

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MELIXICAM TABLETS, USP

For oral use

Initial U.S. Approval: 2000

WARNING: CARDIOVASCULAR and GASTROINTESTINAL RISKS

See full prescribing information for complete boxed warning.

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (5.1)

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal 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 are at greater risk for serious gastrointestinal events. (5.2)

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 2 years of age or older (1.3)

DOSE AND ADMINISTRATION

Use the lowest effective dose for the shortest duration consistent with individual treatment goals for the individual patient.

- 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):
 - 0.25mg/kg once daily up to a maximum of 7.5mg

DOSE FORMS AND STRENGTHS

- Tablets: 7.5 mg, 15 mg (3)

CONTRAINDICATIONS

- Known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to meloxicam (4.1)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4.1)
- Use during the peri-operative period in the setting of coronary artery bypass graft (CABG) surgery (4.2)

WARNINGS AND PRECAUTIONS

- Serious and potentially fatal cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. Patients with known CV disease/risk factors may be at greater risk. (5.1)

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR and GASTROINTESTINAL EVENTS

Cardiovascular Risk

- Nonsteroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See **Warnings and Precautions (5.1)**.)
- Meloxicam is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. (See **Contraindications (4.2)** and **Warnings and Precautions (5.1)**.)

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse reactions 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 are at greater risk for serious gastrointestinal 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) Pauciarticular and Polyarticular Course

Meloxicam 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. DOSE AND ADMINISTRATION

2.1 General Instructions

Carefully consider the potential benefits and risks of meloxicam and other treatment options before deciding to use meloxicam. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals. (See **Warnings and Precautions (5.4)**.)

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 **Warnings and Precautions (5.6)**, *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) Pauciarticular and Polyarticular Course

To improve dosing accuracy in smaller weight children, the use of the meloxicam oral suspension is recommended. For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of meloxicam 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.

3. DOSE FORMS AND STRENGTHS

Tablets:

- 7.5 mg: yellow coloured, round, biconvex, tablets, debossed with "158" on one side and "C" on the other.
- 15 mg: yellow coloured, round, flat bevelled tablets, debossed with "CIPLA" on one side and "159" on the other.

4. CONTRAINDICATIONS

4.1 Allergic Reactions

Meloxicam is contraindicated in patients with known hypersensitivity (e.g., anaphylactoid reactions and serious skin reactions) to meloxicam.

Meloxicam should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid-like reactions to NSAIDs have been reported in such patients. (See **Warnings and Precautions (5.7, 5.13)**.)

4.2 Coronary Surgery

Meloxicam is contraindicated for the treatment of peri-operative pain 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, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. (See **Contraindications (4.2)**.)

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 does increase the risk of serious GI events. (See **Warnings and Precautions (5.2)**.)

5.2 Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

NSAIDs, including meloxicam, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the 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 to 6 months, and in about 2% to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Prescribe NSAIDs, including meloxicam, with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, use the lowest effective dose for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during meloxicam therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of meloxicam until a serious GI adverse event is ruled out. For high-risk patients, consider alternate therapies that do not involve NSAIDs.

5.3 Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including meloxicam. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. (See **Adverse Reactions (6.1)**.)

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with meloxicam. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur

(e.g., eosinophilia, rash, etc.), discontinue meloxicam. (See *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*.)

5.4 Hypertension

NSAIDs, including meloxicam, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. NSAIDs, including meloxicam, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Patients taking ACE inhibitors, thiazides, or loop diuretics may have impaired response to these therapies when taking NSAIDs.

5.5 Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. Use meloxicam with caution in patients with fluid retention, hypertension, or heart failure.

