

MELOXICAM meloxicam tablet
NuCare Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use MELOXICAM TABLETS
safety and effectively. See Full prescribing information for MELOXICAM TABLETS.

MELOXICAM tablets, for oral use

U.S. Approved 2000

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See Full prescribing information for complete boxed warning.
• Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (1.1).
• Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (5.2).
• NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestine, which can be fatal. These events can occur at any time during use and without warning. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2).

RECENT MAJOR CHANGES

Boxed Warning	50316
Indications and Usage, Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course (1.3)	60344
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INDICATIONS AND USAGE
Meloxicam Tablets are indicated for the treatment of the following conditions:
• Osteoarthritis (OA) (1.1)
• Rheumatoid Arthritis (RA) (1.2)
• Juvenile Rheumatoid Arthritis (JRA) in patients who weigh ≥ 60 kg (1.3)

DOSE AND ADMINISTRATION
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1).
• OA (2.1) and RA (2.1):
o Starting dose: 7.5 mg once daily
o Dose may be increased to 15 mg once daily
• RA (2.1) and OA (2.1):
o Starting dose: 7.5 mg once daily in children ≥ 60 kg
• Meloxicam tablets are not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same (2.6).

DOSE FORMS AND STRENGTHS
• Meloxicam Tablets, USP: 7.5 mg and 15 mg (1)

CONTRAINDICATIONS
• History of hypersensitivity to meloxicam or any components of the drug product (4)
• History of peptic ulcer disease or other upper GI tract lesions (5.1)
• In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS
• **Myocardial Infarction:** Inform patients of warning signs and symptoms of myocardial infarction. Discontinue meloxicam if chest pain or signs or symptoms of myocardial infarction occur (5.1).
• **Stroke:** Inform patients of warning signs and symptoms of stroke. Discontinue meloxicam if signs or symptoms of stroke occur (5.1).
• **GI Bleeding, Ulceration, and Perforation:** Inform patients of warning signs and symptoms of GI bleeding, ulceration, and perforation. Discontinue meloxicam if signs or symptoms of GI bleeding, ulceration, and perforation occur (5.2).
• **Heart Failure and Edema:** Inform patients of warning signs and symptoms of heart failure and edema. Discontinue meloxicam if signs or symptoms of heart failure and edema occur (5.5).
• **Renal Impairment:** Avoid use of meloxicam in patients with moderate to severe renal impairment. Inform patients of warning signs and symptoms of renal impairment (5.6).
• **Reversible Infertility:** Inform patients of warning signs and symptoms of reversible infertility. Inform patients of warning signs and symptoms of reversible infertility (5.7).
• **Embryofetotoxicity:** Inform patients of warning signs and symptoms of embryofetotoxicity (5.8).
• **Reproductive Effects:** Inform patients of warning signs and symptoms of reproductive effects (5.9).
• **Teratogenicity:** Inform patients of warning signs and symptoms of teratogenicity (5.9).
• **Maternal Effects of Fetal Ducts Arteriosclerotic:** Avoid use in pregnant women starting at 30 weeks gestation (5.10, 5.11).
• **Reversible Infertility:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.11, 5.12).

ADVERSE REACTIONS
• Most common (≥10% and greater than placebo) adverse events in adults are diarrhea, upper respiratory tract infection, dyspepsia, and influenza-like symptoms (6.1).
• Adverse events observed in pediatric studies were similar in nature to the adult clinical trial experience (6.2).

DRUG INTERACTIONS
• **NSAIDs:** Inform patients of warning signs and symptoms of GI bleeding, ulceration, and perforation. Inform patients of warning signs and symptoms of reversible infertility. Inform patients of warning signs and symptoms of reproductive effects (5.2, 5.7, 5.9).

