Renal Impairment

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**  
12.1 Mechanism of Action  
12.2 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**  
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

**14 CLINICAL STUDIES**  
14.1 Osteoarthritis and Rheumatoid Arthritis  
14.2 Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**  
\* Action or subsection omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

**Cardiovascular Thrombotic Events**

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased 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. See Warnings and Precautions (5.1).**
- **Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. See Contraindications (4) and Warnings and Precautions (5.1).**

**Gastrointestinal Bleeding, Ulceration, and Perforation**

- **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 at any time during use and without warning symptoms. Elderly patients and patients with prior history of upper GI bleeding are at greater risk for serious GI events. See Warnings and Precautions (5.2).**

**1 INDICATIONS AND USAGE**

**1.1 Osteoarthritis (OA)**  
Meloxicam tablets are indicated for relief of the signs and symptoms of osteoarthritis [see Clinical Studies (14.1)].

**1.2 Rheumatoid Arthritis (RA)**  
Meloxicam tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis [see Clinical Studies (14.2)].

**1.3 Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course**  
Meloxicam tablets are indicated for relief of the signs and symptoms of paraceticular or polyarticular course Juvenile Rheumatoid Arthritis in patients who weigh ≥60 kg [see Dosage and Administration (2.4) and Clinical Studies (14.2)].

**2 DOSE AND ADMINISTRATION**

**2.1 General Dosage Instructions**  
Carefully consider the potential benefits and risks of meloxicam tablets and other treatment options before deciding to use meloxicam tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)]. After observing the response to initial therapy with meloxicam tablets, adjust the dose to suit an individual patient's needs.

In adults, the maximum recommended daily oral dose of meloxicam tablets are 15 mg regardless of formulation. In patients with hemodialysis, a maximum daily dosage of 7.5 mg is recommended [see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]. Meloxicam tablets may be taken without regard to timing of meals.

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

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

**2.4 Juvenile Rheumatoid Arthritis (JRA) Paraceticular and Polyarticular Course**  
For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of meloxicam tablets is 7.5 mg once daily in children who weigh ≥60 kg. There was no additional benefit demonstrated by increasing the dose above 7.5 mg in clinical trials. Meloxicam tablets should not be used in children who weigh <60 kg.

**2.5 Renal Impairment**  
The use of meloxicam in subjects with severe renal impairment is not recommended. In patients on hemodialysis, the maximum dosage of meloxicam is 7.5 mg per day [see Clinical Pharmacology (12.3)].

## 2.6 Non-Interchangeability with Other Formulations of Meloxicam

Meloxicam tablets have not shown equivalent systemic exposure to other approved formulations of oral meloxicam. Therefore, meloxicam tablets are not interchangeable with other formulations of oral meloxicam product even if the total milligram strength is the same. Do not substitute similar dose strengths of meloxicam tablets with other formulations of oral meloxicam product.

## 3 DOSAGE FORMS AND STRENGTHS

Meloxicam Tablets, USP:

- 7.5 mg: yellow, round-shaped, flat beveled edge, uncoated tablets debossed with "ZC" and "25" on one side and plain on other side
- 15 mg: yellow, round-shaped, flat beveled edge, uncoated tablets debossed with "ZC" and "26" on one side and plain on other side

## 4 CONTRAINDICATIONS

Meloxicam is contraindicated in the following patients:

- Known hypersensitivity to it, any NSAIDs, reactions and serious skin reactions to meloxicam or any component of the drug product [see Warnings and Precautions (5.7, 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 (5.7, 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 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 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 excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as 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 steps to take if they occur.

There is 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) events [see Warnings and Precautions (5.2)].

Some 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 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-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 additional 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, and without NSAID therapy. GI bleeding, ulceration, and perforation in the 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 during NSAID use compared to their baseline 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 anticoagulants, aspirin, and/or aspirin, and/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.
- Remain 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 concurrent 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. In taking 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 abnormal test results 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 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, 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 NSAID Trialists' Collaboration 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 effects 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

#### 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, 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 have 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 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, hypoadrenergic 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 Cross-Reactions of Asthma Related to Aspirin Sensitivity

A subpopulation 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 the form of aspirin sensitivity [see Contraindications (4)]. When meloxicam is used in patients with pre-existing asthma (to whom 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, Steven-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Advise 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 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 incompletely described effect on 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 pharmacologic activity of meloxicam in reducing inflammation, and possibly fever, may diminish the utility 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 Warning and Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration, and Perforation [see Boxed Warning and 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 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

The use of 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 rates observed in practice.

