

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

- of use (5.1) Meloxicam tablets are contraindicated in the setting of coronary artery bypass graf
- (CABG) surgery (4, 5.1) NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events inclu

bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use ratio. interation, and performing of the soundary of messines, which can be radial tis can occur at any time during use and without warning symptoms. Elderly nd 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 Reaction with Eosinophilia and Systemic Symptoms (5.10) 04/2021 Warnings and Precautions, Fetal Toxicity (5.11) 04/2021

---- INDICATIONS AND USAGE ---Meloxicam tablets are 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 \ge 60 kg (1.3)

---- DOSAGE AND ADMINISTRATION ---Use the lowest effective dosage for the shortest duration consistent with individual patient treatment

- goals (2.1) OA (2.2) and RA (2.3)
- · Starting dose: 7.5 mg once daily
- Dose may be increased to 15 mg once daily JRA (2.4):
- 7.5 mg once daily in children ≥60 kg
- Meloxicam Tablets are not interchangeable with approved formulations of oral meloxicam even it
- the total milligram strength is the same $\left(2.6\right)$ -DOSAGE FORMS AND STRENGTHS--
- Meloxicam Tablets USP: 7.5 mg and 15 mg (3)
- ----- CONTRAINDICATIONS -
- Known hypersensitivity to meloxicam or any components of the drug product (4)
- History of asthma, uriticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
 In the setting of CABG surgery (4)
- ---- WARNINGS AND PRECAUTIONS ---Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if

FULL PRESCRIBING INFORMATION: CONTENTS*

		RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
1.	INDICA	TIONS AND USAGE
	1.1	Osteoarthritis (OA)
	1.2	Rheumatoid Arthritis (RA)
	1.3	Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course
2.	DOSAG	E AND ADMINISTRATION
	2.1	General Dosing Instructions
	2.2	Osteoarthritis
	2.3	Rheumatoid Arthritis
	2.4	Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course
	2.5	Renal Impairment
	2.6	Non-Interchangeability with Other Formulations of Meloxicam
3.	DOSAG	E FORMS AND STRENGTHS
4.	CONTR	AINDICATIONS
5.	WARN	NGS AND PRECAUTIONS
	5.1	Cardiovascular Thrombotic Events
	5.2	Gastrointestinal Bleeding, Ulceration, and Perforation
	5.3	Hepatotoxicity

- Hypertensior Heart Failure and Edema
- 5.5 5.6 Renal Toxicity and Hyperkalemia
- 5.7 5.8 5.9 Anaphylactic Reaction:
- Exacerbation of Asthma Serious Skin Reactions of Asthma Related to Aspirin Sensitivity
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- 5.10 5.11 Fetal Toxicity
- 5.12 Hematologic Toxicity

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 tablets are 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)].

INDICATIONS AND USAGE

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

1.2 Rheumatoid Arthritis (RA)

- Meloxicam tablets are indicated for relief of the signs and symptoms of rheumatoid arthritis [see Clinical Studies (14.1)].
- 1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course Meloxicam tablets are indicated for relief of the signs and symptoms of pauciarticular or polyarticular
- course Juvenile Rheumatoid Arthritis in patients who weigh ≥60 kg [see Dosage and Administration (2.4) and Clinical Studies (14.2)]. DOSAGE AND ADMINISTRATION
- 2.1 **General Dosing Instructio**

- abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop 5.6 Renal Toxicity and Hyperkalemia (5.3)Hypertension: Patients taking some antihypertensive medications may have impaired response to
- these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7) Heart Failure and Edema: Avoid use of Meloxicam in patients with severe heart failure unless
- benefits are expected to outweigh risk of worsening heart failure (5.5) Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure,
- dehydration, or hypovolemia. Avoid use of Meloxicam in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
 - Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs (5.7)
 - Exacerbation of Asthma Related to Aspirin Sensitivity: Meloxicam is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
 - Serious Skin Reactions: Discontinue Meloxicam at first appearance of skin rash or other signs of hypersensitivity (5.9)
 - Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue Meloxicam and evaluate clinically (5.10)
 - Fetal Toxicity: Limit use of NSAIDs, including Meloxicam, between about 20 to 30 weeks in preg-Team routing. This do to so were a micro and the source of dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1)
 - Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)
 - ---- ADVERSE REACTIONS ---Most common (≥5% and greater than placebo) adverse events in adults are diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (6.1) Adverse events observed in pediatric studies were similar in nature to the adult clinical trial unvisioned to the second structure of the second structure
 - experience (6.1)
 - To report SUSPECTED ADVERSE REACTIONS, contact XLCare Pharmaceuticals, Inc. at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
 - ----- DRUG INTERACTIONS -----Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking Meloxicam with drugs that interfere with hemostasis. Concomitant use of Meloxicam and analgesic doses of aspirin is not generally recommended (7)
 - ACE Inhibitors, Angiotensis Receptor Blockers (ARBs) or Beta-Blockers: Concomitant use with Meloxicam may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7) <u>ACE Inhibitors and ARBs</u>; Concomitant use with Meloxicam in elderly, volume-depleted, or those with meloxicate approach and an anti-indepleted and an anti-indepleted and the method is an anti-indepleted of the method.
 - renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
 - <u>Diuretics</u>: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

5.13 Masking of Inflammation and Fever 5.14 Laboratory Monitoring 6. ADVERSE REACTIONS Clinical Trials Experience 6.1 6.2 Postmarketing Experience DRUG INTERACTIONS 8. USE IN SPECIFIC POPULATIONS Pregnancy 8.1 8.2 Lactation Females and Males of Reproductive Potential 83 Pediatric Use 8.4 8.5 Geriatric Use 8.6 Hepatic Impairment 8.7 Renal Impairment 10. OVERDOSAGE 11. DESCRIPTION 12. CLINICAL PHARMACOLOGY 12.1 Mechanism of Action 12.1 Mechanism of Activ 12.3 Pharmacokinetics 13. NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 14. CLINICAL STUDIES 14.1 Osteoarthritis and Rheumatoid Arthritis 14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course IOW SUPPLIED/STORAGE AND HANDLING 17. PATIENT COUNSELING INFORMATION ctions or subsections omitted from the full prescribing information are not listed.

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. the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently NSAIDs, including Meloxicam, may increase the risk of bleeding events. Co-morbid conditions such as at higher doses. coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the le 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 vear post-Mi was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four vears 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 NSAUS, including meioxicam, can cause serious gastrolutestinal (oi) 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 NSAUS. Only one in five patients who develop a serious upper GI adverse event on NSAU therapy is symptomatic. Upper GI ucers, 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

Renal Toxicity

Long-term administration of NSAIDs, including Meloxicam, has resulted in renal papillary necrosi

renal insufficiency, acute renal failure, and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a comper role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

The renal effects of Meloxicam may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some Meloxicam metabolites are excreted by the kidney, monitor patients for signs of worsening renal function.

Correct volume status in dehydrated or hypovolemic patients prior to initiating Meloxicam. Monito 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 outweight 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)].

Hyperkalemia

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

5.7 Anaphylactic Reactions

Meloxicam has been associated with anaphylactic reactions in patients with and without known hypersensitivity to meloxicam and in patients with aspirin-sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs 5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients. Meloxicam is contraindicated in patients with this form of aspirin sensitivity [see Contraindications (4)]. When Meloxicam is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma

5.9 Serious Skin Reactions

Revised: 06/21

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 Epsinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as meloxicam. Some of these events have been fatal or life-threatening. DRESS typically atthough not exclusively, presents with even; 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 Premature Closure of Fetal 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 destational age

the utility of diagnostic signs in detecting infections.

ADVERSE REACTIONS

periodically [see Warnings and Precautions (5.2, 5.3, 5.6)].

Hepatotoxicity [see Warnings and Precautions (5.3)]

Hypertension [see Warnings and Precautions (5.4)]

• Fetal Toxicity [see Warnings and Precautions (5.11)]

and may not reflect the rates observed in practice.

