NDC 71741-228-10 Rx Only

Zybic™
(Meloxicam Oral Suspension, USP
7.5 mg/5 mL)

REDMONT PHARMACEUTICALS

228111-1225

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Zybic™ safely and effectively. See full prescribing information for Zybic™.

Zybic™
Initial U.S. Approval: 2004

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **Zybic™ is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

RECENT MAJOR CHANGES
Warnings and Precautions (5.10) 10/2024

INDICATIONS AND USAGE
Zybic™ is a non-steroidal anti-inflammatory drug indicated for:
- Osteoarthritis (OA) (1.1)
- Rheumatoid Arthritis (RA) (1.2)
- Juvenile Rheumatoid Arthritis (JRA) in patients 2 years of age or older (1.3)

DOSAGE AND ADMINISTRATION
Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (2.1)
- OA (2.2) and RA (2.3):
  - Starting dose: 7.5 mg once daily
  - Dose may be increased to 15 mg once daily
- JRA (2.4):
  - 0.125 mg/kg once daily up to a maximum of 7.5 mg. JRA dosing using the oral suspension should be individualized based on the weight of the child (2.4)
- Zybic™ is not interchangeable with approved formulations of oral meloxicam even if the total milligram strength is the same (2.6)

DOSAGE FORMS AND STRENGTHS
- Zybic™: 7.5 mg/5 mL (3)

CONTRAINDICATIONS
- Known hypersensitivity to meloxicam or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

WARNINGS AND PRECAUTIONS
- Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- Hypertension: Patients taking 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 Zybic™ 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 Zybic™ 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: Zybic™ is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- Serious Skin Reactions: Discontinue Zybic™ at first appearance of skin rash or other signs of hypersensitivity (5.9)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): Discontinue and evaluate clinically (5.10)
- Fetal Toxicity: Limit use of NSAIDs, including Zybic™, between about 20 to 30 weeks in pregnacy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of fetal ductus arteriosus (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

ADVERSE REACTIONS
- Most common (≥5% and greater than placebo) adverse events in adults are diarrhea, upper respiratory tract infections, dyspepsia, and influenza-like symptoms (6.1)
- Adverse events observed in pediatric studies were similar in nature to the adult clinical trial experience (6.1)

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

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

USE IN SPECIFIC POPULATIONS
- Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of Zybic™ in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2024

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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)]*.**
- **Zybic™ is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

Gastrointestinal Bleeding, Ulceration, and Perforation
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events *[see Warnings and Precautions (5.2)]*.**

1 INDICATIONS AND USAGE

1.1 Osteoarthritis (OA)
Zybic™ is indicated for relief of the signs and symptoms of osteoarthritis *[see Clinical Studies (14.1)]*.

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

1.3 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course
Zybic™ is indicated for relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis in patients 2 years of age and older *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions
Carefully consider the potential benefits and risks of Zybic™ and other treatment options before deciding to use Zybic™. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
After observing the response to initial therapy with Zybic™, adjust the dose to suit an individual patient's needs.
In adults, the maximum recommended daily oral dose of Zybic™ 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)]*.
Zybic™ 7.5 mg/5 mL or 15 mg/10 mL may be substituted for meloxicam tablets 7.5 mg or 15 mg, respectively.

Shake the oral suspension gently before using.

Zybic™ 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 Zybic™ 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 Zybic™ is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.

2.4 Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course
To improve dosing accuracy in smaller weight children, the use of the Zybic™ is recommended. Zybic™ is available in the strength of 7.5 mg/5 mL. For the treatment of juvenile rheumatoid arthritis, the recommended oral dose of Zybic™ is 0.125 mg/kg once daily up to a maximum of 7.5 mg. There was no additional benefit demonstrated by increasing the dose above 0.125 mg/kg once daily in these clinical trials.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Zybic™ is contraindicated in the following patients:
- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to meloxicam or any components of the drug product *[see Warnings and Precautions (5.7, 5.9)]*
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients *[see Warnings and Precautions (5.7, 5.8)]*
- In the setting of coronary artery bypass graft (CABG) surgery *[see Warnings and Precautions (5.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events
Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

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

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

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

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

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

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

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

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

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

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

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue Zybic™ 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 Zybic™, 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 controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

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

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

5.6 Renal Toxicity and Hyperkalemia
Renal Toxicity
Long-term administration of NSAIDs, including Zybic™, has resulted in renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injury.