#### Adults

##### Osteoarthritis and Rheumatoid Arthritis

The meloxicam Phase 2b clinical trial database includes 10,122 OA patients and 1012 RA patients treated with meloxicam 7.5 mg/day, 3005 OA patients and 1331 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 cardiovascular trials and 2307 of these patients were treated in two placebo- and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across meloxicam studies.

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 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 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 a 12-week placebo-controlled rheumatoid arthritis trial.

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

	Placebo 150	Meloxicam 75 mg daily 150	Meloxicam 15 mg daily 150	Placebo 150
<b>No. of Patients</b>	157	251	173	153
<b>Concomitant Medication</b>	17.2	20.1	17.3	20.1
<b>Adverse Events</b>				
Headache	2.5	1.9	2.6	3.3
Dizziness	1.8	7.8	3.2	4.2
Diarrhea	4.2	4.5	4.1	5.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	1.9	2.8	2.9	2.9
<b>Body as a Whole</b>				
Edema (nondependent)	1.0	4.5	2.2	2.6
Edema	2.5	1.9	4.5	3.3
Fatigue	0.6	2.0	0.6	1.3
<b>Cardiovascular System</b>				
<b>Central and Peripheral Nervous System</b>				
Dizziness				
Headache	3.2	2.6	3.8	3.0
Headache	10.2	7.8	8.3	5.9
<b>Respiratory</b>				
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3
<b>Skin</b>				
Rash <sup>b</sup>	2.5	2.6	0.6	2.0

<sup>a</sup>WHO preferred terms, edema, edema dependent, edema peripheral, and edema legs combined  
<sup>b</sup>WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

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

	Placebo 150	Meloxicam 75 mg daily 150	Meloxicam 15 mg daily 150
<b>No. of Patients</b>	469	441	427
<b>Concomitant Medications</b>	14.1	19.9	19.8
<b>Adverse Events</b>			
Headache	4.2	3.9	3.9
Diarrhea	3.8	3.8	4.0
Nausea	2.6	3.3	3.8
<b>General Disorders and Administration Site Conditions</b>			
Edema (nondependent)	2.1	2.9	2.3
<b>Infection and Infestations</b>			
Upper respiratory tract infections (unspecified)	4.1	7.0	6.5
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Joint pain (not specified)	1.9	1.5	2.3
<b>Nervous System Disorders</b>			
Dizziness	0.4	0.4	0.5
<b>Skin and Subcutaneous Tissue Disorders</b>			
Rash (not specified)	1.8	2.1	2.1

<sup>a</sup>WHO preferred terms, edema, edema dependent, edema peripheral, and edema legs combined  
<sup>b</sup>WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

The adverse events that occurred with meloxicam in ≥2% of patients treated (short-term to 6 weeks) and long-term (months to years) are presented in Table 2.

Table 2a Adverse Events (%) Occurring in ≥2% of Meloxicam Patients in 4 to 6 Weeks and 6 Month Active-Controlled Osteoarthritis Trial

	4 to 6 Weeks Controlled Trial Meloxicam 75 mg daily 150	Meloxicam 15 mg daily 150	6 Month Controlled Trial Meloxicam 75 mg daily 150	Meloxicam 15 mg daily 150
<b>No. of Patients</b>	185	196	169	186
<b>Concomitant Medication</b>	11.8	10.8	20.6	24.2
<b>Adverse Events</b>				
Headache	0.8	1.2	1.8	2.6
Dizziness	1.0	2.1	3.0	2.6
Diarrhea	1.4	1.4	2.0	2.6
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.2	4.7	2.2
Vomiting	0.6	0.8	1.8	2.6
<b>Body as a Whole</b>				
Edema (nondependent)	0.0	0.0	0.6	2.0
Edema	0.0	0.0	2.4	1.6
Fatigue	0.9	2.0	3.6	3.2
<b>Cardiovascular System</b>				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.2	3.6	2.6
<b>Hematologic</b>				
Anemia	0.1	0.0	4.1	2.9
<b>Musculoskeletal</b>				
Arthralgia	0.5	0.0	5.3	1.3
Muscle pain	0.5	0.4	3.0	0.7
<b>Psychiatric</b>				
Anxiety	0.4	0.6	3.6	1.6
<b>Respiratory</b>				
Cough	0.2	0.8	2.4	1.0
Upper respiratory tract infection	0.2	0.0	4.3	7.5
<b>Skin</b>				
Alopecia	0.4	1.2	2.4	0.0
Rash <sup>b</sup>	0.3	1.2	3.0	1.3
<b>Urology</b>				
Urinary tract infection	0.1	0.4	2.4	1.3
Urinary frequency	0.3	0.4	4.7	6.0