USE IN SPECIFIC POPULATIONS
• **Pregnancy:** Inform patients of warning signs and symptoms of embryofetotoxicity (5.8). Inform patients of warning signs and symptoms of reversible infertility (5.7). Inform patients of warning signs and symptoms of reproductive effects (5.9).
• **Lactation:** Inform patients of warning signs and symptoms of reversible infertility (5.7). Inform patients of warning signs and symptoms of reproductive effects (5.9).
• **Reproductive Effects:** Inform patients of warning signs and symptoms of reproductive effects (5.9).
• **Teratogenicity:** Inform patients of warning signs and symptoms of teratogenicity (5.9).
• **Maternal Effects of Fetal Ducts Arteriosclerotic:** Inform patients of warning signs and symptoms of maternal effects of fetal ducts arteriosclerotic (5.10, 5.11).
• **Reversible Infertility:** Inform patients of warning signs and symptoms of reversible infertility (5.7).
• **Embryofetotoxicity:** Inform patients of warning signs and symptoms of embryofetotoxicity (5.8).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. **Revised: 10/2018**

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See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events
• Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (see Warnings and Precautions (5.1)).
• Meloxicam is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (see Contraindications (4) and Warnings and Precautions (5.2)).

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 intestine, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (see Warnings and Precautions (5.2)).

1 INDICATIONS AND USAGE

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

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

1.3 Juvenile Rheumatoid Arthritis (JRA) 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)).

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions
Carefully consider the potential benefits and risks of meloxicam tablets and other treatment options before deciding to use meloxicam tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see Warnings and Precautions (5.1)).

After observing the response to initial therapy with meloxicam tablets, adjust the dose to suit an individual patient's needs.

In adults, the maximum recommended daily oral dose of meloxicam tablets are 15 mg regardless of formulation. In patients with hematology, a maximum daily dosage of 7.5 mg is recommended (see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)).

Meloxicam tablets may be taken without regard to timing of meals.

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

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

2.4 Juvenile Rheumatoid Arthritis (JRA) 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 ≥60 kg. There was no additional benefit demonstrated by increasing the dose above 7.5 mg in clinical trial. Meloxicam tablets should not be used in children who weigh <60 kg.

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

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

3 DOSAGE FORMS AND STRENGTHS

Meloxicam Tablets, USP:
• 7.5 mg, yellow, round-shaped, flat beveled edge, uncoated tablets debossed with '20' and '25' on the side and plain on other side
• 15 mg, yellow, round-shaped, flat beveled edge, uncoated tablets debossed with '20' and '26' on the side and plain on other side

4 CONTRAINDICATIONS

Meloxicam is contraindicated in the following patients:
• Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product (see Warnings and Precautions (5.1, 5.2, 5.9))
• History of asthma, urticaria, or other allergic-type reactions after taking aspirin or

other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Warnings and Precautions (5.7, 5.8)]

- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.2)]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of newer COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative risks of serious CV thrombotic events over periods conforming to NSAID use appear 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 for CV disease have absolute incidences of excess serious CV thrombotic events, due to their increased baseline risk. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first few weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as meloxicam, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)]

Specific Post Coronary Artery Bypass Graft (CABG) Surgery Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)]

Post-MI Patients Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year after MI was 20% per 100 person-years in NSAID-treated patients compared to 12 per 100 person-years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

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

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including meloxicam, can cause serious gastrointestinal (GI) adverse events including ulcers, 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. Patients treated with NSAIDs should be alert for signs and symptoms of GI adverse events. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy (e.g., dyspepsia, upper GI 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 shorter-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 3-fold increased risk for developing a GI ulcer compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs), smoking, use of alcohol, older age, and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additional patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

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

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

5.3 Hepatotoxicity

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

Elevations of ALT or AST less than three times (3X) may occur in up to 15% of patients treated with NSAIDs, including meloxicam. In many patients, the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms), if present, are mild and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., anaphylaxis, rash, etc.), discontinuous meloxicam immediately, and perform a clinical evaluation of the patient [see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]

