

## FULL PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use meloxicam oral suspension safely and effectively. See full prescribing information for meloxicam oral suspension.**

**Meloxicam oral suspension**  
Initial U.S. Approval: 2004

<b>WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS</b> <i>See full prescribing information for complete boxed warning.</i>
<ul style="list-style-type: none"><li>• <b>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).</b></li><li>• <b>Meloxicam oral suspension is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)</b></li><li>• <b>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 a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)</b></li></ul>

## RECENT MAJOR CHANGES

Warnings and Precautions, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (5.10) 04/2021  
Warnings and Precautions, Fetal Toxicity (5.11) 04/2021

## INDICATIONS AND USAGE

Meloxicam oral suspension is a non-steroidal anti-inflammatory drug indicated for:

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years of age or older (1.3)

## DOSAGE AND ADMINISTRATION

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

- **OA (2.2) and RA (2.3):**
  - Starting dose: 7.5 mg once daily
  - Dose may be increased to 15 mg once daily
- **JRA (2.4):**
  - 0.125 mg/kg once daily up to a maximum of 7.5 mg. JRA dosing using the oral suspension should be individualized based on the weight of the child (2.4)
- Meloxicam oral suspension is not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same (2.6)

## DOSAGE FORMS AND STRENGTHS

- Meloxicam oral suspension: 7.5 mg/5 mL (3)

## CONTRAINDICATIONS

- Known hypersensitivity to meloxicam or any components of the drug product (4)
- 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

- **Hepatotoxicity:** Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- **Hypertension:** Patients taking common antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- **Heart Failure and Edema:** Avoid use of meloxicam oral suspension in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)
- **Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of meloxicam oral suspension in patients with advanced renal dysfunction unless benefits are expected to outweigh risk of worsening renal function (5.6)
- **Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs (5.7)
- **Exacerbation of Asthma Related to Aspirin Sensitivity:** Meloxicam oral suspension is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- **Serious Skin Reactions:** Discontinue meloxicam oral suspension at first appearance of skin rash or other signs of hypersensitivity (5.9)
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Discontinue and evaluate clinically (5.10)
- **Fetal Toxicity:** Limit use of NSAIDs, including meloxicam oral suspension, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of fetal ductus arteriosus (5.11, 8.1)
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 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)

**To Report SUSPECTED ADVERSE REACTIONS, contact Avondale Pharmaceuticals, LLC at (800) 528-3058 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

## DRUG INTERACTIONS

- **Drugs that Interfere with Hemostasis** (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking meloxicam oral suspension with drugs that interfere with hemostasis. Concomitant use of meloxicam oral suspension and analgesic doses of aspirin is not generally recommended (7)
- **ACE Inhibitors, Angiotensin Receptor Blockers (ARBs) or Beta-Blockers:** Concomitant use with meloxicam oral suspension may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- **ACE Inhibitors and ARBs:** Concomitant use with meloxicam oral suspension in elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- **Diuretics:** NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)

## USE IN SPECIFIC POPULATIONS

- **Lactating:** NSAIDs are associated with reversible infanticide. Consider withdrawal of meloxicam oral suspension in women who have difficulties conceiving (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

Revised: 04/2022

## FULL PRESCRIBING INFORMATION: CONTENTS\*

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

#### 1 INDICATIONS AND USAGE

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

#### 2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Instructions
- 2.2 Osteoarthritis
- 2.3 Rheumatoid Arthritis
- 2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course
- 2.5 Renal Impairment
- 2.6 Non-Interchangeability with Other Formulations of Meloxicam

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

- 5 **WARNINGS AND PRECAUTIONS**
  - 5.1 Cardiovascular Thrombotic Events
  - 5.2 Gastrointestinal Bleeding, Ulceration, and Perforation
  - 5.3 Hepatotoxicity
  - 5.4 Hypertension
  - 5.5 Heart Failure and Edema
  - 5.6 Renal Toxicity and Hyperkalemia
  - 5.7 Anaphylactic Reactions
  - 5.8 Exacerbation of Asthma Related to Aspirin Sensitivity
  - 5.9 Serious Skin Reactions
  - 5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
  - 5.11 Fetal Toxicity
  - 5.12 Hematologic Toxicity
  - 5.13 Masking of Inflammation and Fever
  - 5.14 Laboratory Monitoring

#### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials 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
  - 12.3 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) Pauciarticular and Polyarticular Course

## 16 HOW SUPPLIED/STORAGE AND HANDLING

## 17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

<b>WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS</b> <b>Cardiovascular Thrombotic Events</b>
<ul style="list-style-type: none"><li>• <b>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 <i>Warnings and Precautions</i> (5.1)].</b></li><li>• <b>Meloxicam oral suspension is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see <i>Contraindications</i> (4) and <i>Warnings and Precautions</i> (5.1)].</b></li></ul>
<b>Gastrointestinal Bleeding, Ulceration, and Perforation</b>
<ul style="list-style-type: none"><li>• <b>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 a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see <i>Warnings and Precautions</i> (5.2)].</b></li></ul>

## 1 INDICATIONS AND USAGE

### 1.1 Osteoarthritis (OA)

Meloxicam oral suspension is indicated for relief of the signs and symptoms of osteoarthritis [see *Clinical Studies* (14.1)].

### 1.2 Rheumatoid Arthritis (RA)

Meloxicam oral suspension is indicated for relief of the signs and symptoms of rheumatoid arthritis [see *Clinical Studies* (14.1)].

### 1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

Meloxicam oral suspension is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older [see *Clinical Studies* (14.2)].

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of meloxicam oral suspension and other treatment options before deciding to use meloxicam oral suspension. 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 oral suspension, adjust the dose to suit an individual patient's needs.

In adults, the maximum recommended daily oral dose of meloxicam oral suspension is 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 oral suspension 7.5 mg/5 mL or 15 mg/10 mL may be substituted for meloxicam tablets 7.5 mg or 15 mg, respectively.

**Shake the oral suspension gently before using.**

Meloxicam oral suspension 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 oral suspension 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 oral suspension is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

### 2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

To improve dosing accuracy in smaller weight children, the use of the meloxicam oral suspension is recommended. Meloxicam oral suspension is available in the strength of 7.5 mg/5 mL. For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of meloxicam oral suspension is 0.125 mg/kg once daily up to a maximum of 7.5 mg. There was no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in these clinical trials.

**Juvenile Rheumatoid Arthritis dosing using the oral suspension should be individualized based on the weight of the child:**

	Dose	0.125 mg/kg
<b>Weight</b>	<b>(1.5 mg/mL)</b>	<b>Delivered dose</b>
12 kg (26 lb)	1.0 mL	1.5 mg
24 kg (54 lb)	2.0 mL	3.0 mg
36 kg (80 lb)	3.0 mL	4.5 mg
48 kg (106 lb)	4.0 mL	6.0 mg
>60 kg (132 lb)	5.0 mL	7.5 mg

### 2.5 Renal Impairment

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

### 2.6 Non-Interchangeability with Other Formulations of Meloxicam

Meloxicam oral suspension has not shown equivalent systemic exposure to other approved formulations of oral meloxicam. Therefore, meloxicam oral suspension is 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 oral suspension with other formulations of oral meloxicam product.

## 3 DOSAGE FORMS AND STRENGTHS

Meloxicam oral suspension:

- yellowish green tinged viscous suspension containing 7.5 mg meloxicam per 5 mL.

## 4 CONTRAINDICATIONS

Meloxicam oral suspension is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any components 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, and sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see *Warnings and Precautions* (5.7, 5.8)]
- 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 in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of 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 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) events [see *Warnings and Precautions* (5.2)].

### Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 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 reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

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

### 5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including meloxicam, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

### Risk Factors for GI Bleeding, Ulceration, and Perforation

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

### Strategies to Minimize the GI 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 oral suspension until a serious GI adverse event is ruled out.**
- **In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see *Drug Interactions* (7)].**

### 5.3 Hepatotoxicity

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

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

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, 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 oral suspension 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 oral suspension, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking antihypertensive converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see *Drug Interactions* (7)].