<sup>a</sup>WHO preferred terms, edema, edema dependent, edema peripheral, and edema legs combined  
<sup>b</sup>WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

Higher doses of meloxicam (2.5 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**  
**Placental and Fetal/Infant Exposure**  
 Three hundred and eighty-two patients with placental and fetal/infant exposure (FR) were exposed to meloxicam with doses ranging from 125 to 0.375 mg/kg per day in active 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 placental studies with meloxicam were similar to those in the adult clinical trial population, although there were differences in frequency. In particular, the following most common adverse events, abdominal pain, vomiting, diarrhea, headache, and dizziness, were more common in the pediatric than in the adult study. Rash was reported in fewer (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.

<b>Body as a Whole</b>	allergic reaction, face edema, fatigue, fever, hot flashes, malaise, syncope, weight decrease, weight increase
<b>Cardiovascular</b>	angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis
<b>Central and Peripheral Nervous System</b>	amblyopia, ataxia, dizziness, vertigo
<b>Constitutional</b>	chills, dry mouth, distal edema, emaciation, eosinophilia, gastric stasis, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematochezia, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative
<b>Heart Rate and Rhythm</b>	bradycardia, palpitation, tachycardia
<b>Hematologic</b>	leukopenia, neutropenia, thrombocytopenia
<b>Kidney and Urinary System</b>	UTI (not specified), AST increased, bilirubinemia, GGT increased, hepatitis
<b>Musculoskeletal</b>	arthralgia
<b>Psychiatric</b>	abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence
<b>Respiratory</b>	asthma, bronchospasm, dyspnea
<b>Skin and Appendages</b>	alopecia, angioedema, bullous eruption, photosensitivity reaction, pruritus, sweating increased, urticaria
<b>Special Senses</b>	abnormal vision, color blindness, taste perversion, tinnitus
<b>Urology</b>	hematuria, UTI (not specified), creatinine increased, hematuria, renal failure

**4.2 Postmarketing 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. Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. Adverse reactions reported in worldwide post marketing experience or the literature include: acute urinary retention; agranulocytosis; abnormal mood (such as mood elevation); amplified reaction including shock; epidermal necrolysis; exfoliative dermatitis; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome toxic epidermal necrolysis, and uterine fibroids.