Heart Failure and Edema [see Warnings and Precautions (5.5)]

Anaphylactic Reactions [see Warnings and Precautions (5.7)]

Serious Skin Reactions [see Warnings and Precautions (5.9]]

Hematologic Toxicity [see Warnings and Precautions (5.12)]

Renal Toxicity and Hyperkalemia [see Warnings and Precautions (5.6]]

upproximately in a speciational ages 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 observations are accounted in the second seco 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 oligohydran 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

In tool beaution is necessary vertice about 20 more and so the set of the set

saprin), 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

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

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]]

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [see Warnings and Precautions (5.10]

occurs and follow up according to clinical practice [see Use in Specific Populations (8.

Carefully consider the potential benefits and risks of Meloxicam tablets and other treatment options before deciding to use Melia before the boots of meliana tables and other becaute of the boots before deciding to use Melian and tables. Use the lowest effective docage for the shortest duration consistent with individual patient treatment goals [see Warnings and Precautions (5)].

After observing the response to initial therapy with Meloxicam tablets, adjust the dose to suit an ndividual patient's needs

In adults, the maximum recommended daily oral dose of Meloxicam tablets 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 tablets may be taken without regard to timing of meals

2.2 Osteoarthritis

For the relief of the signs and symptoms of osteoarthritis the recommended starting and maintenance For the refer of me softs and symptoms or osteodal into the recommended starting oral dose of Meloxicam tablets is 7.5 mg once daily. Some patients may receive ad increasing the dose to 15 mg once daily.

2.3 Rheumatoid Arthritis

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

2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of Meloxicam tablets is 7.5 mg once daily in children who weigh \geq 60 kg. There was no additional benefit demonstrated by increasing the dose above 7.5 mg in clinical trials.

Meloxicam tablets should not be used in children who weigh <60 kg

2.5 Renal Impairment

The use of Meloxicam tablets in subjects with severe renal impairment is not recommended.

In patients on hemodialysis, the maximum dosage of Meloxicam tablets 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.

DOSAGE FORMS AND STRENGTHS

- 7.5 mg: Light yellow, round flat beveled edge tablet with "T" on one side and "152" on the
- 15 mg: Light yellow, capsule shaped biconvex tablet with "T" on one side and "153" on the

CONTRAINDICATIONS

Meloxicam tablets are contraindicated in the following patients:

Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any

- components of the drug product [see Warnings and Precautions (5.7, 5.9)] History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Morning and Gregoriting ($\overline{2}, \overline{5}, 0$)] Warnings and Precautions (5.7, 5.8)]
- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV Intraction (will allo stoke, which can be rate) beach of available data, it is inclear that the rate of or thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher ous CV thrombotic events over 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

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 reater is with a price line and the second s health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSID at a time. Avoid administration of more than one NSID at a time. Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Bemain alert for signs and symptoms of GLulceration and bleeding during NSAID therapy
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue Meloxicam until a serious GI adverse event is ruled out. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding *[see Drug Interactions (7)]*.

5.3 Hepatotoxicity Elevations of ALT or AST (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

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

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Meloxicam immediately, and perform a clinical evaluation of the patient [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]

5.4 Hypertension

NSAIDs, including Meloxicam, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)].

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

5.5 Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta analysis of randomized controll 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)1.

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.

Adults Osteoarthritis and Rheumatoid Arthritis

6.1 Clinical Trials Experience

The Meloxicam Phase 2/3 clinical trial database includes 10.122 OA patients and 1012 BA patients Treated with Meloxicam 7.5 mg/day, 3505 OA patients and 1351 RA patients that of the Meloxicam 7.5 mg/day. 3505 OA patients and 1351 RA patients treated with Meloxicam 15 mg/day. Meloxicam at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in 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.

