

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: 2000

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, 5.1).**

- **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 a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2).**

RECENT MAJOR CHANGES
Warnings and Precautions, Drug Interactions with Enophthalmitis and Systemic Symptoms (5.10) 04/2021
Warnings and Precautions (5.1) 04/2021

INDICATIONS AND USAGE

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

- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- 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 (2.2) and RA (2.3):
 - Starting dose: 7.5 mg once daily
 - Dose may be increased to 15 mg once daily
- JRA (2.4):
 - 7.5 mg once daily in children ≥60 kg
 - Meloxicam tablets are not interchangeable with approved formulations of oral meloxicam even in the total milligram strength in the same (2.6)

DOSE FORMS AND STRENGTHS

- Meloxicam tablets: 7.5 mg and 15 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity to meloxicam or any components of the drug product (4)
- History of asthma, urticaria, or other 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 results persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)

USE IN SPECIFIC POPULATIONS

See **TY** for **PATIENT COUNSELING INFORMATION AND Medication Guide**.

DESCRIPTION

1.1 Osteoarthritis (OA)
1.2 Rheumatoid Arthritis (RA)
1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarthral and Polyarthral Course

2.1 General Dosage Instructions

2.2 Osteoarthritis
2.3 Rheumatoid Arthritis
2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarthral and Polyarthral Course
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3.1 Pregnancy
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3.3 Females and Males of Reproductive Potential
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4.6 Anaphylactic Reactions
4.7 Exacerbation of Asthma Related to Aspirin Sensitivity
4.8 Serious Skin Reactions
4.9 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
4.11 Fetal Toxicity

5.1 Osteoarthritis (OA)

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

5.2 Rheumatoid Arthritis (RA)

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

5.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarthral and Polyarthral Course

Meloxicam is indicated for relief of the signs and symptoms of juvenile rheumatoid arthritis in patients who weigh ≥60 kg [see *Dosage and Administration* (2.4) and *Clinical Studies* (14.2)].

6.1 Pregnancy

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.2 Lactation

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.3 Females and Males of Reproductive Potential

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.4 Pediatric Use

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.5 Geriatric Use

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.6 Hepatic Impairment

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.7 Renal Impairment

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.8 Anaphylactic Reactions

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.9 Exacerbation of Asthma Related to Aspirin Sensitivity

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.10 Serious Skin Reactions

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.11 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

6.12 Fetal Toxicity

Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Warnings and Precautions* (5.1)].

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 a prior history of peptic ulcer disease and/or 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 is indicated for relief of the signs and symptoms of osteoarthritis [see *Clinical Studies* (14.1)].

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

1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarthral and Polyarthral Course
Meloxicam is indicated for relief of the signs and symptoms of juvenile rheumatoid arthritis in patients who weigh ≥60 kg [see *Dosage and Administration* (2.4) and *Clinical Studies* (14.2)].

2. DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions
Carefully consider the potential benefits and risks of meloxicam and other treatment options before deciding to use meloxicam. 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, adjust the dose to suit an individual patient's needs. In adults, the maximum recommended daily oral dose of meloxicam 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 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 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 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) Pauciarthral and Polyarthral Course
For the relief of the signs and symptoms of juvenile rheumatoid arthritis, the recommended oral dose of meloxicam is 7.5 mg once daily in children who weigh ≥60 kg. There was no additional benefit demonstrated by increasing the dose to 15 mg once daily 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).

2.7 DOSE FORMS AND STRENGTHS
Meloxicam tablets, USP:

- 7.5 mg: yellow colored, round, biconvex tablets, debossed with "15P" on one side and "C" on the other.
- 15 mg: yellow colored, oval, flat bevelled tablets, debossed with "C/PLA" on one side and "15P" on the other.

4. CONTRAINDICATIONS
Meloxicam 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. Serious, 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 of 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 to 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 persons years in NSAID-treated patients compared to 12 per 100 persons years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

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

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

Risk Factors for GI Bleeding, Ulceration, and Perforation
Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase

the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Monitor renal health status and monitor for signs of GI bleeding in NSAID-treated patients.

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 disease, consider alternate therapies other than NSAIDs.

- GI bleeding, ulceration, and perforation: promptly initiate evaluation and treatment, and discontinue meloxicam until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see *Drug Interactions* (7)].