**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 (12.1).

Table 3 Clinically Significant Drug Interactions with Meloxicam

Drug that Interacts with Meloxicam	Interaction
<b>Aspirin</b>	Meloxicam and aspirin such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants has an increased risk of serious bleeding compared to the use of either drug alone. Serious bleeding by patients plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with systems responsible and an NSAID may increase the risk of bleeding more than an NSAID alone.
<b>Aspirin</b>	Monitor patients with concomitant use of meloxicam with aspirin (e.g., aspirin, aspirin/acetaminophen, or aspirin/ibuprofen) for signs of bleeding (see Warnings and Precautions (5.11)).
<b>Aspirin</b>	Controlled clinical studies showed that the concomitant use of NSAIDs and aspirin does not provide a 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 the adverse risk of bleeding (see Warnings and Precautions (5.11)).
<b>Aspirin</b>	Concomitant use of meloxicam and low dose aspirin or aspirin of aspirin is not generally recommended because of the increased risk of bleeding (see Warnings and Precautions (5.11)).
<b>ACE Inhibitors</b>	Meloxicam is not a substrate for low dose aspirin for cardiovascular protection.
<b>ACE Inhibitors/Angiotensin Receptor Blockers</b>	
<b>Clinical Impact</b>	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (see Labeling, Contraindications). Concomitant use of NSAID with ACE inhibitors or ARBs may result in deteriorated renal function, including possible acute renal failure. These effects are usually reversible.
<b>Intervention</b>	When concomitant use of meloxicam and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
<b>Aspirin</b>	When 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)).
<b>Aspirin</b>	When these drugs are different concentrations, aspirin should be administered at the beginning of the concomitant treatment and aspirin should be discontinued.
<b>Clinical Impact</b>	Clinical studies, as well as post-
<b>Intervention</b>	In clinical observations, NSAIDs reduced the antiplatelet effect of loop diuretics (e.g., furosemide) and diuretic diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. However, studies with furosemide agents and meloxicam have not demonstrated a reduction in antiplatelet effect. Furosemide (single and multiple dose pharmacokinetics and pharmacodynamics) are not affected by multiple doses of meloxicam.
<b>Intervention</b>	During concomitant use of meloxicam with diuretics, observe patients for signs of worsening renal function, in addition to ensuring diuretic efficacy including antihypertensive effects (see Warnings and Precautions (5.6)).
<b>Lithium</b>	
<b>Clinical Impact</b>	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 17%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis (see Clinical Pharmacology (12.7)).
<b>Intervention</b>	When concomitant use of meloxicam and lithium, monitor patients for signs of lithium toxicity.
<b>Methotrexate</b>	
<b>Clinical Impact</b>	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
<b>Intervention</b>	When concomitant use of meloxicam and methotrexate, monitor patients for signs of worsening renal function.
<b>Cyclosporine</b>	
<b>Clinical Impact</b>	Concomitant use of meloxicam and cyclosporine may increase cyclosporine's nephrotoxicity.
<b>Intervention</b>	When concomitant use of meloxicam and cyclosporine, monitor patients for signs of worsening renal function.
<b>NSAIDs and Salicylates</b>	
<b>Clinical Impact</b>	Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, valsalan) increases the risk of GI toxicity, with little or no increase in efficacy (see Warnings and Precautions (5.2)).

<b>Intervention:</b>	The concomitant use of meloxicam with other NSAIDs or salicylates is not recommended.
<b>Precaution:</b>	
<b>Clinical Impact:</b>	Concomitant use of meloxicam and piroxicam may increase the risk of piroxicam-associated myelosuppression, renal, and GI toxicity (see the piroxicam prescribing information).
<b>Intervention:</b>	During concomitant use of meloxicam and piroxicam, in patients with renal impairment whose creatinine clearance ranges from 45 to 70 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 piroxicam administration. In patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with piroxicam 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 risks 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 at oral doses equivalent to 0.6- and 2.4-times the maximum recommended human dose (MRHD) of meloxicam. Increased incidence of vaginal birth defects were observed in ratios treated throughout embryogenesis with meloxicam at oral doses equivalent to 0.6-times the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystic, delayed parturition, and decreased offspring survival at 0.6- and 2.4-times MRHD of meloxicam. No teratogenic effects were observed in ratios, and ratios treated with meloxicam during organogenesis at an oral dose equivalent to 2.4- and 26-times the MRHD [see Data].

Based on animal data, prostaglandin have been shown to have an important role in endometrial vascular permeability, mucinocyte implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors, such as meloxicams, resulted in increased pre- and post-implantation loss.

#### Clinical Consideration

#### 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 (5.6-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 fetal defects of the heart at oral doses of 50 mg/kg/day (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (6-fold greater than the MRHD based on BSA comparison). In rats and rabbits, embryofetal deaths occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.6 and 3.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystic, delayed parturition, and decreased offspring survival at meloxicam doses of 0.12 mg/kg/day or greater (0.86-times MRHD based on BSA comparison).

### 8.2 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 or from the underlying breast condition.

#### Data

#### Animal Data

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

### 8.3 Females and Males of Reproductive Potential

#### Infertility - Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including meloxicam, may delay or prevent ovulation of ovaal follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to delay 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.

### 8.4 Pediatric Use

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

### 8.5 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, 5.10)].

### 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 (2.1) and Clinical Pharmacology (12.3)].

## 10 OVERDOSAGE

Symptoms following acute NSAID overdosage 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, acute renal failure, respiratory depression, and coma have occurred, but were rare [see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)].