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

The renal effects of Zybic™ may hasten the progression of renal dysfunction in patients with preexisting renal disease. Because some Zybic™ 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 Zybic™. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of Zybic™ *[see Drug Interactions (7)]*.

No information is available from controlled clinical studies regarding the use of Zybic™ in patients with advanced renal disease. Avoid the use of Zybic™ in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If Zybic™ 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, Zybic™ is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]*. When Zybic™ is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions
NSAIDs, including meloxicam, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. NSAIDs can also cause fixed drug eruption (FDE). FDE may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE), which can be life-threatening. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of Zybic™ at the first appearance of skin rash or any other sign of hypersensitivity. Zybic™ is contraindicated in patients with previous serious skin reactions to NSAIDs *[see Contraindications (4)]*.

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

5.11 Fetal Toxicity
Premature Closure of Fetal Ductus Arteriosus
Avoid use of NSAIDs, including Zybic™, in pregnant women at about 30 weeks gestation and later. NSAIDs, including Zybic™, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

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

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

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

5.12 Hematologic Toxicity
Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with Zybic™ has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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

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

5.14 Laboratory Monitoring
Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically *[see Warnings and Precautions (5.2, 5.3, 5.6)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:
- Cardiovascular Thrombotic Events *[see Boxed Warning and Warnings and Precautions (5.1)]*
- GI Bleeding, Ulceration, and Perforation *[see Boxed Warning and Warnings and Precautions (5.2)]*
- 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 Hyperkalemia *[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 (5.12)]*

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

Adults
Osteoarthritis and Rheumatoid Arthritis
The meloxicam Phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with meloxicam 7.5 mg/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.
A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of meloxicam with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of meloxicam with placebo.

Table 1a depicts adverse events that occurred in ≥2% of the meloxicam treatment groups in a 12-week placebo-and active-controlled osteoarthritis trial.

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

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

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily	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				
Accident household	1.9	4.5	3.2	2.6
Edema [1]	2.5	1.9	4.5	3.3
Fall	0.6	2.6	0.0	1.3
Influenza-like symptoms	5.1	4.5	5.8	2.6
Central and Peripheral Nervous System				
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 combined
[2] WHO preferred terms rash, rash erythematous, and rash maculo-papular combined.

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

	Placebo	Meloxicam 7.5 mg daily	Meloxicam 15 mg daily
No. of Patients	**469**	**481**	**477**
Gastrointestinal Disorders	14.1	18.9	16.8
Abdominal pain NOS[2]	0.6	2.9	2.3
Dyspeptic signs and symptoms[1]	3.8	5.8	4.0
Nausea[2]	2.6	3.3	3.8
General Disorders and Administration Site Conditions			
Influenza-like illness[2]	2.1	2.9	2.3
Infection and Infestations			
Upper respiratory tract infections-pathogen class unspecified[1]	4.1	7.0	6.5
Musculoskeletal and Connective Tissue Disorders			
Joint related signs and symptoms[1]	1.9	1.5	2.3
Nervous System Disorders			
Headaches NOS[2]	6.4	6.4	5.5
Skin and Subcutaneous Tissue Disorders			
Rash NOS[2]	1.7	1.0	2.1

[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 (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling)
[2] MedDRA preferred term: nausea, abdominal pain NOS, influenza-like illness, headaches NOS, and rash NOS

The adverse events that occurred with Zybic™ in ≥2% of patients treated short-term (4 to 6 weeks) and long-term (6 months) in active-controlled osteoarthritis trials are presented in Table 2.