5.3 Hypertension
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.

Monitor liver enzymes (ALT and AST) in patients with risk factors for liver disease. If ALT or AST is elevated, 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 antihypertensive converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired responses to these therapies when taking NSAIDs [see *Drug Interactions* (7)].

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 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 Hypocalcemia
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 acute 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 hasten the progression of renal dysfunction in patients with preexisting renal disease. Before the treatment of juvenile rheumatoid arthritis, the recommended oral dose of meloxicam is 7.5 mg once daily in children who weigh ≥60 kg. There was no additional benefit demonstrated by increasing the dose to 15 mg once daily in clinical trials.

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)].

Hypocalcemia
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 hypothalamic-hypoadrenalism 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 is contraindicated in patients with the form of aspirin sensitivity [see *Contraindications* (4)]. When meloxicam is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

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

5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs associated with liver, 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 and evaluate the patient immediately.

5.11 Fetal Toxicity
Prenatal/Neonatal Ductus Arteriosus
Avoid use of NSAIDs, including meloxicam, in pregnant women at about 30 weeks gestation and later. NSAIDs, including meloxicam, 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, 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.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit meloxicam use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if meloxicam treatment extends beyond 48 hours. Discontinue meloxicam if oligohydramnios occurs and follow up according to clinical practice [see *Use in Specific Populations* (8.7)].

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 has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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

5.13 Masking of Inflammation and Fever
The pharmacological activity of meloxicam in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.14 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)]
- Hypertension [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 Hypocalcemia [see *Warnings and Precautions* (5.6)]
- Anaphylactic Reactions [see *Warnings and Precautions* (5.7)]
- Serious Skin Reactions [see *Warnings and Precautions* (5.9)]
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see *Warnings and Precautions* (5.10)]
- Fetal Toxicity [see *Warnings and Precautions* (5.11)]
- Hematologic Toxicity [see *Warnings and Precautions* (5.12)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults
Osteoarthritis and Rheumatoid Arthritis
The meloxicam Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with meloxicam 7.5 mg daily, 3505 OA patients and 1351 RA patients treated with meloxicam 15 mg daily. 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 ten placebo- and/or active-controlled osteoarthritis trials and 2363 of these patients were treated in ten placebo- and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across meloxicam trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of meloxicam with placebo and with 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 two 12-week placebo-controlled rheumatoid arthritis trials.

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

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diplacebo 100 mg daily
No. of Patients	157	154	156	153
Gastrointestinal	17.2	20.1	17.3	28.1
Abdominal pain	2.5	1.9	2.6	1.3
Constipation	3.8	7.8	3.2	9.2
Diarrhea	4.5	4.5	4.5	6.5
Dyspepsia	4.5	4.5	4.5	6.5
Flatulence	4.5	3.2	3.2	3.9
Nausea	3.2	3.9	3.8	7.2
Body as a Whole				
Accident household	1.9	4.5	3.2	2.6
Edema ^a	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-like symptoms	5.1	4.5	5.8	2.6
Central and Peripheral Nervous System				

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

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). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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

Manufactured by: Cipla Ltd., Kurkumbh, India

Manufactured for: Cipla USA, Inc.

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Revised: 5/2021

7 DRUG INTERACTIONS
See Table 3 for clinically significant drug interactions with meloxicam. See also Warnings and Precautions (5.2, 5.6, 5.12) and Clinical Pharmacology (12.3).