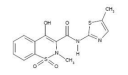
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (50 to 100 grams adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion in patients with large overdosage (6 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 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 is a nonsteroidal anti-inflammatory drug (NSAID). Each yellow meloxicam tablet contains 7.5 mg or 15 mg meloxicam for oral administration. Meloxicam is chemically designated as 4-hydroxy-2-methyl-5-(1-methyl-2-thiazolyl)-1,2,4-thiazolidine-3-carboxamide, 1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> and it has the following structural formula:



Meloxicam USP is a pale yellow powder, practically insoluble in water, slightly soluble in acetone, soluble in dimethylformamide, very slightly soluble in ethanol (5% w/v) and in methanol. Meloxicam has an apparent partition coefficient (log P<sub>ow</sub>) of 0.1 in octanol/buffer pH 7.4. Meloxicam has pKa values of 3.1 and 4.2.

Each meloxicam tablet USP marked for oral administration contains 7.5 mg or 15 mg of meloxicam. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyvidone 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.

### 12.3 Pharmacokinetics

#### Absorption

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C<sub>max</sub> was achieved within four to five hours after 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 1. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

Meloxicam oral suspension doses of 7.5 mg/5 mL and 15 mg/10 mL have been found to be bioequivalent to meloxicam 7.5 mg and 15 mg capsules, respectively. Meloxicam capsules have been shown to be bioequivalent to 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	
	7.5 mg tablets (n=18)	15 mg capsules (n=9)	15 mg capsules (n=9)	15 mg capsules (n=9)	15 mg capsules (n=9)	15 mg capsules (n=9)
C <sub>max</sub> (ng/mL)	115 (20)	23 (20)	3.2 (24)	0.39 (26)	0.84 (29)	
t <sub>1/2</sub> (hr)	4.9 (6)	3 (12)	6 (27)	4 (16)	10 (37)	
AUC <sub>0-24</sub> (ng·hr/mL)	26 (12)	27 (13)	24 (14)	10 (45)	16 (29)	
C <sub>12</sub> (ng/mL)	18 (20)	19 (20)	5 (12)	13 (42)	11 (44)	
V <sub>d</sub> (L)	18 (13)	15 (42)	10 (30)	26 (44)	14 (29)	

The apparent volume of distribution (V<sub>d</sub>) is based on plasma concentrations.

AUC<sub>0-24</sub> is the area under the curve.

C<sub>12</sub> is the concentration at 12 hours.

### Food and Animal Effects

Administration of meloxicam capsules following a high fat breakfast (75% of fat) resulted in mean peak drug levels (i.e., C<sub>max</sub>) being achieved by approximately 27% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T<sub>max</sub>) was achieved between 5 and 6 hours. In comparison, either the AUC or the C<sub>max</sub> values for meloxicam capsules were affected following a similar high fat meal, while mean T<sub>max</sub> values were increased to approximately 7 hours. No pharmacokinetic interaction was detected with concurrent administration of omeprazole. Based on these results, meloxicam can be administered without regard to timing of meals or concurrent administration of omeprazole.

### Distribution

The mean volume of distribution (V<sub>d</sub>) of meloxicam is approximately 10 L. Meloxicam is ~99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration over the clinically relevant concentration range, but decreases to ~99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam. Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this phenomenon is unknown.

### Elimination

#### Metabolism

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate meloxicam 5'-hydroxymethyl meloxicam which also undergoes a subsequent 6'-hydroxylation. *In vivo* studies indicate that CYP2C9 cytochrome P450 metabolizing enzyme plays an important role in this metabolic pathway with a minor contribution of the CYP2C8 enzyme. P-glycoprotein activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. All the four metabolites are not known to have any *in 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 into the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for radiolabeled multiple 7.5 mg doses: 6.2% in urine, and 17% of the dose were found in stool in the form of meloxicam and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or renal secretion of the drug. This was observed 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<sub>1/2</sub>) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 dL/min.

#### Specific Populations

**Pediatric:** After a single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/d), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg [see Dosage and Administration (2.4)]. The meloxicam mean (SD) elimination half-life was 12.7 (1.0) and 13.0 hours (3.0) for 2- to 6-year-old patients, and 7 to 16-year-old patients, respectively.