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

### 5.5 Heart Failure and Edema

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

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

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

### 5.6 Renal Toxicity and Hyperkalemia

#### Renal Toxicity

Long-term administration of NSAIDs, including meloxicam oral suspension, 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 oral suspension may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some meloxicam oral suspension 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 oral suspension. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of meloxicam oral suspension [see *Drug Interactions* (7)].

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

### Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-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* (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

### 5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic 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 oral suspension is contraindicated in patients with this form of aspirin sensitivity [see *Contraindications* (4)]. When meloxicam oral suspension is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

### 5.9 Serious Skin Reactions

NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of meloxicam oral suspension at the first appearance of skin rash or any other sign of hypersensitivity. Meloxicam oral suspension is contraindicated in patients with previous serious skin reactions to NSAIDs [see *Contraindications* (4)].

### 5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as meloxicam oral suspension. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue meloxicam oral suspension and evaluate the patient immediately.

### 5.11 Fetal Toxicity

#### Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including meloxicam oral suspension, in pregnant women at about 30 weeks gestation and later. NSAIDs, including meloxicam oral suspension, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

#### Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including meloxicam oral suspension, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation.

Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

NSAID treatment is necessary between about 20 weeks and 30 weeks gestation. Limit meloxicam oral suspension use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if meloxicam oral suspension treatment extends beyond 48 hours. Discontinue meloxicam oral suspension if oligohydramnios occurs and follow up according to clinical practice [see *Use in Specific Populations* (8.1)].

### 5.12 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 oral suspension has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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

### 5.13 Masking of Inflammation and Fever

Cyclosporine
<span></span>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Clinical Impact:</i></b></div><div>Concomitant use of meloxicam and cyclosporine may increase cyclosporine's nephrotoxicity.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Intervention:</i></b></div><div>During concomitant use of meloxicam oral suspension and cyclosporine, monitor patients for signs of worsening renal function.</div></div></div></div></div>
NSAIDs and Salicylates
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Clinical Impact:</i></b></div><div>Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy <span>[</span><i>see Warnings and Precautions (5.2)</i><span>]</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Intervention:</i></b></div><div>The concomitant use of meloxicam oral suspension with other NSAIDs or salicylates is not recommended.</div></div></div></div></div>
Penmetrexed
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Clinical Impact:</i></b></div><div>Concomitant use of meloxicam and penmetrexed may increase the risk of penmetrexed-associated myelosuppression, renal, and GI toxicity (see the penmetrexed prescribing information).</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Intervention:</i></b></div><div>During concomitant use of meloxicam oral suspension and penmetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 75 mL/min, monitor for myelosuppression, renal and GI toxicity.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div>Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following penmetrexed administration.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div>Patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with penmetrexed is not recommended.</div></div></div></div></div>
Sodium Polystyrene Sulfonate
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Clinical Impact:</i></b></div><div>Cases of intestinal necrosis (possibly fatal) have been described in patients who received concomitant sorbitol and sodium polystyrene sulfonate. Due to the presence of sorbitol in meloxicam oral suspension, use with sodium polystyrene sulfonate is not recommended.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Intervention:</i></b></div><div>The concomitant use of meloxicam oral suspension with sodium polystyrene sulfonate is not recommended.</div></div></div></div></div>

*Clinical Impact:* During concomitant use of meloxicam oral suspension and penmetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 75 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 penmetrexed administration.

In patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with penmetrexed is not recommended.

Sodium Polystyrene Sulfonate
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Clinical Impact:</i></b></div><div>Cases of intestinal necrosis (possibly fatal) have been described in patients who received concomitant sorbitol and sodium polystyrene sulfonate. Due to the presence of sorbitol in meloxicam oral suspension, use with sodium polystyrene sulfonate is not recommended.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Intervention:</i></b></div><div>The concomitant use of meloxicam oral suspension with sodium polystyrene sulfonate is not recommended.</div></div></div></div></div>

*Clinical Impact:* Cases of intestinal necrosis (possibly fatal) have been described in patients who received concomitant sorbitol and sodium polystyrene sulfonate. Due to the presence of sorbitol in meloxicam oral suspension, use with sodium polystyrene sulfonate is not recommended.

