OXAPROZIN- oxaprozin tablet
Amneal Pharmaceuticals NY LLC

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

OXAPROZIN tablets, for oral use
Initial U.S. Approval: 1992

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)**
- **Oxaprozin 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, Serious Skin Reactions (5.9) 11/2024

INDICATIONS AND USAGE

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

- Relief of signs and symptoms of Osteoarthritis (OA). (1)
- Relief of signs and symptoms of Rheumatoid Arthritis (RA).(1)
- Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA). (1)

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2.1)
- OA: 1200 mg (two 600 mg tablets) given orally once a day. (2.2, 2.5, 14.1)
- RA: 1200 mg (two 600 mg tablets) given orally once a day. (2.3, 2.5, 14.2)
- JRA: 600 mg once daily in patients 22 to 31 kg. 900 mg once daily in patients 32 to 54 kg. 1200 mg once daily in patients ≥ 55 kg. (2.4, 2.5)

DOSAGE FORMS AND STRENGTHS

Oxaprozin tablets: 600 mg. (3)

CONTRAINDICATIONS

- Known hypersensitivity to oxaprozin 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 oxaprozin 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 oxaprozin 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: Oxaprozin is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
- Serious Skin Reactions: Discontinue oxaprozin 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 oxaprozin, between about 20 to 30 weeks in pregnancy 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 the fetal ductus arteriosus. (5.11, 8.1)
- Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.12, 7)

ADVERSE REACTIONS

Most common adverse reactions (> 3%) are: constipation, diarrhea, dyspepsia, nausea, rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]): Monitor patients for bleeding who are concomitantly taking oxaprozin with drugs that interfere with hemostasis. Concomitant use of oxaprozin and analgesic doses of aspirin is not generally recommended. (7)
- Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with oxaprozin may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
- ACE Inhibitors and ARBs: Concomitant use with oxaprozin 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)
- Digoxin: Concomitant use with oxaprozin can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.(7)

USE IN SPECIFIC POPULATIONS

Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of oxaprozin in women who have difficulties conceiving. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2024

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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)]*.**
- **Oxaprozin 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

Oxaprozin tablets are indicated:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis
- For relief of the signs and symptoms of juvenile rheumatoid arthritis

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of oxaprozin tablets and other treatment options before deciding to use oxaprozin tablets. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.

2.2 Osteoarthritis

For OA, the dosage is 1,200 mg (two 600 mg tablets) given orally once a day *[see Dosage and Administration (2.5)]*.

2.3 Rheumatoid Arthritis

For RA, the dosage is 1,200 mg (two 600 mg tablets) given orally once a day *[see Dosage and Administration (2.5)]*.

2.4 Juvenile Rheumatoid Arthritis

For JRA, in patients 6 to 16 years of age, the recommended dosage given orally once per day should be based on body weight of the patient as given in Table 1 *[see Dosage and Administration (2.5)]*.

Table 1. Recommended Daily Dose of Oxaprozin Tablets by Body Weight in Pediatric Patients

Body Weight Range (kg)	Dose (mg)
22 to 31	600
32 to 54	900
≥ 55	1,200

2.5 Individualization of Dosage

After observing the response to initial therapy with oxaprozin tablets, the dose and frequency should be adjusted to suit an individual patient's needs. In osteoarthritis and rheumatoid arthritis and juvenile rheumatoid arthritis, the dosage should be individualized to the lowest effective dose of oxaprozin tablets to minimize adverse effects. The maximum recommended total daily dose of oxaprozin tablets in adults is 1,800 mg (26 mg/kg, whichever is *lower*) in divided doses. In children, doses greater than 1,200 mg have not been studied.

Patients with low body weight should initiate therapy with 600 mg once daily. Patients with severe renal impairment or on dialysis should also initiate therapy with 600 mg once daily. If there is insufficient relief of symptoms in such patients, the dose may be cautiously increased to 1,200 mg, but only with close monitoring *[see Clinical Pharmacology (12.3)]*.

In adults, in cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allows therapy to be started with a one-time loading dose of 1,200 mg to 1,800 mg (not to exceed 26 mg/kg). Doses larger than 1,200 mg/day on a chronic basis should be reserved for patients who weigh more than 50 kg, have normal renal and hepatic function, are at low risk of peptic ulcer, and whose severity of disease justifies maximal therapy. Physicians should ensure that patients are tolerating doses in the 600 mg/day to 1,200 mg/day range without gastroenterologic, renal, hepatic, or dermatologic adverse effects before advancing to the larger doses. Most patients will tolerate once-a-day dosing with oxaprozin tablets, although divided doses may be tried in patients unable to tolerate single doses.

3 DOSAGE FORMS AND STRENGTHS

Oxaprozin tablets USP, 600 mg are white, capsule-shaped, beveled edged, biconvex, film-coated tablets, debossed with "AA59" on one side and scored on the other side.