5.6 Renal Effects

Long-term administration of NSAIDs, including meloxicam, can result 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 a nonsteroidal anti-inflammatory drug 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, heart failure, liver dysfunction, those taking diuretics, ACE-inhibitors, and angiotensin II receptor antagonists, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

A pharmacokinetic study in patients with mild and moderate renal impairment revealed that no dosage adjustments in these patient populations are required. Patients with severe renal impairment have not been studied. The use of meloxicam in patients with severe renal impairment with CrCl less than 20 mL/min is not recommended. A study performed in patients on hemodialysis revealed that although overall C_{max} was diminished in this population, the proportion of free drug not bound to plasma was increased. Therefore it is recommended that meloxicam dosage in this population not exceed 7.5 mg per day. Closely monitor the renal function of patients with impaired renal function who are taking meloxicam. (See **Dosage and Administration (2.1)**, *Use in Specific Populations (8.7)*, and *Clinical Pharmacology (12.3)*.)

Use caution when initiating therapy with meloxicam in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with meloxicam. Caution is also recommended in patients with pre-existing kidney disease.

The extent to which metabolites may accumulate in patients with renal impairment has not been studied with meloxicam. Because some meloxicam metabolites are excreted by the kidney, monitor patients with significant renal impairment closely.

5.7 Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions have occurred in patients without known prior exposure to meloxicam. Meloxicam should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. (See **Contraindications (4.1)** and **Warnings and Precautions (5.12)**.) Seek emergency help in cases where an anaphylactoid reaction occurs.

5.8 Adverse Skin Reactions

NSAIDs, including meloxicam, can cause serious skin adverse events 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 manifestations and discontinue use of the drug at the first appearance of skin rash or any other sign of hypersensitivity.

5.9 Pregnancy

Starting at 30 weeks gestation, avoid the use of meloxicam because it may cause premature closure of the ductus arteriosus. (See *Use in Specific Populations (8.1)* and *Patient Counseling Information (17.8)*.)

5.10 Corticosteroid Treatment

Meloxicam cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Slowly taper patients on prolonged corticosteroid therapy if a decision is made to discontinue corticosteroids.

5.11 Masking of Inflammation and Fever

The pharmacological activity of meloxicam in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

5.12 Hematological Effects

Anemia may occur in patients receiving NSAIDs, including meloxicam. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including meloxicam, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.

5.13 Use in Patients with Pre-existing Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, meloxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

5.14 Monitoring

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, meloxicam should be discontinued.

6. ADVERSE REACTIONS

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.

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular thrombotic events. (See **Boxed Warning and Warnings and Precautions (5.1)**)
- Gastrointestinal effects – risk of GI ulceration, bleeding, and perforation. (See **Boxed Warning and Warnings and Precautions (5.2)**.)
- Hepatic effects. (See **Warnings and Precautions (5.3)**.)
- Hypertension. (See **Warnings and Precautions (5.4)**.)
- Congestive heart failure and edema. (See **Warnings and Precautions (5.5)**.)
- Renal effects. (See **Warnings and Precautions (5.6)**.)
- Anaphylactoid reactions. (See **Warnings and Precautions (5.7)**.)
- Adverse skin reactions. (See **Warnings and Precautions (5.8)**.)

6.1 Clinical Trials Experience

Adults

Osteoarthritis and Rheumatoid Arthritis

The meloxicam Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with meloxicam 7.5 mg/day, 3508 OA patients and 1351 RA patients treated with meloxicam 15 mg/day. Meloxicam at these doses was administered to 961 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 $\geq 2\%$ of the meloxicam treatment groups in a 12-week placebo- and active-controlled osteoarthritis trial.