*Intervention:* The concomitant use of meloxicam oral suspension with sodium polystyrene sulfonate is not recommended.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Risk Summary</i></b></div><div>Use of NSAIDs, including meloxicam oral suspension, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of meloxicam oral suspension use between about 20 and 30 weeks of gestation, and avoid meloxicam oral suspension use at about 30 weeks of gestation and later in pregnancy <span>(see Clinical Considerations, Data)</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Premature Closure of Fetal Ductus Arteriosus</i></b></div><div>Use of NSAIDs, including meloxicam oral suspension, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Oligohydramnios/Neonatal Renal Impairment</i></b></div><div>Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.</div></div></div></div></div>

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. 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 6.5-times the maximum recommended human dose (MRHD) of meloxicam oral suspension. Increased incidence of septal heart defects were observed in rabbits treated throughout embryogenesis with meloxicam at an oral dose equivalent to 78-times the MRHD. In pre- and post-natal reproduction studies, there was an increased incidence of dystocia, delayed parturition, and decreased offspring survival with meloxicam at oral doses equivalent to 1.1 and 4.2 times the MRHD, respectively. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as meloxicam, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

**Clinical Considerations**  
**Fetal/Neonatal Adverse Reactions**  
**Premature Closure of Fetal Ductus Arteriosus:** Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including meloxicam oral suspension, can cause premature closure of the fetal ductus arteriosus (see Data).

**Oligohydramnios/Neonatal Renal Impairment:** If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If meloxicam oral suspension treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue meloxicam oral suspension and follow up according to clinical practice (see Data).

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

**Data**  
**Human Data**  
**Premature Closure of Fetal Ductus Arteriosus:** Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.  
**Oligohydramnios/Neonatal Renal Impairment:** Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the fullterm infant exposed to NSAIDs through maternal use is uncertain.

**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 conversion). In rats and rabbits, embryofetally occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65- and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered throughout organogenesis.

Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of 0.125 mg/kg/day or greater (0.08-times MRHD based on BSA comparison).

8.2 Lactation
Risk Summary
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div>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 oral suspension and any potential adverse effects on the breastfed infant from the meloxicam oral suspension or from the underlying maternal condition.</div></div></div></div></div>

**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
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b><i>Fertility:</i></b></div><div>Females</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div>Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including meloxicam oral suspension, may delay or prevent nupture of ovarian 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 disrupt prostaglandin-mediated follicular nupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including meloxicam oral suspension, in women who have difficulties conceiving or who are undergoing investigation of infertility.</div></div></div></div></div>
8.4 Pediatric Use
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> The safety and effectiveness of meloxicam in pediatric JRA patients from 2 to 17 years of age has been evaluated in three clinical trials <span>(see Dosage and Administration (2.3), Adverse Reactions (6.1) and Clinical Studies (14.2))</span>.</div></div></div></div></div>
8.5 Geriatric Use
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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 <span>(see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14))</span>.</div></div></div></div></div>
8.6 Hepatic Impairment
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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 <span>(see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3))</span>.</div></div></div></div></div>
8.7 Renal Impairment
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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 oral suspension 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 <span>(see Dosage and Administration (2.1) and Clinical Pharmacology (12.3))</span>.</div></div></div></div></div>
10 OVERDOSAGE
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare <span>(see Warnings and Precautions (5.1, 5.2, 5.4, 5.6))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in 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 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.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> For additional information about overdosage treatment, call a poison control center (1-800-222-1222).</div></div></div></div></div>