In a covariate analysis, utilizing population pharmacokinetics, body weight, but not age, was the single predictive covariate for differences in the meloxicam apparent oral plasma clearance. The body-weight normalized apparent oral clearance values were adequate predictors of meloxicam exposure in pediatric patients.

The pharmacokinetics of 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 plasma clearance similar to young males. Elderly females (≥ 65 years of age) had a 47% higher AUC, a 32% higher C<sub>max</sub>, and 32% higher C<sub>min</sub> as compared to younger females (5 years of age) after body weight normalization. Despite the increased oral concentration in the elderly females, the adverse event profile was comparable to that in 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 23.4 hours for the male group. At steady state, the data were similar (17.0 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<sub>max</sub> or T<sub>max</sub> across gender.

#### 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 1) or moderate (Child-Pugh Class 2) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)].

#### Renal Impairment

Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentration of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment but 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 drug in which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of 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 (8.7)].

#### Hemodialysis

Following a single dose of meloxicam, the free C<sub>max</sub> plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.2% 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 (8.7)].

#### Drug Interaction Studies

##### Aspirin

When NSAIDs were administered with aspirin, the proton-inhibiting NSAIDs were reduced, although the clearance of free NSAID was not altered. When meloxicam was administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and C<sub>max</sub> (24%) of meloxicam. The clinical significance of this interaction is not known [see Table 3 for clinically significant drug interaction of NSAIDs with aspirin [see Drug Interactions (7)].

##### Cholestyramine

Pre-treatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t<sub>1/2</sub> from 18.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

##### Cimetidine

Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 20 mg meloxicam.

##### Digoxin

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after  $\beta$ -acetylcholinesterase administration for 7 days at clinical doses.

In vitro testing found no protein-binding drug interaction between digoxin and meloxicam.

##### Lithium

In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 80 to 107 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 vitro, mefenamic acid did not displace meloxicam from its human serum-binding sites [see Drug Interactions (7)].

##### Nifedipine

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 was 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 experience changes in INR and an increased risk of bleeding complications when a new medication is introduced [see Drug Interactions (7)].

## 11 NONCLINICAL TOXICOLOGY

### 11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### Carcinogenesis

There was no increase in tumor incidence in long-term carcinogenicity studies in rats (84 weeks) and mice (93 weeks) administered meloxicam oral doses up to 0.8 mg/kg/day in rats and up to 0.8 mg/kg/day in mice (up to 5- and 2.6-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 *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 15 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and total WOMAC score in 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 trial. Meloxicam (7.5 mg, 15 mg, and 15 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 (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 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: approved and two doses of meloxicam. In both studies, meloxicam dosing began at 12.5 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and approved dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 mg/kg/day (22.5 mg maximum of meloxicam and 15 mg/kg/day of approved).

The efficacy analysis used the ACR Pediatric 30 responder definition, a composite of parent or investigator assessment, counts of active joints, and joint with limited range of motion and erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Meloxicam Tablets USP, 15 mg are yellow, round-shaped, flat beveled edge, uncoated tablet debossed with "75" and "75" on one side and plain on other side and are supplied as follows:  
NDC 4230-027-30 in bottles of 30 tablets

#### Storage

Store at 20° to 25° C (68° to 77° F) [see USP Controlled Room Temperature]. Keep meloxicam tablets 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 health-care provider immediately [see Warnings and Precautions (5.1)].

#### Concomitant Blooding, Ulceration, and Perforation

Advise patients to report symptoms of ulceration and bleeding, including epigastric pain, dyspepsia, reflux, and hematemesis to their health-care provider. In the setting of concomitant 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)].

#### Hepatoxicity

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 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)].

#### Serious Skin Reactions

Advise patients to stop meloxicam immediately if they develop any type of rash and to contact their health-care provider as soon as possible [see Warnings and Precautions (5.3)].

#### Female Fertility

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

#### Fetal Toxicity

Inform pregnant women to avoid use of meloxicam 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 (5.1) and Use in Specific Populations (8.1)].

#### Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of meloxicam with other NSAIDs or salicylates (e.g., difflucal, salicylate) is not recommended due to the increased risk of gastrointestinal toxicity, and that the increase in efficacy [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 colds, fever, or pain.

#### Use of NSAIDs and Low-Dose Aspirin

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

\*Ketoconazole is a registered trademark of Sandoz-Aventis.