5.4 Hypertension

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

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

5.5 Heart Failure and Edema

The COX-2 and nonselective NSAID Tricor Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients in a Danish National Registry study of patients with heart failure. NSAID use increased the risk of MI, hospitalization for heart failure, and death. Additionally, fluid retention and edema have been observed in some patients taking NSAIDs. Use of meloxicam in patients with a history of severe heart failure, especially those at high risk for medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers (ARBs)) [see Drug Interactions (7)]

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

5.6 Renal Toxicity and Hypokalemia

Long-term administration of NSAIDs, including meloxicam, has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other secondary renal toxicity that is also seen in patients in whom renal prostaglandin formation is a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate acute renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

The renal effects of meloxicam may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some meloxicam medications are excreted by the kidney, monitor patients for signs of worsening renal function. Correct volume status in dehydrated or hypovolemic patients prior to initiating meloxicam. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of meloxicam [see Drug Interactions (7)]

Information is available from controlled clinical studies regarding the use of meloxicam in patients with advanced renal disease. Avoid the use of meloxicam in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If meloxicam is used in patients with advanced renal disease, monitor patients for signs of worsening renal function [see Clinical Pharmacology (12.3)]

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

5.7 Anaphylactic Reactions

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

Seek emergency help if an anaphylactic reaction occurs.

5.8 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 hypersensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

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

5.10 Premature Closure of Fetal Ductus Arteriosus

Meloxicam may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including meloxicam, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.2)]

5.11 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an idiosyncratic decrease effect on erythropoiesis. If a patient treated with meloxicam has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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

5.12 Masking of Inflammation and Fever

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

5.13 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.8)]

6 ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [see Boxed Warning and Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration, and Perforation [see Boxed Warning and Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hypokalemia [see Warnings and Precautions (5.6)]
- Anaphylactic Reactions [see Warnings and Precautions (5.7)]
- Serious Skin Reactions [see Warnings and Precautions (5.9)]
- Hematologic Toxicity [see Warnings and Precautions (5.11)]

6.1 Clinical Trials Experience

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

Adults

Osteoarthritis and Rheumatoid Arthritis The meloxicam Phase 2/3 clinical trial database includes 16,122 OA patients and 1012 RA patients treated with meloxicam, 7 months, 355 OA patients and 120 RA patients treated with meloxicam 15 mg daily. Results from these trials are summarized in Table 1.

Patients for at least 6 months, and to 312 patients, for at least one year. Approximately 15,020 patients safely were treated in placebo- and/or active-controlled trials in osteoarthritis trials and 2,363 of these patients were treated in two placebo- and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across meloxicam trials.

In 13-week meloxicam double-blind, controlled trials conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of meloxicam with placebo with or without celecoxib. Two 12-week meloxicam 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/or active-controlled osteoarthritis trial.

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

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

	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Placebo
No. of Patients	139	153	156
GI/Intestinal	12.2	20.3	17.3
Other	6.4	6.0	7.5

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

	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	Placebo
No. of Patients	139	153	156
GI/Intestinal	12.2	20.3	17.3
Other	6.4	6.0	7.5

[24&3-Pain Class, III] have not been adequately studied | see Warnings and Precautions (3.3) 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 with free AUC values were similar in all groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of meloxicam in subjects with severe renal impairment is not recommended | see Dosage and Administration (2.5), 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 (3x free fraction) in comparison to healthy volunteers (0.3x 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 (2.3), and Use in Specific Populations (8.7).

Drug Interaction Studies

Aspirin

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. When meloxicam is administered with aspirin (100 mg three times daily) to healthy volunteers, it tended to increase the AUC (10x) and C_{max} (20x) of meloxicam. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin | see Drug Interactions (7).

Cholestyramine

Pre-treatment for four days with cholestyramine significantly increased the clearance of meloxicam by 50%. This resulted in a decrease in t_{1/2} from 19.2 hours to 3.2 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.

Concomitant

Concomitant administration of 200 mg cimetidine four times daily did not alter the single-dose pharmacokinetics of 50 mg meloxicam.

Digoxin

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after ³H-digoxin 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 25% in subjects receiving lithium doses ranging from 600 to 3372 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 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).