11 DESCRIPTION																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam oral suspension, USP is a nonsteroidal anti-inflammatory drug (NSAID). Each bottle of meloxicam oral suspension contains 7.5 mg meloxicam per 5 mL. Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-[5-methyl-2-thiazolyl]-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> and it has the following structural formula:</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> For additional information about overdosage treatment, call a poison control center (1-800-222-1222).</div></div></div></div></div>																																																														
11 DESCRIPTION																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam oral suspension, USP is a nonsteroidal anti-inflammatory drug (NSAID). Each bottle of meloxicam oral suspension contains 7.5 mg meloxicam per 5 mL. Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-[5-methyl-2-thiazolyl]-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>S<sub>2</sub> and it has the following structural formula:</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam, is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P<sub>app</sub>) = 0.1 in n-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam is available as an oral suspension containing 7.5 mg meloxicam per 5 mL.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> The inactive ingredients in meloxicam oral suspension include colloidal silicon dioxide, hydroxyethylcellulose, sorbitol, glycerol, xylitol, monobasic sodium phosphate (dihydrate), saccharin sodium, sodium benzoate, citric acid (monohydrate), raspberry flavor, and purified water.</div></div></div></div></div>																																																														
12 CLINICAL PHARMACOLOGY																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>12.1 Mechanism of Action</b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam has analgesic, anti-inflammatory, and antipyretic properties.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> The mechanism of action of meloxicam oral suspension, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Meloxicam is a potent inhibitor of prostaglandin synthesis <i>in vitro</i>. Meloxicam concentrations reached during therapy have produced <i>in vivo</i> 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 prostaglandins in peripheral tissues.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>12.3 Pharmacokinetics</b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Absorption.</b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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 a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Table 4 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and % CV)<sup>1</sup></b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <table><thead><tr><th rowspan="2">Pharmacokinetic (% CV)</th><th colspan="2">Steady State</th><th colspan="2">Elderly</th><th colspan="2">Single Dose</th></tr><tr><th>Healthy male Parameters</th><th>Elderly males adults (Fed)<sup>2</sup></th><th>Healthy males adults (Fed)<sup>2</sup></th><th>Elderly females (Fasted)</th><th>Renal failure (Fasted)</th><th>Hepatic insufficiency (Fasted)</th></tr></thead><tbody><tr><td></td><td>7.5 mg<sup>3</sup> tablets</td><td>15 mg<sup>3</sup> capsules</td><td>15 mg<sup>3</sup> capsules</td><td>15 mg<sup>3</sup> capsules</td><td>15 mg<sup>3</sup> capsules</td><td>15 mg<sup>3</sup> capsules</td></tr><tr><td><b>N</b></td><td><b>18</b></td><td><b>5</b></td><td><b>8</b></td><td><b>12</b></td><td><b>12</b></td><td><b>12</b></td></tr><tr><td>C<sub>max</sub> (μg/mL)</td><td>1.05 (20)</td><td>2.3 (59)</td><td>3.2 (24)</td><td>0.59 (36)</td><td>0.84 (29)</td><td></td></tr><tr><td>T<sub>max</sub> (h)</td><td>4.9 (8)</td><td>5 (12)</td><td>6 (27)</td><td>4 (65)</td><td>10 (87)</td><td></td></tr><tr><td>t<sub>1/2</sub> (h)</td><td>20.1 (29)</td><td>21 (24)</td><td>24 (24)</td><td>18 (46)</td><td>16 (29)</td><td></td></tr><tr><td>Cl<sub>T</sub> (mL/min)</td><td>8.8 (29)</td><td>9.9 (7.6)</td><td>5.1 (22)</td><td>19 (43)</td><td>11 (44)</td><td></td></tr><tr><td>V<sub>d</sub><sup>4</sup> (L)</td><td>14.7 (32)</td><td>15 (42)</td><td>10 (30)</td><td>26 (44)</td><td>14 (29)</td><td></td></tr></tbody></table></div></div></div></div></div>	Pharmacokinetic (% CV)	Steady State		Elderly		Single Dose		Healthy male Parameters	Elderly males adults (Fed) <sup>2</sup>	Healthy males adults (Fed) <sup>2</sup>	Elderly females (Fasted)	Renal failure (Fasted)	Hepatic insufficiency (Fasted)		7.5 mg <sup>3</sup> tablets	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	<b>N</b>	<b>18</b>	<b>5</b>	<b>8</b>	<b>12</b>	<b>12</b>	<b>12</b>	C <sub>max</sub> (μg/mL)	1.05 (20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)		T <sub>max</sub> (h)	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)		t <sub>1/2</sub> (h)	20.1 (29)	21 (24)	24 (24)	18 (46)	16 (29)		Cl <sub>T</sub> (mL/min)	8.8 (29)	9.9 (7.6)	5.1 (22)	19 (43)	11 (44)		V <sub>d</sub> <sup>4</sup> (L)	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)	
Pharmacokinetic (% CV)		Steady State		Elderly		Single Dose																																																								
	Healthy male Parameters	Elderly males adults (Fed) <sup>2</sup>	Healthy males adults (Fed) <sup>2</sup>	Elderly females (Fasted)	Renal failure (Fasted)	Hepatic insufficiency (Fasted)																																																								
	7.5 mg <sup>3</sup> tablets	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules	15 mg <sup>3</sup> capsules																																																								
<b>N</b>	<b>18</b>	<b>5</b>	<b>8</b>	<b>12</b>	<b>12</b>	<b>12</b>																																																								
C <sub>max</sub> (μg/mL)	1.05 (20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)																																																									
T <sub>max</sub> (h)	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)																																																									
t <sub>1/2</sub> (h)	20.1 (29)	21 (24)	24 (24)	18 (46)	16 (29)																																																									
Cl <sub>T</sub> (mL/min)	8.8 (29)	9.9 (7.6)	5.1 (22)	19 (43)	11 (44)																																																									
V <sub>d</sub> <sup>4</sup> (L)	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)																																																									
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <sup>1</sup>The parameter values in the table are from various studies</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <sup>2</sup> not under high fat conditions</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <sup>3</sup> meloxicam tablets</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <sup>4</sup> V<sub>d</sub> /l = Dose/(AUC×K<sub>el</sub>)</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Food and Antacid Effects</b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e., C<sub>max</sub>) being increased by approximately 22% 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, neither the AUC nor the C<sub>max</sub> values for meloxicam suspension 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 concomitant administration of antacids. Based on these results, meloxicam oral suspension can be administered without regard to timing of meals or concomitant administration of antacids.</div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Distribution</b></div></div></div></div></div>																																																														
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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.</div></div></div></div></div>																																																														