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

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis A t2-week induction, double-bind, randomized that was conducted in patients with oscillation 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 \geq 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	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				

bouy us a miloio				
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 Sy	stem			
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Respiratory				
Pharyngitis	1.3	0.6	3.2	1.3
Upper respiratory tract infection	1.9	3.2	1.9	3.3
Skin				
Rash ²	2.5	2.6	0.6	2.0

¹ WHO preferred terms edema, edema dependent, edema peripheral, and edema legs WHO preferred terms rash, rash erythematous, and rash maculo-papular combined

	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

Table 1b Adverse Events (%) Occurring in ≥2% of Meloxicam Patients in two 12-Week

469

14.1

06

38

2.6

4.1

6.4

¹ MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms

MedDRA preferred term: nausea, abdominal pain NOS, influenza-like illness, headaches NOS, and

The adverse events that occurred with Meloxicam in ≥2% of patients treated short-term (4 to 6 weeks)

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

4-6 Weeks

Controlled Trials

15 mg

daily

256

18.0

2.3

1.2

2.7

74

0.4

4.7

0.8

0.0

2.0

2.0

1.6

2.7

0.0

0.0

0.4

0.0

0.8

0.0

1.2

1.2

0.4

and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 2.

7.5 mg

daily

895

11.8

2.7

0.8

1.9

3.8

0.5

2.4

0.6

0.0

0.6

0.9

1.1

2.4

0.1

0.5

0.5

0.4

0.2

0.2

0.4

0.3

0.3

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

serious GI events; therefore, the daily dose of Meloxicam should not exceed 15 mg.

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

events did not demonstrate an age or gender-specific subgroup effect.

clinical trials involving approximately 16,200 patients.

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

Higher doses of Meloxicam (22.5 mg and greater) have been associated with an increased risk of

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 trails. Rash was reported in seven (<2%) patients receiving Meloxicam. No unexpected adverse events were identified during the course of the trials. The adverse

The following is a list of adverse drug reactions occurring in $<\!\!2\%$ of patients receiving Meloxicam in

allergic reaction, face edema, fatigue, fever, hot flushes,

angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis

colitis. drv mouth. duodenal ulcer, eructation, esophagitis,

malaise, syncope, weight decrease, weight increase

convulsions, paresthesia, tremor, vertigo

nerforation melena nancreatit

gastric ulcer, gastritis, gastroesophageal reflux

gastrointestinal hemorrhage, hematemesis, hem

duodenal ulcer, hemorrhagic gastric ulcer, intestinal

(arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling)

7.5 mg

daily

481

18.9

2.9

5.8

3.3

2.9

7.0

1.5

6.4

1.0

6 Month

Controlled Trials

7.5 mg

daily

169

26.6

4.7

1.8

5.9

8.9

3.0

4.7

1.8

0.6

2.4

3.6

2.4

3.6

4.1

5.3

3.0

3.6

2.4

8.3

2.4

3.0

4.7

Meloxican

15 mg

daily

306

24.2

2.9

2.6

2.6

9.5

2.6

7.2

2.6

2.9

1.6

5.2

2.6

2.6

2.9

1.3

0.7

1.6

1.0

7.5

0.0

1.3

6.9

rhagic

perforated duodenal ulc

15 mg

daily

477

16.8

2.3

4.0

3.8

2.3

6.5

2.3

5.5

Rheumatoid Arthritis Placebo- Controlled Trials

General Disorders and Administration Site Condi

Upper Respiratory tract infections-pathogen

Skin and Subcutaneous Tissue Disorders

Joint related signs and symptoms

Musculoskeletal and Connective Tissue Disorders

No. of Patients

Nausea

Gastrointestinal Disorders

Dyspeptic signs and symptoms

Abdominal pain NOS²

Influenza-like illness

class unspecified

Headaches NOS²

Rash NOS

rash NOS

No. of Patients

Gastrointestinal

Constipation

Diarrhea

Dyspepsia

Flatulence

Nausea

Edema¹

Dizziness

Headache

Hematologic

Anemia

Arthralgia

Back pain

Psychiatric

Insomnia

Respiratory

Coughing

Skin

Pruritus

Rash²

Urinary Micturition frequency

Pediatrics

Body as a Whole

Cardiovascular

Gastrointestinal

System

Central and Peripheral Nervous

Upper respir

tract infection

Urinary tract infection

Musculoskeleta

Pain

Vomiting

Body as a Whole

Accident household

Central and Peripheral Nervous Sys

Abdominal pain

Infection and Infestations

Nervous System Disorders

6.2 Postmarketing Experience

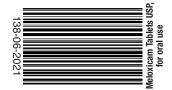
The following adverse reactions have been identified during post approval use of Meloxicam. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to whether to include an adverse event from spontaneous reports in labeling are typically based on 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 causa relationship to the unity. Averse 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; exoliative dermatilits; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome; toxic epidermal necrolysis, and infertility female