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

	4 to 6 Weeks Controlled Trials		6 Month Controlled Trials	
	Meloxicam 7.5 mg daily	**Meloxicam 15 mg daily**	**Meloxicam 7.5 mg daily**	**Meloxicam 15 mg daily**
No. of Patients	**8955**	**256**	**169**	**306**
Gastrointestinal	11.8	18.0	26.6	24.2
Abdominal pain	2.7	2.3	4.7	2.9
Constipation	0.8	1.2	1.8	2.6
Diarrhea	1.9	2.7	5.9	2.6
Dyspepsia	3.8	7.4	8.9	9.5
Flatulence	0.5	0.4	3.0	2.6
Nausea	2.4	4.7	4.7	7.2
Vomiting	0.6	0.8	1.8	2.6
Body as a Whole				
Accident household	0.0	0.0	0.6	2.9
Edema[1]	0.6	2.0	2.4	1.6
Pain	0.9	2.0	3.6	5.2
Central and Peripheral Nervous System				
Dizziness	1.1	1.6	2.4	2.6
Headache	2.4	2.7	3.6	2.6
Hematologic				
Anemia	0.1	0.0	4.1	2.9
Musculoskeletal				
Arthralgia	0.5	0.0	5.3	1.3
Back pain	0.5	0.4	3.0	0.7
Psychiatric				
Insomnia	0.4	0.0	3.6	1.6
Respiratory				
Coughing	0.2	0.8	2.4	1.0
Upper respiratory tract infection	0.2	0.0	8.3	7.5
Skin				
Pruritus	0.4	1.2	2.4	0.0
Rash [2]	0.3	1.2	3.0	1.3
Urinary				
Micturition frequency	0.1	0.4	2.4	1.3
Urinary tract infection	0.3	0.4	4.7	6.9

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

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

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

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

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

6.2 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 reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions about whether to include an adverse event from spontaneous reports in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) number of reports, or (3) strength of causal relationship to the drug. Adverse reactions reported in worldwide post marketing experience or the literature include: acute urinary retention; agranulocytosis; alterations in mood (such as mood elevation); anaphylactoid reactions including shock; erythema multiforme; exfoliative dermatitis; interstitial nephritis; jaundice; liver failure; Stevens-Johnson syndrome; fixed drug eruption (FDE); 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

Drugs that Interfere with Hemostasis

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-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.

Intervention:
Monitor patients with concomitant use of Zybic™ 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)]*.

Aspirin

Clinical Impact:
Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone *[see Warnings and Precautions (5.2)]*.

Intervention:
Concomitant use of Zybic™ 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)]*.
Zybic™ is not a substitute for low dose aspirin for cardiovascular protection.

ACE Inhibitors, Angiotensin 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 propranolol).
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration 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 Zybic™ and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.
- During concomitant use of Zybic™ 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 Zybic™ 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 *[see Clinical Pharmacology (12.3)]*.

Intervention:
During concomitant use of Zybic™ and lithium, monitor patients for signs of lithium toxicity.

Methotrexate

Clinical Impact:
Concomitant use of NSAIDs and methotrexate may increase the risk of methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).

Intervention:
During concomitant use of Zybic™ and methotrexate, monitor patients for methotrexate toxicity.

Cyclosporine

Clinical Impact:
Concomitant use of meloxicam and cyclosporine may increase cyclosporine's nephrotoxicity.

Intervention:
During concomitant use of Zybic™ and cyclosporine, monitor patients for signs of worsening renal function.

NSAIDs and Salicylates

Clinical Impact:
Concomitant use of meloxicam with other NSAIDs or salicylates (e.g., 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 Zybic™ 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 Zybic™ and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.

Patients taking meloxicam should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.

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

Sodium Polystyrene Sulfonate

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

Intervention:
The concomitant use of Zybic™ with sodium polystyrene sulfonate is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
Use of NSAIDs, including Zybic™, 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 Zybic™ use between about 20 and 30 weeks of gestation, and avoid Zybic™ use at about 30 weeks of gestation and later in pregnancy *(see Clinical Considerations, Data)*.