Table 3 Clinically Significant Drug Interactions with Meloxicam

Drugs that Interfere with Hemostasis	
Clinical Impact:	<ul style="list-style-type: none">Meloxicam and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of meloxicam and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. Spontaneous release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone (see Warnings and Precautions (5.2)).
Intervention:	Monitor patients with concomitant use of meloxicam with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [See Warnings and Precautions (5.2)].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [See Warnings and Precautions (5.2)].
Intervention:	Concomitant use of meloxicam and low dose aspirin or analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [See Warnings and Precautions (5.2)]. Meloxicam is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, or Beta-Blockers	
Clinical Impact:	<ul style="list-style-type: none">NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, coadministration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	<ul style="list-style-type: none">During concomitant use of meloxicam and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. During concomitant use of meloxicam and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [See Warnings and Precautions (5.6)]. When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide 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 natriuretic effect. Furosemide single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam.
Intervention:	During concomitant use of meloxicam with diuretics, observe patients for signs of worsening renal function, in addition to assessing diuretic efficacy including antihypertensive effects [See Warnings and Precautions (5.6)].
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis [See Clinical Pharmacology (12.3)].
Intervention:	During concomitant use of meloxicam and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of meloxicam and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of meloxicam and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of meloxicam and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., difflural, salicylate) increases the risk of GI toxicity, with little or no increase in efficacy [See Warnings and Precautions (5.2)].
Intervention:	The concomitant use of meloxicam with other NSAIDs or salicylates is not recommended.
Penicillared	
Clinical Impact:	Concomitant use of meloxicam and penicillared may increase the risk of penicillared-associated myelosuppression, renal, and GI toxicity (see the penicillared prescribing information).
Intervention:	During concomitant use of meloxicam and penicillared, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following penicillared administration. In patients with creatinine clearance below 45 mL/min, the concomitant administration of meloxicam with penicillared is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Use of NSAIDs, including meloxicam, 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 use between about 20 and 30 weeks of gestation, and avoid meloxicam use at about 30 weeks of gestation and later in pregnancy (see [Clinical Considerations, Data](#)).

Premature Closure of Fetal Ductus Arteriosus: Use of NSAIDs, including meloxicam, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment: 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.

Data from observational studies regarding 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 0.85- and 5-times the maximum recommended human dose (MRHD) of meloxicam. 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 at 0.05-times MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.9 to 28-times the MRHD (See [Data](#)).

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, 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 treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue meloxicam and follow up according to clinical practice (see [Data](#)).

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 stillbirths.

Data

Human Data
Premature Closure of Fetal Ductus Arteriosus: Avoid 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 4 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 and timing of drug exposure, and concomitant use of other medications. These limitations have precluded 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 findings to the full-term infant exposed to NSAIDs during 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 (16-fold greater than the MRHD) or 15 mg/kg 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 (28-fold greater than the MRHD based on BSA conversion). In rats and rabbits, embryofetality 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 (1.08-times MRHD based on BSA comparison).

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 maternal condition.

DGI

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

Female

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

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 \(5.1, 5.2, 5.6, 5.4, 5.14\)](#)].

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 \(6.3\)](#) 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 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 [See [Warnings and Precautions \(5.1, 5.2, 5.4, 5.6\)](#)].

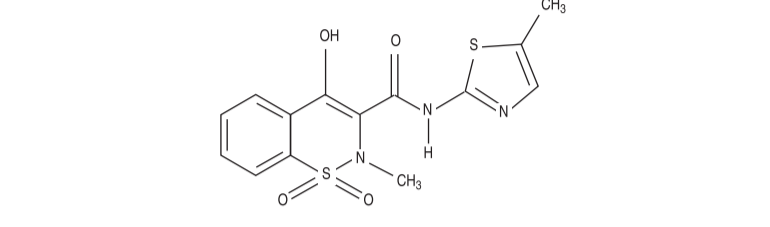
Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalization of urine, hemodialysis, or

hemoperfusion may not be useful due to high protein binding.

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

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

DESCRIPTION
Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID). Each tablet contains 7.5 mg of 15 mg meloxicam, USP for oral administration. 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 C₁₄H₁₄N₂O₅ and it has the following structural formula:



Meloxicam is a pale yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P)_{ow} of 1.1 in n-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.

Meloxicam is available as a tablet for oral administration containing 7.5 mg and 15 mg meloxicam, USP.

The active ingredients in meloxicam tablets, USP include starch, microcrystalline cellulose, lactose anhydrous, colloidal silicon dioxide, sodium citrate dihydrate, magnesium stearate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meloxicam has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of meloxicam, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis *in vitro*. Meloxicam concentrations reached during therapy have produced *in vivo* effects. Prostaglandins 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.

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_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prostaglandin synthesis inhibitor with steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

Meloxicam capsules have been shown to be bioequivalent to meloxicam tablets.