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

2.6	Drugs that Interfe	ere with Hemostasis
3.3 1.3 2.6	Clinical Impact:	 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. Serotonin release by platelets plays an important role in hemostasis. Case-
2.0		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.
5.9 1.3 3.3	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 (5.12].
3.3	Aspirin	
2.0 s combined	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 (6.2)].
	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. 12)]. Meloxicam is not a substitute for low dose aspirin for cardiovascular protection.
	ACE Inhibitors, A	ngiotensin Receptor Blockers, or Beta-Blockers



Clinical Impact:	 NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta- blockers (including propranolo). 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:	 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 assuring 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 <i>[see Clinical Pharmacology (12.3)]</i> .
Intervention:	During concomitant use of Meloxicam and lithium, monitor patients for signs

Methotrexate Concomitant use of NSAIDs and methotrexate may increase the risk for Clinical Impact: methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). During concomitant use of Meloxicam and methotrexate, monitor patients for Intervention. methotrexate toxicity. Cyclosporine

Clinical Impact ncomitant use of Meloxicam and cyclosporine may increase cyclosporir nephrotoxicity. During concomitant use of Meloxicam and cyclosporine, monitor patients fo Interventio signs of worsening renal function NSAIDs and Sali

NSAIDS and Sancylates				
Clinical Impact:	Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see Warnings and Precautions (5.2)].			
Intervention:	The concomitant use of meloxicam with other NSAIDs or salicylates is not recommended.			
Pemetrexed				
Clinical Impact:	Concomitant use of Meloxicam and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).			
Intervention:	During concomitant use of Meloxicam and pemetrexed, in patients with renal			

impairment whose creatinine clearance ranges from 45 to 79 mL/min, monito for myelosuppression, renal and Gi toxicity. If the set of a methin, many for myelosuppression, renal and Gi toxicity dosing for at least five days before the day of, and two days following pemetrexed administration. In patients with creatinine clearance below 45 mL/min, the concomitan administration of meloxicam with pemetrexed is not recommended

USE IN SPECIFIC POPULATIONS

8.1 Pregna

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*

gestation, and avoid motions of Considerations, Data). Premature Closure of Fetal Ductus Arterios 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.

vdramnios/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 neorest dispersion of incomposition in control with the studies of the stu first or second trimesters of pregnancy are inconclusive.

In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maxim 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 0.08-times MRHD of meloxicam. No technological for the une not decreased offspring survival at 0.08-times MRHD of meloxicam. No teratogenic effects were observed in rats and rabbits treated with meloxicam during organogenesis at an oral dose equivalent to 2.6 and 26-times the MRHD [see Data].

Based on animal data, prostagiandins 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 melosicam, 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 kidnev development when administered at clinically relevant doses.

Inipair Note: 9 development when administered a connear 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.

<u>Clinical Considerations</u> 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)

Ilightydramios/Neonata 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 stillbirth.

Data

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment have not been adequately studied. Since meloxicam is significantly metabolized in the liver and hepatotoxicity may occur, use meloxicam with caution in patients with hepatic impairment *(see Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*. pairment *[see N* nal 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

case of measure during has occurred, integration, added the measure of the measu within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful

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

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

Meloxicam Tablets USP are a nonsteroidal anti-inflammatory drug (NSAID). Each tablet contains 7.5 mg or 15 mg meloxicam for oral administration. Meloxicam is chemically designated as 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide. The molecular weight is 351.4. Its empirical formula is $C_{14}H_{13}N_3O_4S_2$ and it has the following structural formula:

> CH_3 CH₂ 0″ \searrow_0

Meloxicam is a pastel yellow solid, practically insoluble in water, with higher solubility observed in strong acids and bases. It is very slightly soluble in methanol. Meloxicam has an apparent partition coefficient (log P)ann = 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 The inactive ingredients in Meloxicam tablets USP include colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium citrate dihydrate. 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Meloxicam has analgesic, anti-inflammatory, and antipyretic properties.