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

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

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 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
Diarrhea	3.8	7.8	3.2	9.2
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	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
Accident household	1.9	4.5	3.2	2.6
Edema ¹	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	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9

Respiratory	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3

Skin	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Diclofenac 100 mg daily
Rash ²	2.5	2.6	0.6	2.0

¹WHO preferred terms edema, edema dependent, edema peripheral, and edema legs combined

²WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

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

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily
No. of Patients	469	481	477
Gastrointestinal Disorders	14.1	18.9	16.8
Abdominal pain NOS ¹	0.6	2.9	2.3
Dyspeptic signs and symptoms ¹	3.8	5.8	4.0
Nausea ²	2.6	3.3	3.8

General Disorders and Administration Site Conditions

Influenza-like illness²

2.1 2.9 2.3

Infection and Infestations

Upper respiratory tract infections-pathogen class unspecified¹

4.1 7.0 6.5

Musculoskeletal and Connective Tissue Disorders

Joint related signs and symptoms¹

1.9 1.5 2.3

Nervous System Disorders

Get emergency help right away if you have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body

Stop your NSAID medicine and call your healthcare provider right away if you have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms

- slurred speech
- swelling of the face or throat
- 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 and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

- Aspirin is an NSAID medicine 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 of these NSAID medicines 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.

Generic Name	Tradename
Celecoxib	Celebrex
Diclofenac	Flector, Cataflam, Voltaren, Arthrotec (combined with misoprostol)
	Dolobid
Diflunisal	Lodine, Lodine XL
Fenoprofen	Nalfon, Nalfon 200
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Tab-Profen, Vicoprofen (combined with hydrocodone), Combunox (combined with oxycodone)
Indomethacin	Indocin, Indocin SR, Indo-Lemmon, Indomethagan
Ketoprofen	Oruvail
Ketorolac	Toradol
Mefenamic Acid	Bonstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Anaprox DS, EC-Naproxyn, Naprelan, Naprapac (copackaged with lansoprazole)
	Daypro
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

- Vicoprofen contains the same dose of ibuprofen as over-the-counter (OTC) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID label warns that long term continuous use may increase the risk of heart attack or stroke.

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

Pediatrics

Pauciarticular and Polyarticular Course
Juvenile Rheumatoid Arthritis (JRA)

Three hundred and eighty-seven patients with pauciarticular and polyarticular course JRA were exposed to meloxicam with doses ranging from 0.125 to 0.375 mg/kg per day in three clinical trials. These studies consisted of two 12 week multicenter, double-blind, randomized trials (one with a 12 week open-label extension and one with a 40 week extension) and one 1 year open-label PK study. The adverse events observed in these pediatric studies with meloxicam were similar in nature to the adult clinical trial experience, although there were differences in frequency. In particular, the following most common adverse events, abdominal pain, vomiting, diarrhea, headache, and pyrexia, were more common in the pediatric than in the adult trials. Rash was reported in seven (< 2%) patients receiving meloxicam. No unexpected adverse events were identified during the course of the trials. The adverse events did not demonstrate an age or gender-specific subgroup effect.

The following is a list of adverse drug reactions occurring in < 2% of patients receiving meloxicam in clinical trials involving approximately 16,200 patients.

Body as a Whole	allergic reaction, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase
Cardiovascular	angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis
Central and Peripheral Nervous System	convulsions, paresthesia, tremor, vertigo
Gastrointestinal	colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative
Heart Rate and Rhythm	arrhythmia, palpitation, tachycardia
Hematologic	leukopenia, purpura, thrombocytopenia
Liver and Biliary System	ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis
Metabolic and Nutritional	dehydration
Psychiatric	abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence
Respiratory	asthma, bronchospasm, dyspnea
Skin and Appendages	alopecia, angioedema, bullous eruption, photosensitivity reaction, pruritus, sweating increased, urticaria
Special Senses	abnormal vision, conjunctivitis, taste perversion, tinnitus
Urinary System	albuminuria, BUN increased, creatinine increased, hematuria, renal failure

6.2 Post Marketing Experience

The following adverse reactions have been identified during post approval use of meloxicam. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. Adverse reactions reported in worldwide post marketing experience or the literature include: acute urinary retention; agranulocytosis; alterations in mood (such as mood elevation); anaphylactoid reactions including shock; erythema multiforme; exfoliative dermatitis; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome, and toxic epidermal necrolysis.