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

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, embryofetal death was observed in rats and rabbits treated during the period of organogenesis with meloxicam at oral doses equivalent to 0.65- and 6.5-times the maximum recommended human dose (MRHD) of Zybic™. 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 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, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as meloxicam, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

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

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

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

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

Data
Human Data
Premature Closure of Fetal Ductus Arteriosus:
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

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

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

Animal Data
Meloxicam was not teratogenic when administered to pregnant rats during fetal organogenesis at oral doses up to 4 mg/kg/day (2.6-fold greater than the MRHD of 15 mg of meloxicam based on BSA comparison). Administration of meloxicam to pregnant rabbits throughout embryogenesis produced an increased incidence of septal defects of the heart at an oral dose of 60 mg/kg/day (78-fold greater than the MRHD based on BSA comparison). The no effect level was 20 mg/kg/day (26-fold greater than the MRHD based on BSA conversion). In rats and rabbits, embryolethality occurred at oral meloxicam doses of 1 mg/kg/day and 5 mg/kg/day, respectively (0.65- and 6.5-fold greater, respectively, than the MRHD based on BSA comparison) when administered 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 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 Zybic™ and any potential adverse effects on the breastfed infant from the Zybic™ 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
Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Zybic™, 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 Zybic™, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

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

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects *[see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)]*.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been studied. The use of Zybic™ in subjects with severe renal impairment is not recommended. In patients on hemodialysis, meloxicam should not exceed 7.5 mg per day. Meloxicam is not dialyzable *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare *[see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)]*.

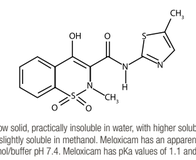
Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within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

11 DESCRIPTION

Zybic™, USP is a nonsteroidal anti-inflammatory drug (NSAID). Each bottle of Zybic™ contains 7.5 mg meloxicam per 5 mL. 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:



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) $_{app}$ = 0.1 in *n*-octanol/buffer pH 7.4. Meloxicam has pKa values of 1.1 and 4.2.

Meloxicam is available as an oral suspension containing 7.5 mg meloxicam per 5 mL.

The inactive ingredients in Zybic™ include colloidal silicon dioxide, hydroxyethylcellulose, sorbitol, glycerol, xylitol, monobasic sodium phosphate (dihydrate), saccharin sodium, sodium benzoate, citric acid (monohydrate), raspberry flavor, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

The mechanism of action of Zybic™, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Meloxicam is a potent inhibitor of prostaglandin synthesis *in vitro*. Meloxicam concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because meloxicam is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of meloxicam capsules was 89% following a single oral dose of 30 mg compared with 30 mg IV bolus injection. Following single intravenous doses, dose-proportional pharmacokinetics were shown in the range of 5 mg to 60 mg. After multiple oral doses the pharmacokinetics of meloxicam capsules were dose-proportional over the range of 7.5 mg to 15 mg. Mean C_{max} was achieved within four to five hours after a 7.5 mg meloxicam tablet was taken under fasted conditions, indicating a prolonged drug absorption. With multiple dosing, steady-state concentrations were reached by Day 5. A second meloxicam concentration peak occurs around 12 to 14 hours post-dose suggesting biliary recycling.

Zybic™ doses of 7.5 mg/5 mL and 15 mg/10 mL have been found to be bioequivalent to meloxicam 7.5 mg and 15 mg capsules, respectively. Meloxicam capsules have been shown to be bioequivalent to meloxicam tablets.

Table 4 Single Dose and Steady-State Pharmacokinetic Parameters for Oral 7.5 mg and 15 mg Meloxicam (Mean and % CV)[1]

		Steady State			Single Dose	
Pharmacokinetic (% CV)		Healthy male Parameters (Fed)[2]	Elderly males adults (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)

[1] The parameter values in the table are from various studies
[2] not under high fat conditions
[3] meloxicam tablets
[4] $V_z/f = Dose/(AUC \bullet \lambda_{el})$

Food and Antacid Effects
Administration of meloxicam capsules following a high fat breakfast (75 g of fat) resulted in mean peak drug levels (i.e., C_{max}) being increased by approximately 22% while the extent of absorption (AUC) was unchanged. The time to maximum concentration (T_{max}) was achieved between 5 and 6 hours. In comparison, neither the AUC nor the C_{max} values for meloxicam suspension were affected following a similar high fat meal, while mean T_{max} values were increased to approximately 7 hours. No pharmacokinetic interaction was detected with concomitant administration of antacids. Based on these results, Zybic™ 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.