Meloxical has analysis, anterminantiatory, and anapyreus 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. Prostaglanding sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of nflammation. 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

Absorption The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg The absolute bioavailability of metoxicain capsules was 69% 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 meloxicain capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean Came, was achieved within four to five hours after a 7.5 mg meloxicain tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state consent of the ways multiple to the bolic part of the source of the source accurated to the source accurate of the source accurate accurate of the source of the source accurate of 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 oxicam (Mean and % CV)1

			Steady State	Single Dose		
Pharmacokinetic Parameters (%CV)		Healthy male adults (Fed) ²	Elderly males (Fed) ²	Elderly females (Fed) ²	Renal failure (Fasted)	Hepatic insufficiency (Fasted)
		7.5 mg ³ tablets	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/f	[mL/min]	8.8 (29)	9.9 (76)	5.1 (22)	19 (43)	11 (44)
V _z /f ⁴	[L]	14.7 (32)	15 (42)	10 (30)	26 (44)	14 (29)

The parameter values in the table are from various studies

² not under high fat cond ³ Meloxicam tablets

Vz/f=Dose/(AUC•Ke Food and Antacid Effects

Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak

Administration of microsoftan registers biownig angular to transfer (σ) of an an restrict and 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 (r_{max}) was achieved between 5 and 6 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 (Vss) 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.

Meloxican 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

Metabolisn

severe renal impairment is not recommended [see Dosage and Administration (2.5), Warnings and Precautions (5.6) and Use in Specific Populations (8.7)]. Hemodialvsis

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 dose are not necessary after hemodialysis. Meloxicam is not dialyzable [see Dosage and Administration (2.1) and Use in Specific Populations (8.7)1.

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

to metoxically the chindra significant to the metacody interaction in the known operations of the chindray significant true of NSAIbs with aspirin [see Drug Interactions (7)]. Cholestyramine: Pretreatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in $t_{\rm yi}$, 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-

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)].

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 is inflictant effect on the pharmacokinetics of ningle doses of methorexate. In virto, methorexate did not displace meloxicam from its human serum binding sites [see Drug Interactions (7)]. Warfarin: The effect of meloxicam on the anticoagulant effect of warfarin was studied in a group of

healthy subjects receiving daily doses of warfarin that produced an INR (International Normalized Ratio) between 1.2 and 1.8. In these subjects, meloxicam did not alter warfarin pharmacokinetics and the severage anticogulant effect of warfarin as determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering Meloxicam with warfarin since patients on warfarin may experience changes in INR and an increased risk of bleeding complications when a new medication is introduced [see Drug Interactions (7)]. NONCLINICAL TOXICOLOGY 13

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in tumor incidence in long-term carcinogenicity studies in rats (104 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 0.8 mo/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 0.5- and 2.6-times, respectively, the maximum recommended human dose [MRHD] of 15 mg/day Meloxicam based on body surface area [BSA] comparison). Mutagenesis

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an in vivo micronucleus test in mouse bone marrow.

Impairment of Fertility Meloxicam did not imoair male and female fertility in rats at oral doses up to 9 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA compariso CLINICAL STUDIES 14

14.1 Osteoarthritis and Rheumatoid Arthritis

14.1 Osteoardinus and internation Andrumus The use of Meloxicam for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a 12-week, double-blind, controlled trial. Meloxicam (3.75 mg, 7.5 mg, and 15 mg daily) was compared to placebo. The four primary endpoints were investigator's global assessment, patient global assessment, patient pain assessment, and total WOMAC score (a self-administered questionnaire addressing pain, function, and stiffness). Patients on Meloxicam 7.5 mg daily and Meloxicam 15 mg daily showed significant improvement in each of these endpoints compared with

The use of Meloxicam for the management of signs and symptoms of osteoarthritis was evaluated in six double-blind, active-controlled trials outside the U.S. ranging from 4 weeks' to 6 months' duration. In these trials, the efficacy of Meloxicam, in doses of 7.5 mg/day and 15 mg/day, was comparable to piroxicam 20 mg/day and diclofenac SR 100 mg/day and consistent with the efficacy seen in the U.S. trial.