7. DRUG INTERACTIONS

See also Clinical Pharmacology (12.3).

7.1 ACE-inhibitors

NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking meloxicam concomitantly with ACE-inhibitors.

7.2 Aspirin

When meloxicam is administered with aspirin (1000 mg three times daily) to healthy volunteers, an increase in the AUC (10%) and C_{max} (24%) of meloxicam was noted. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of meloxicam and aspirin is not generally recommended because of the potential for increased adverse effects.

Concomitant administration of low-dose aspirin with meloxicam may result in an increased rate of GI ulceration or other complications, compared to use of meloxicam alone. Meloxicam is not a substitute for aspirin for cardiovascular prophylaxis.

7.3 Diuretics

Clinical studies, as well as post marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to 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 pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with meloxicam, patients should be observed closely for signs of renal failure (see *Warnings and Precautions (5.6)*), as well as to ensure diuretic efficacy.

7.4 Lithium

In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam 15 mg every day as compared to subjects receiving lithium alone. These effects have been attributed to inhibition of renal prostaglandin synthesis by meloxicam. Closely monitor patients on lithium treatment for signs of lithium toxicity when meloxicam is introduced, adjusted, or withdrawn.

7.5 Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. Therefore, NSAIDs may reduce the elimination of methotrexate, thereby enhancing the toxicity of methotrexate. Use caution when meloxicam is administered concomitantly with methotrexate (see *Clinical Pharmacology (12.3)*).

7.6 Cyclosporine

Meloxicam, like other NSAIDs, may affect renal prostaglandins, thereby altering the renal toxicity of certain drugs. Therefore, concomitant therapy with meloxicam may increase cyclosporine's nephrotoxicity. Use caution when meloxicam is administered concomitantly with cyclosporine.

7.7 Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Monitor anticoagulant activity, particularly in the first few days after initiating or changing meloxicam therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding than with the use of either drug alone. Use caution when administering meloxicam with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced (See *Clinical Pharmacology (12.3)*).

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C, Category D starting 30 weeks gestation

There are no adequate and well-controlled studies in pregnant women. Meloxicam crosses the placental barrier. Prior to 30 weeks gestation, use meloxicam during pregnancy only if the potential benefit justifies the potential risk to the fetus. Starting at 30 weeks gestation, avoid meloxicam and other NSAIDs. In pregnant women as premature closure of the ductus arteriosus in the fetus may occur. If this drug is used during this time period in pregnancy, inform the patient of the potential hazard to a fetus (see *Warnings and Precautions (5.9) and Patient Counseling Information (17.8)*).

Teratogenic Effects

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 maximum recommended human daily dose (MRHD) based on body surface area [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. The no effect level was 20 mg/kg/day (21.6-fold greater than the MRHD based on BSA conversion).

Nonteratogenic Effects

In rats and rabbits, embryolethality 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 through

organogenesis.

8.2 Labor and Delivery

The effects of meloxicam on labor and delivery of pregnant women are unknown. 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 (at least 12.5 times lower than the maximum recommended human daily dose based on body surface area comparison).

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from meloxicam, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

Of the total number of subjects in clinical studies, 5157 were age 65 and over (4044 in OA studies and 1113 in RA studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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, the use of meloxicam in these patients should be done with caution (see *Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)*).

8.7 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been studied. The use of meloxicam in subjects with severe renal impairment is not recommended. 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). Therefore, it is recommended that meloxicam dosage in this population not exceed 7.5 mg per day. Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable (See *Dosage and Administration (2.1), Warnings and Precautions (5.6), and Clinical Pharmacology (12.3)*).

8.8 Females of Reproductive Potential

Data from several small studies in humans and from studies in animals indicate that NSAIDs, including meloxicam, may be associated with a reversible delay in ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, use of meloxicam is not recommended.