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
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Metabolism</b></div><div>Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (8% of dose). <i>In vitro</i> studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. All the four metabolites are not known to have any <i>in vivo</i> pharmacological activity.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Excretion</b></div><div>Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6%, and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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 mL/min.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Specific Populations</b></div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Pediatric</b></div><div>After single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg <span>(see Dosage and Administration (2.4))</span>. The meloxicam mean (SD) elimination half-life was 15.2 (10.1) and 13.0 hours (3.0) for the 2 to 6 year old patients, and 7 to 16 year old patients, respectively.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> 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.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> The pharmacokinetics of meloxicam oral suspension in pediatric patients under 2 years of age have not been investigated.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Geriatric</b></div><div>Elderly males (&gt;65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (&gt;65 years of age) had a 47% higher AUC<sub>0-24</sub> and 32% higher C<sub>max,ss</sub> as compared to younger females (&lt;55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Sex</b></div><div>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 (17.9 hours vs 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C<sub>max</sub> or T<sub>max</sub> across genders.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Hepatic Impairment</b></div><div>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 <span>(see Warnings and Precautions (5.3) and Use in Specific Populations (8.6))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Renal Impairment</b></div><div>Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of meloxicam oral suspension in subjects with severe renal impairment is not recommended <span>(see Dosage and Administration (2.5), Warnings and Precautions (5.6) and Use in Specific Populations (8.7))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Hemodialysis</b></div><div>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 (0.3% free fraction). However, the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable <span>(see Dosage and Administration (2.1) and Use in Specific Populations (8.7))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Aspirin:</b> 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 (100 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 interactions of NSAIDs with aspirin <span>(see Drug Interactions (7))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Cholestyramine:</b> Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t<sub>1/2</sub> from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Cimetidine:</b> Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 30 mg meloxicam.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Digoxin:</b> Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. <i>In vitro</i> testing found no protein binding drug interaction between digoxin and meloxicam.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Lithium:</b> 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 <span>(see Drug Interactions (7))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Methotrexate:</b> A study in 13 rheumatoid arthritis (RA) patients evaluated the effects of multiple doses of meloxicam on the pharmacokinetics of methotrexate taken once weekly. Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. <i>In vitro</i>, methotrexate did not displace meloxicam from its human serum binding sites <span>(see Drug Interactions (7))</span>.</div></div></div></div></div>
<div><div><div><div><span></span><div><div><span><span></span></span></div></div></div><div><div> <b>Warfarin:</b> The effect of meloxicam on the anticoagulant</div></div></div></div></div>