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 average anticoagulant effect of warfarin as measured 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).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in tumor incidence in long-term carcinogenicity studies in rats (124 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 5.8 mg/kg/day in rats and up to 8.0 mg/kg/day in mice (up to 5.5 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 impair male and female fertility in rats at oral doses up to 8 mg/kg/day in males and 5 mg/kg/day in females (up to 5.8- and 3.2-times greater, respectively, than the MRHD based on BSA comparison).

14 CLINICAL STUDIES

14.1 Osteoarthritis and Rheumatoid Arthritis

The use of meloxicam for the treatment of the signs and symptoms of osteoarthritis of the knee and hip was evaluated in a 12-week, double-blind, controlled trial: meloxicam (12.5 mg, 7.5 mg, and 15 mg daily) was compared to placebo. The four primary endpoints were investigator global assessment, patient global assessment, patient pain assessment, and total WOMAC score in self-administered questionnaire addressing pain, function, and stiffness. Patients on meloxicam 7.5 mg daily and meloxicam 15 mg daily showed significant improvement in each of these endpoints compared with placebo.

The use of meloxicam for the management of signs and symptoms of osteoarthritis was evaluated in six double-blind, active-controlled trials outside the U.S., ranging from 4 weeks to 18 weeks. Generally, the efficacy of meloxicam in doses of 7.5 mg/day and 15 mg/day was comparable to placebo (20 mg/day and diclofenac 50-100 mg/day and consistent with the efficacy seen in the U.S. trial.

The use of meloxicam for the treatment of the signs and symptoms of rheumatoid arthritis was evaluated in a 12-week, double-blind, controlled multinational trial: meloxicam (7.5 mg, 15 mg, and 22.5 mg daily) was compared to placebo. The primary endpoints in this trial were the ACR20 response rate, a composite measure of CDAI, disability, and functional measures in RA patients. Adults having moderate to severe disease throughout the 12-week dosing period, while the other incorporated a 4-week titration phase to doses of 0.25 mg/kg/day and 0.75 mg/kg/day (2.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR response rate responder definition, a composite of parent 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.

14.2 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course

The use of meloxicam for the treatment of the signs and symptoms of pauciarticular or polyarticular course juvenile rheumatoid arthritis in patients 2 years of age and older was evaluated in two 12-week, double-blind, parallel arm, active-controlled trials. Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam dosing began at 0.25 mg/kg/day (7.5 mg maximum) or 0.75 mg/kg/day (15 mg maximum) and was increased to 1.5 mg/kg/day. Only 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 0.75 mg/kg/day (2.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR response rate responder definition, a composite of parent 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

Meloxicam Tablets USP, 15 mg are yellow, round-shaped, flat beveled edges, uncoated tablet debossed with ZC and 26 on one side and plain on other side and are supplied as follows:

NDC 68071-3030-7 BOTTLES OF 7

NDC 68071-3030-5 BOTTLES OF 15

NDC 68071-3030-9 BOTTLES OF 90

Storage

Store at 20° to 25° (68° to 77° F) [see USP Controlled Room Temperature]. Keep meloxicam tablets in a dry place.

Dispense tablets in a tight container.

Keep this and all medications out of the reach of children.

17 PATIENT COUNSELING INFORMATION

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

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

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their healthcare provider immediately | see Warnings and Precautions (5.1).

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematochezia to their healthcare provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for the signs and symptoms of GI bleeding | see Warnings and Precautions (5.2).

Hepatotoxicity

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

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, edema and to contact their healthcare provider if such symptoms occur | see Warnings and Precautions (5.3).

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur | see Contraindications (4) and Warnings and Precautions (5.1).

Serious Skin Reactions

Advise patients to stop meloxicam immediately if they develop any type of rash and to contact their healthcare provider as soon as possible | see Warnings and Precautions (5.5).