10. OVERDOSAGE

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose, all recovered. Cholestyramine is known to accelerate the clearance of meloxicam.

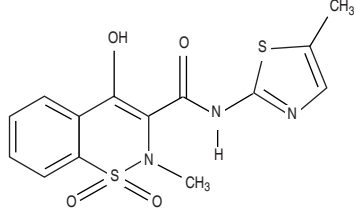
Symptoms following acute NSAID overdose include lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Administration of activated charcoal is recommended for patients who present 1 to 2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. 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 overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

11. DESCRIPTION

Meloxicam, an oximic derivative, is a member of the enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each tablet contains 7.5 mg or 15 mg meloxicam USP for oral administration. Meloxicam is chemically designated as 4-hydroxy-2-methyl-N-(5-methoxy-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is C₁₄H₁₃N₃O₅ 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)_{app} = 0.1 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 or 15 mg meloxicam USP.

The inactive 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

The mechanism of action of meloxicam, like that of other NSAIDs, may be related to prostaglandin synthetase (cyclo-oxygenase) inhibition which is involved in the initial steps of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacyclin. It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy.

12.2 Pharmacodynamics

Meloxicam exhibits anti-inflammatory, analgesic, and antipyretic activities.

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 prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

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

Pharmacokinetic Parameters (%CV)	Steady State		Single Dose	
	Healthy male adults (Fed) ²	Elderly males (Fed) ²	Renal failure (Fasted)	Hepatic insufficiency (Fasted)
	7.5 mg ¹ tablets	15 mg capsules	15 mg capsules	15 mg capsules
N	18	5	8	12
C _{max}	1.05 (20)	2.3 (59)	0.59 (36)	0.84 (29)
t _{max}	4.9 (8)	5 (12)	6 (27)	10 (67)
t _{1/2}	20.1 (29)	21 (34)	24 (34)	18 (46)
CL _T	8.8 (29)	9.9 (76)	5.1 (22)	19 (43)
V _d ¹ (L)	14.7 (32)	15 (42)	10 (30)	26 (44)

¹The parameter values in the table are from various studies

²not under high fat conditions

³Meloxicam tablets

⁴V_d≠Dose/ (AUC×K_a)

Food and Antacid Effects

Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e., C_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T_{max}) was achieved between 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_{ss}) 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.

Metabolism

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5-carboxy meloxicam (60% of dose), from P-450 mediated metabolism formed by oxidation of an intermediate 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 the 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% 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%.

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.

Special Populations

Pediatric

After single (0.25 mg/kg) dose administration and after achieving steady state (0.375 mg/kg/day), there was a general trend of approximately 30% lower exposure in younger patients (2 to 6 years old) as compared to the older patients (7 to 16 years old). The older patients had meloxicam exposures similar (single dose) or slightly reduced (steady state) to those in the adult patients, when using AUC values normalized 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) 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 47% higher AUC_{0-∞} and 32% higher C_{max} as compared to younger females (< 55 years of age) after body weight normalization. Despite the increased 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.

Gender

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_{max} or t_{max} across genders.

Hepatic Impairment

Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied (see *Warnings and Precautions (5.3) and Use in Specific Populations (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 *Warnings and Precautions (5.6) 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 total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable (See *Dosage and Administration (2.1), Warnings and Precautions (5.6), and Use in Specific Populations (8.7)*).

Drug Interactions

Aspirin: 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 *Drug Interactions (7.2)*).

Cholestyramine: Pretreatment 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 recirculation pathway for meloxicam in the gastrointestinal tract. The clinical relevance of this interaction has not been established.

Cimetidine: Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 30 mg meloxicam.

Digoxin: 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. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Lithium: In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam 15 mg QD every day as compared to subjects receiving lithium alone (see *Drug Interactions (7.4)*).

Methotrexate: 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. *In vitro*, methotrexate did not displace meloxicam from its human serum binding sites (see *Drug Interactions (7.5)*).

Warfarin