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

Elimination

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

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

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

Specific Populations

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

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

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

Geriatric
Elderly males (≥65 years of age) exhibited meloxicam plasma concentrations and steady-state pharmacokinetics similar to young males. Elderly females (≥65 years of age) had a 47% higher AUC_{ss} and 32% higher $C_{max,ss}$ as compared to younger females (≤55 years of age) after body weight normalization. Despite the increased total concentrations in the elderly females, the adverse event profile was comparable for both elderly patient populations. A smaller free fraction was found in elderly female patients in comparison to elderly male patients.

Sex
Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg meloxicam, the mean elimination half-life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C_{max} or T_{max} across genders.

Hepatic Impairment
Following a single 15 mg dose of meloxicam there was no marked difference in plasma concentrations in patients with mild (Child-Pugh Class I) or moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not affected by hepatic impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

Renal Impairment
Meloxicam pharmacokinetics have been investigated in subjects with mild and moderate renal impairment. Total drug plasma concentrations of meloxicam decreased and total clearance of meloxicam increased with the degree of renal impairment while free AUC values were similar in all groups. The higher meloxicam clearance in subjects with renal impairment may be due to increased fraction of unbound meloxicam which is available for hepatic metabolism and subsequent excretion. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment have not been adequately studied. The use of Zybic™ 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 (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Hemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after hemodialysis. Meloxicam is not dialyzable *[see Dosage and Administration (2.1) and Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Aspirin: When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. When meloxicam is administered with aspirin (1000 mg three times daily) to healthy volunteers, it tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known. See Table 3 for clinically significant drug interactions of NSAIDs with aspirin *[see Drug Interactions (7)]*.

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

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

Digoxin: Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after β-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Lithium: In a study conducted in healthy subjects, mean pre-dose lithium concentration and AUC were increased by 21% in subjects receiving lithium doses ranging from 804 to 1072 mg twice daily with meloxicam 15 mg QD every day as compared to subjects receiving lithium alone *[see Drug Interactions (7)]*.

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 determined by prothrombin time. However, one subject showed an increase in INR from 1.5 to 2.1. Caution should be used when administering Zybic™ 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 (104 weeks) and mice (99 weeks) administered meloxicam at oral doses up to 0.8 mg/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 Zybic™ 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* micronuclear test in mouse bone marrow.

Impairment of Fertility
Meloxicam did not impair 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 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 (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 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 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 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 endpoint in this study was the ACR20 response rate, a compocite 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-blind, parallel-arm, active-controlled trials.

Both studies included three arms: naproxen and two doses of meloxicam. In both studies, meloxicam dosing began at 0.125 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 mg/kg/day (22.5 mg maximum) of meloxicam and 15 mg/kg/day of naproxen.

The efficacy analysis used the ACR Pediatric 30 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

Zybic™ is available as a yellowish green tinged viscous oral suspension containing 7.5 mg meloxicam in 5 mL.

Zybic™ 7.5 mg/5 mL: NDC 71741-228-10; Bottles of 100 mL

Storage
Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Keep oral suspension container tightly closed.

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 hematemesis 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 Zybic™ 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, 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 or throat). 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 Zybic™ immediately if they develop any type of rash or fever 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 Zybic™, 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 Zybic™ and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with Zybic™ 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)]*.

Avoid Concomitant Use of NSAIDs
Inform patients that the concomitant use of Zybic™ with other NSAIDs or salicylates (e.g., diflunisal, 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 treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin
Inform patients not to use low-dose aspirin concomitantly with Zybic™ until they talk to their healthcare provider *[see Drug Interactions (7)]*.

For current prescribing information, call Redmont Pharmaceuticals, LLC at 800-528-3058.

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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:
  - 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 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 (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime 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
- taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:

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

What are NSAIDs?
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.

Who should not take NSAIDs?
Do not take NSAIDs:

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

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

- have liver or kidney problems
- have high blood pressure
- have asthma
- 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 and around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

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

What are the possible side effects of NSAIDs?
NSAIDs can cause serious side effects, including:
See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?"

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

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

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

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

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

If you take too much of your NSAID, call your healthcare provider or get medical help right away.
These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs:

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.
If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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