4 CONTRAINDICATIONS

Oxaprozin is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to oxaprozin 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 CABG surgery *[see Warnings and Precautions (5.1)].*

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase-2 (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 oxaprozin, 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 to 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 oxaprozin in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If oxaprozin is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including oxaprozin, 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 to 6 months, and in about 2% to 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-times 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, antiplatelet drugs (such as 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 oxaprozin 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 alanine aminotransferase (ALT) or aspartate aminotransferase (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 oxaprozin.

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), discontinue oxaprozin

immediately, and perform a clinical evaluation of the patient.

5.4 Hypertension

NSAIDs, including oxaprozin, can lead to new onset of hypertension 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 oxaprozin 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 oxaprozin in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If oxaprozin 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 has resulted in renal papillary necrosis 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.

No information is available from controlled clinical studies regarding the use of oxaprozin in patients with advanced renal disease. The renal effects of oxaprozin may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating oxaprozin. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of oxaprozin *[see Drug Interactions (7)].* Avoid the use of oxaprozin in patients with advanced renal disease unless the benefits

are expected to outweigh the risk of worsening renal function. If oxaprozin is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

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

Oxaprozin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to oxaprozin 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, oxaprozin is contraindicated in patients with this form of aspirin sensitivity *[see Contraindications (4)]*. When oxaprozin 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 oxaprozin, 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 oxaprozin at the first appearance of skin rash or any other sign of hypersensitivity. Oxaprozin 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 oxaprozin. 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 oxaprozin and evaluate the patient immediately.

5.11 Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including oxaprozin, in pregnant women at about 30 weeks gestation and later. NSAIDs, including oxaprozin, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including oxaprozin, 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 post-marketing 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 oxaprozin use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if oxaprozin treatment extends beyond 48 hours. Discontinue oxaprozin 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 oxaprozin has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including oxaprozin, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), 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 oxaprozin 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 complete blood count (CBC) and a chemistry profile periodically *[see Warnings and Precautions (5.2, 5.3, 5.6)]*.

5.15 Photosensitivity

Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials.

6 ADVERSE REACTIONS

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

- Cardiovascular Thrombotic Events *[see Warnings and Precautions (5.1)].*
- GI Bleeding, Ulceration and Perforation *[see 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.

Adverse reaction data were derived from patients who received oxaprozin in multidose, controlled, and open-label clinical trials. Rates for events from clinical trial experience are based on 2,253 patients who took 1,200 mg to 1,800 mg oxaprozin per day in clinical trials. Of these, 1,721 patients were treated for at least 1 month, 971 patients for at least 3 months, and 366 patients for more than 1 year.

Incidence Greater than 1%: In clinical trials of oxaprozin or in patients taking other NSAIDs, the following adverse reactions occurred at an incidence greater than 1%.

Cardiovascular system: edema.

Digestive system: abdominal pain/distress, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastrointestinal ulcers (gastric/duodenal), gross bleeding/perforation, heartburn, liver enzyme elevations, nausea, vomiting.

Hematologic system: anemia, increased bleeding time.

Nervous system: CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep, dizziness, headache.

Skin and appendages: pruritus, rash.

Special senses: tinnitus.

Urogenital system: abnormal renal function, dysuria or frequency.

Incidence Greater than 1%: The following adverse reactions were reported in clinical trials or in patients taking other NSAIDs.

Body as a whole: appetite changes, death, drug hypersensitivity reactions including anaphylaxis, fever, infection, sepsis.

Cardiovascular system: arrhythmia, blood pressure changes, congestive heart failure, hypertension, hypotension, myocardial infarction, palpitations, tachycardia, syncope, vasculitis.

Digestive system: alteration in taste, dry mouth, eructation, esophagitis, gastritis, glossitis, hematemesis, jaundice, liver function abnormalities including liver failure, stomatitis, hemorrhoidal or rectal bleeding.

Hematologic system: aplastic anemia, ecchymoses, eosinophilia, hemolytic anemia, lymphadenopathy, melena, purpura, thrombocytopenia, leukopenia.

Metabolic system: hyperglycemia, weight changes.

Nervous system: anxiety, asthenia, coma, convulsions, dream abnormalities, drowsiness, hallucinations, insomnia, malaise, meningitis, nervousness, paresthesia, tremors, vertigo, weakness.

Respiratory system: asthma, dyspnea, pulmonary infections, pneumonia, sinusitis, symptoms of upper respiratory tract infection, respiratory depression.

Skin: alopecia, angioedema, urticaria, photosensitivity, sweat.

Special senses: blurred vision, conjunctivitis, hearing decrease.

Urogenital: cystitis, hematuria, increase in menstrual flow, oliguria/ polyuria, proteinuria, renal insufficiency, decreased menstrual flow.

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of oxaprozin. 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.

Body as a whole: serum sickness.

Digestive system: hepatitis, pancreatitis.

Hematologic system: agranulocytosis, pancytopenia.

Skin: pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson Syndrome, fixed drug eruption (FDE), toxic epidermal necrolysis (Lyell's syndrome).

Urogenital: acute interstitial nephritis, nephrotic syndrome, acute renal failure.