The use of Meloxicam for the treatment of the signs and symptoms of rheumatoid arthritis was valuated in a 12-week, double-blind, controlled multinational trial. Meloxicam (7.5 mg, 15 mg, 16 mg, 22.5 mg daily) was compared to placebo. The primary endpoint in this study was the ACR20 response rate, a composite measure of clinical, laboratory, and functional measures of RA response. Patients receiving Meloxicam 7.5 mg and 15 mg daily showed significant improvement in the primary endpoint compared with placebo. No incremental benefit was observed with the 22.5 mg dose compared to the 15 mg dose.

14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

The use of Meloxicam for the treatment of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older was evaluated in two 12-week, double-bilind, parallel-arm, active-controlled trials. Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam

dosing began at 0.125 mg/kg/day (7.5 mg maximum) or 0.25 mg/kg/day (15 mg maximum), and naproxen dosing began at 10 mg/kg/day. One study used these doses throughout the 12-week dosing period, while the other incorporated a titration after 4 weeks to doses of 0.25 mg/kg/day and 0.375 period, while the other incorporated a function and 15 mg/kg/day and corporate and corporate and the mg/kg/day (22.5 mg/kg/day) and corporate and 15 mg/kg/day (22.5 mg/kg/day) and corporate and 15 mg/kg/day of an another mg/kg/day (25.5 mg/kg/day) and corporate and investigator assessments, counts of active joints and joints with limited range of motion, and

erythrocyte sedimentation rate. The proportion of responders were similar in all three groups in both studies, and no difference was observed between the meloxicam dose groups

16 HOW SUPPLIED/STORAGE AND HANDLING

Meloxican tablets USP are available as a light yellow, round flat beveled edge tablet with "T" on one side and "152" on the other side for 7.5 mg and light yellow, capsule shaped biconvex tablet with "T" on one side and "153" on the other side for 15 mg. Meloxicam Tablets USP 7.5 mg are available as follows NDC 72865-137-90: Bottles of 90 NDC 72865-137-01; Bottles of 100 NDC 72865-137-10; Bottles of 1,000 Meloxicam Tablets USP 15 mg are available as follows: NDC 72865-138-90; Bottles of 90 NDC 72865-138-01: Bottles of 100

NDC 72865-138-10; Bottles of 1,000

Storage Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Keep Meloxi-cam Tablets USP in a dry place.

Dispense tablets in a tight container Keep this and all medications out of the reach of children.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed.

Inform patients, families or their caregivers of the following information before initiating therapy with in NSAID and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia,

nelena, and hematemesis to their healthcare provider. In the setting of conco itant use of low-dose

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Antiry Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including: Increased risk of a heart attack or stroke that can lead to death. This risk may happer early in treatment and may increase

with increasing doses of NSAIDs

with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypas Do not take months right before of ander a mark and an energy of the second sec

from the mouth to the stomach), stomach and intestines anvtime during use

- without warning symptoms
- that may cause death
- The risk of getting an ulcer or bleeding increases with:
- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs older age
- longer use of NSAIDs poor health
 - advanced liver disease
 - bleeding problems

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

on take NSAIDs:
 if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including

are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**

Tell your healthcare provider about all of the medicines you take, including prescription or over-the counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interac with each other and cause serious side effects. Do not start taking any new medicine without talking

See "What is the most important information I should know about medicines called Nonsteroida

Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn

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

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 provide 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

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

Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to you

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 i

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask you

rmacist or healthcare provider for information about NSAIDs that is written for health profess

healthcare provider before using over-the-counter NSAIDs for more than 10 days

General information about the safe and effective use of NSAIDs

hey have the same symptoms that you have. It may harm them.

vomit blood

slurred speech

black and sticky like tar

· skin rash or blisters with fever

unusual weight gain

swelling of the face or throat

· there is blood in your bowel movement or it is

• swelling of the arms, legs, hands and feet

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

NSAIDs should only be used:

What are NSAIDs?

if you

smoking

drinking alcohol

for the shortest time needed

Vho should not take NSAIDs?

right before or after heart bypass surgery.

are breastfeeding or plan to breast feed.