Female Fertility

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

Fetal Toxicity

Inform pregnant women to avoid use of meloxicam and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closure of the fetal ductus arteriosus | see Warnings and Precautions (5.10) and Use in Specific Populations (8.3).

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of meloxicam with other NSAIDs or salicylates (e.g., effervescent, buffered or chewable tablets) is not recommended due to the increased risk of gastrointestinal toxicity, and 80% or more increase in efficacy | see Warnings and Precautions (5.2) and Drug Interactions (7). Advise patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

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

KeyBrand

KeyBrand is a registered trademark of Sanofi-Aventis.

Please address medical inquiries to: MedicalAffairs@zyrosusa.com | Tel.: 1-877-993-8776.

Manufactured by:

Zylo Pharmaceuticals USA Inc.

Hempstead, NY 08534

Rev. 02/18

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

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

NSAIDs can cause serious side effects, including:

- increased risk of a heart attack or stroke that can lead to death. This risk may happen early in treatment and may increase

o with increasing doses of NSAIDs

o with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

Increased risk of bleeding, ulcers, and tears (perforations) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:

o anytime during use

o without warning symptoms

o that may cause death

The risk of getting an ulcer or bleeding increases with:

o past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs

- o taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"

- o increasing doses of NSAIDs

- o older age
- o longer use of NSAIDs

- o poor health or smoking
- o advanced liver disease

- o drinking alcohol
- o bleeding problems

- o NSAIDs should only be used:

- o exactly as prescribed
- o at the lowest dose possible for your treatment
- o for the shortest time needed

- o What are NSAIDs?

- o 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.

- o Who should not take NSAIDs?

- o Do not take NSAIDs:

- o if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- o right before or after heart bypass surgery.

- o Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:

- o have liver or kidney problems
- o have high blood pressure
- o have asthma

- o are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 28 weeks of pregnancy.
- o are breastfeeding or plan to breast feed

- o Tell your healthcare provider about all of the medicines you take, including prescriptions or over-the-counter medicines, vitamins or herbal supplements.

- o NSAIDs and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your healthcare provider first.

- o What are the possible side effects of NSAIDs?

- o NSAIDs can cause serious side effects, including:

- o See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- o Heart failure
- o liver problems including liver failure
- o kidney problems including kidney failure
- o low red blood cells (anemia)
- o gastrointestinal (GI) reactions
- o life-threatening allergic reactions
- o Other side effects of NSAIDs include: stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

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

- o shortness of breath or trouble breathing
- o blurred vision
- o chest pain
- o swelling of the face or throat
- o weakness in one part or side of your body

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

- o dizziness
- o nosebleed
- o more tired or weaker than usual
- o there is blood in your stool (movement or if it is diarrhea black and sticky like tar)
- o itching
- o unusual weight gain
- o dark tan or black stools with blood
- o indigestion or stomach pain
- o swelling of the arms, legs, hands and feet
- o flu-like symptoms

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

- o These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

- o Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

- o Other information about NSAIDs:

- o Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- o Some NSAIDs are used 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.

- o General information about the safe and effective use of NSAIDs: Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them if you do so without first getting medical advice from your healthcare provider. You may also wish to tell your doctor about all the medicines you are taking.

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

- o Please address medical inquiries to: MedicalAffairs@zydususa.com | Tel: 1-877-993-8779

- o The Medication Guide has been approved by the U.S. Food and Drug Administration. The product's label may have been updated. For current full prescribing information, please visit www.zydususa.com.

- o Manufactured by:

- o Zydus Pharmaceuticals USA Inc.

- o Parsippany, NJ 08534

- o Rev: 0716

- o PACKAGE LABEL-PRINCIPAL DISPLAY PANEL

- o NuCare Pharmaceuticals, Inc.

- o NDC: 68071-9320-7

- o Meloxicam 15mg

- o #7 Tablets

- o Rx Only

- o Please see important information about this medication on the adjacent display panel.

- o Keep out of reach of children.

- o Store at controlled temperature 20° to 25° (68° to 77° F).

- o See USP Controlled Room Temperature.

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