Table 4 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and CV)

Pharmacokinetic Parameters (%CV)	Steady State				Single Dose	
	Healthy male adults (Fast)	Elderly males (Fast)	Elderly females (Fast)	Renal failure (Fasted)	Hepatic Insufficiency (Fasted)	
	7.5 mg capsules	15 mg capsules	15 mg capsules	15 mg capsules	15 mg capsules	
N	18	5	8	12	12	
C _{max} (µg/mL)	1.05 (20)	2.3 (59)	3.2 (24)	0.59 (36)	0.84 (29)	
t _{max} (h)	4.9 (8)	5 (12)	6 (27)	4 (65)	10 (87)	
t _{1/2} (h)	20.1 (29)	21 (34)	24 (34)	18 (46)	16 (29)	
CL _R (mL/min)	8.8 (29)	9.9 (76)	5.1 (22)	19 (43)	11 (44)	
V _d * (L)	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)	

* The parameter values in the table are from various studies

*Fast under high fat conditions

*Meloxicam tablets

*V_d = Dose/(AUC)×k

Food and Antacid Effects

Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug (i.e., C_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T_{max}) was achieved between 5 and 6 hours. In comparison, neither the AUC nor the C_{max} values for meloxicam suspension were affected following a similar high fat meal, while mean T_{max} values were increased to approximately 7 hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Based on these results, meloxicam can be administered without regard to timing of meals or concomitant administration of antacids.

Distribution.
The mean volume of distribution (V_d) of meloxicam is approximately 10 L. Meloxicam is ~99.4% bound to human plasma proteins (primarily albumin) within the therapeutic dose range. The fraction of protein binding is independent of drug concentration, over the clinically relevant concentration range, but decreases to ~99% in patients with renal disease. Meloxicam penetration into human red blood cells, after oral dosing, is less than 10%. Following a radiolabeled dose, over 90% of the radioactivity detected in the plasma was present as unchanged meloxicam.

Meloxicam concentrations in synovial fluid, after a single oral dose, range from 40% to 50% of those in plasma. The free fraction in synovial fluid is 2.5 times higher than in plasma, due to the lower albumin content in synovial fluid as compared to plasma. The significance of this penetration is unknown.

Elimination

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate metabolite 5'-hydroxymethyl meloxicam which is also excreted to a lesser extent (9% of dose). *In vitro* studies indicate that CYP2C9 (cytochrome P450 metabolizing enzyme) plays an important role in this metabolic pathway with a minor contribution of the CYP3A4 isozyme. Patients' peroxidase activity is probably responsible for the other two metabolites which account for 16% and 4% of the administered dose, respectively. All the four metabolites are not known to have any *in vivo* pharmacological activity.

Excretion
Meloxicam excretion is predominantly in the form of metabolites, and occurs to equal extents in the urine and feces. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and feces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6%, and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively. There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of cholestyramine following a single oral dose of meloxicam decreased the AUC of meloxicam by 50%.

The mean elimination half-life (t_{1/2}) ranges from 15 hours to 20 hours. The elimination half-life is constant across dose levels indicating linear metabolism within the therapeutic dose range. Plasma clearance ranges from 7 to 9 mL/min.

Specific Populations

After single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized to a dose of 0.25 mg/kg [See [Dosage and Administration \(2.4\)](#)]. The meloxicam mean (SD) elimination half-life was 15.2 (10.1) h and 13.0 hours (3.0) for the 2 to 6 year old patients, and 7 to 16 year old patients, respectively.

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

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

Geriatric
Elderly males (>65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (>65 years of age) had a 4.7% higher AUC₀₋₂₄ and 52% higher C_{max} as compared to younger females (<55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

Sex

Young female 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 no gender difference in plasma concentrations and no appreciable difference in the C_{max} or T_{max} across genders.

Hepatic Impairment

Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentration in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied [See [Warnings and Precautions \(6.3\)](#) and [Use in Specific Populations \(8.6\)](#)].

Renal Impairment
Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of meloxicam in subjects with severe renal impairment is not recommended [See [Dosage and Administration \(2.3\)](#), [Warnings and Precautions \(6.6\)](#) and [Use in Specific Populations \(8.7\)](#)].

Hemodialysis

Following a single dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic hemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the meloxicam plasma concentrations. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, 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 protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. When meloxicam is administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin [See [Drug Interactions \(7\)](#)].

Cholestyramine: Pre-treatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t_{1/2} from 19.2 hours to 12.5 hours, and a 35% reduction in AUC. This suggests the existence of a reabsorption pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been studied.