†Ketoconazole is a registered trademark of Sandoz-Aventis.

#### Manufacturer

Cellia Healthcare Ltd.

India

#### Distributed by

Zelbo Pharmaceuticals USA Inc.

Pennington, NJ 08534

Rev.: 02/18

**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:
  - 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 (perforations) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**

- anytime 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", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- older age
- longer use of NSAIDs
- poor health or smoking
- alcohol or liver disease
- drinking alcohol
- 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.

**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 NSAIDs
- 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
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Tell us your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 28 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)?"

- new or worse high blood pressure
- 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:**

shortness of breath or trouble breathing

- changed speech
- chest pain
- swelling of the face or throat
- weakness in one part or side of your body

**Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:**

- nausea
- vomit blood
- more tired or weaker than usual
- there is blood in your bowel movement or it is
- diarrhea black and sticky like tar
- itching
- unusual weight gain
- your skin or eyes look yellow
- skin rash or blisters with fever
- indigestion or stomach pain
- swelling of the arm, legs, hand and feet
- flu-like symptoms

**If you take too much of your NSAID, call your healthcare provider or get medical help right away.**

These 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). Tell us 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. Keep them from you. 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. Please address medical inquiries to: (Medi-Alerts@zylaxis.com) Tel.: 1-877-993-8779.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

This product's label may have been updated. For current full prescribing information, please visit [www.zylaxis.com](http://www.zylaxis.com).

**Manufactured by:**

Cadila Healthcare Ltd.

India.

**Distributed by:**

Zylaxis Pharmaceuticals USA Inc.

Pennington, NJ 08534

Rev.: 07/16

**PACKAGE LABEL-PRINCIPAL DISPLAY PANEL**

NDC 42768-017-30 in bottle of 30 tablets

Meloxicam Tablets USP, 15 mg

Rx only

30 tablets

OPICARMA

Dosage: See package insert Sample - Not for sale

NDC 42768-017-30  
30 TABLETS  
OPICARMA

**Meloxicam USP  
Tablets, 15mg  
30 Tablets**

Take \_\_\_\_ hr(s)  
\_\_\_\_ times daily or  
every \_\_\_\_ hour(s)  
\_\_\_\_ day(s).

STORE AT CONTROLLED ROOM TEMPERATURE

(See Us @Pharm, Inc. Keep container tightly closed. Keep out of reach of children.) **Rx Only**

MELOXICAM			
meloxicam tablet			
<b>Product Information</b>			
Product Type	Human Prescription Drug	Item Code (Ean/Upi)	NDC 42768-017-30/30 30 302-0101
Route of Administration	Oral		
<b>Active Ingredient/Active Moiety</b>			
MELoxicam (C18H19NO4)	Ingredient Name	Ratio of Strength	[Strength]
MELoxicam (C18H19NO4)	MELoxicam		15 mg
<b>Inactive Ingredients</b>			
LACTOSE MONOHYDRATE (E136)	Ingredient Name		Strength
MAGNESIUM HYDROXIDE (E172)			
SILICON DIOXIDE (E171)			
TITANIUM DIOXIDE (E171)			
HYDROXYMETHYLCELLULOSE (E413)			
POLYBUTYLENE ADIPATE (E312)			
HYDROXYMETHYLCELLULOSE (E413)			
HYDROXYMETHYLCELLULOSE (E413)			
HYDROXYMETHYLCELLULOSE (E413)			
<b>Product Characteristics</b>			
Color	Yellow/White	Score	No score
Shape	Round/Beveled	Size	6 mm
Imprint		Imprint Code	ALCA
Contains			
<b>Packaging</b>			
30 Tablets	Package Description	Marketing Start Date	Marketing End Date
30 Tablets	30 in 1 BOTTLE, Type 1, N14 Combination Product	14/02/08	
<b>Marketing Information</b>			
Marketing Category	Application Number and Monograph Classification	Marketing Start Date	Marketing End Date
ANDA	ANDA07922	07/16/2008	
<b>Labels</b> - QP/Pharm Inc (03922088)			
<b>Registrant</b> - Zylaxis Pharmaceuticals (USA) Inc (15041065)			
<b>Establishment</b>			
Name	Address	DEPT	Business Operations
Pharm, Inc.		16410166	3090/ALCA/08-075