What are the possible side effects of NSAIDs?

new or worse high blood pressure

liver problems including liver failure

low red blood cells (anemia)

life-threatening skin reactions

life-threatening allergic reactions

nausea, vomiting, and dizziness

more tired or weaker than usual

• your skin or eyes look yellow

· indigestion or stomach pain

Other information about NSAIDs:

flu-like symptoms

and intestines

shortness of breath or trouble breathing

· weakness in one part or side of your body

kidney problems including kidney failure

NSAIDs can cause serious side effects, including

ory Drugs (NSAIDs)?'

have liver or kidney problems

have high blood pressure

to your healthcare provider first.

have asthma

heart failure

chest pain

sympto

nausea

diarrhea

itching

exactly as prescribed at the lowest dose possible for your treatment

Human Data Premature Closure of Fetal Ductus Arteriosus

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen on average after and in some cases, neonatal rena impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in anniotic 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.

initide information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Milling Data Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of Meloxicam based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA comparison). In rats and rabbits, 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 MDUb based on DSA comparison). MRHD based on BSA comparison) when administered throughout organogenesis. Oral administration of meloxicam to pregnant rats during late gestation through lactation increased the incidence of dystocia, delayed parturition, and decreased offspring survival at meloxicam doses of

0.125 mg/kg/day or greater (0.08-times MRHD based on BSA comparison)

8.2 Lactation

Risk Summary There are no human data available on whether meloxicam is present in human milk, or on the effects the developmental and health benefits of breastfeeding 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. Data

Animal Data

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

8.3 Females and Males of Reproductive Potential

Infertility

remains 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 ndergoing investigation of infertility

8.4 Pediatric Use

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

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5, 14]]

Meloxicam is extensively metabolized in the liver. Meloxicam metabolites include 5'-carboxy metoxican is exclassively metabolized in the web metabolism formed by oxidation of an intermediate 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

Malovician averation is predominantly in the form of matabolites, 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

scretion of the drug. This was demonstrated when oral administration of cholestynamic following a single V dose of meloxicam decreased the AUC of meloxicam by 50%. The mean elimination half-life (t/s) 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

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 wades holmanzed to dose of 20 mg/kg *feet bloage and Palminstration* (2.4). The more 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

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_{ss} and 32% higher C_{maxes} 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 emale patients in comparison to elderly male patients.

Sex Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg Meloxicam, the mean elimination half-life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 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 Demoteting of Clust)*. *Constants Constants Constants* Rev: 06/21 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 implaneant production action and back introduction implantation of the action of the a 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

aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)]. Hepatotoxicity

nform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop Meloxicam tablets and seek immediate medical therapy [see Warnings and Precautions (5.3)

Precations (3.3). Heart failure and Edema Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face n patients of the signs of an anaphyticule reaction (e.g., clinical), a contraindications (4) roat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7).

Serious Skin Reactions, including DRESS

Advise patients to stop taking Meloxicam tablets immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.9, 5.10]]. Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including Meloxicam tablets, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8,3)]. Fetal Toxicity

ant women to avoid use of Meloxicam tablets and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with Meloxicam tablets is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1]]

Noti Spee warmings and recations (c. r) and use in openine robustions (c. r). Avoid Concommittant Use of NSADs Inform patients that the concomitant use of Meloxicam tablets with other NSAIDs or salicylates (e.g., diffunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7]]. Alert patients that NSAIDs may be present in "over the counter" medications for tre

Use of NSAIDs and Low-Dose Aspirin

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

Please address medical inquiries to 1-866-495-1995

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

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