7 DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with oxaprozin *[see Clinical Pharmacology (12.3)]*.

Table 2: Clinically Significant Drug Interactions with Oxaprozin

Drugs That Interfere with Hemostasis	
	• Oxaprozin and anticoagulants such as warfarin have a synergistic effect

Clinical Impact:	on bleeding. The concomitant use of oxaprozin 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 oxaprozin with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and 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 oxaprozin and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding *[see Warnings and Precautions (5.12)]*. Oxaprozin is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, 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 oxaprozin and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of oxaprozin 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.
Intervention:	During concomitant use of oxaprozin 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)]*.

Digoxin	
Clinical Impact:	The concomitant use of oxaprozin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of oxaprozin and digoxin, monitor serum digoxin levels.
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.
Intervention:	During concomitant use of oxaprozin and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction) because NSAID administration may result in increased plasma levels of methotrexate, especially in patients receiving high doses of methotrexate.
Intervention:	During concomitant use of oxaprozin and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of oxaprozin and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of oxaprozin and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of oxaprozin 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 oxaprozin with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of oxaprozin and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of oxaprozin and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Corticosteroids	
Clinical Impact:	Concomitant use of corticosteroids with oxaprozin may increase the risk of GI ulceration or bleeding.

Intervention:	Monitor patients with concomitant use of oxaprozin with corticosteroids for signs of bleeding *[see Warnings and Precautions (5.2)]*.
Glyburide	
Clinical Impact:	While oxaprozin does alter the pharmacokinetics of glyburide, co-administration of oxaprozin to type II non-insulin dependent diabetic patients did not affect the area under the glucose concentration curve nor the magnitude or duration of control.
Intervention:	During concomitant use of oxaprozin and glyburide, monitor patient's blood glucose in the beginning phase of cotherapy.

Laboratory Test Interactions

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking oxaprozin. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of oxaprozin therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish oxaprozin from benzodiazepines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including oxaprozin, 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 oxaprozin use between about 20 and 30 weeks of gestation, and avoid oxaprozin 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 oxaprozin, 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, oral administration of oxaprozin to pregnant rabbits at doses 0.1-times the maximum daily human dose (based on body surface area) resulted in evidence of teratogenicity; however, oral administration of oxaprozin to pregnant mice and rats during organogenesis at doses equivalent to the maximum recommended human dose revealed no evidence of teratogenicity or embryotoxicity. In rat reproduction studies in which oxaprozin was administered through late gestation failure to deliver and a reduction in live birth index was observed at doses equivalent to the maximum recommended human dose. 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 oxaprozin, 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 oxaprozin, 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 oxaprozin treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue oxaprozin and follow up according to clinical practice *(see Data).*

Labor or Delivery

There are no studies on the effects of oxaprozin during labor or delivery. In animal studies, NSAIDs, including oxaprozin, 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 full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal data

Teratology studies with oxaprozin were performed in mice, rats, and rabbits in pregnant animals administered oral doses up to 200 mg/kg/day, 200 mg/kg/day, and 30 mg/kg/day, respectively, during the period of organogenesis. In rabbits, malformations were observed at doses greater than or equal to 7.5 mg/kg/day of oxaprozin (0.1 times the maximum recommended human daily dose [MRHD] of 1,800 mg based on body surface area). However, in mice and rats, no drug-related developmental abnormalities or embryo-fetal toxicity were observed at doses up to 50 and 200 mg/kg/day of oxaprozin, respectively (0.1 times and 1.1 times the maximum recommended human daily dose of 1,800 mg based on a body surface area comparison, respectively).

In fertility/reproductive studies in rats, 200 mg/kg/day oxaprozin was orally administered to female rats for 14 days prior to mating through lactation day (LD) 2, or from gestation day (GD) 15 through LD 2 and the females were mated with males treated with 200 mg/kg/day oxaprozin for 60 days prior to mating. Oxaprozin administration resulted in failure to deliver and a reduction in live birth index at 200 mg/kg/day (1.1-times the maximum recommended human daily dose of 1,800 mg based on a body surface area comparison).

8.2 Lactation

Risk Summary

Lactation studies have not been conducted with oxaprozin. It is not known whether oxaprozin is excreted in human milk. Oxaprozin should be administered to lactating women only if clearly indicated. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for oxaprozin and any potential adverse effects on the breastfed infant from the oxaprozin or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Infertility

Females

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

Males

Testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the maximum recommended human daily dose based on body surface area) of oxaprozin for 42 days or 6 months *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

Safety and effectiveness of oxaprozin in pediatric patients below the age of 6 years of age have not been established. The effectiveness of oxaprozin for the treatment of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in pediatric patients aged 6 to 16 years is supported by evidence from adequate and well controlled studies in adult rheumatoid arthritis patients, and is based on an extrapolation of the demonstrated efficacy of oxaprozin in adults with rheumatoid arthritis and the similarity in the course of the disease and the drug's mechanism of effect between these two patient populations. Use of oxaprozin in JRA patients 6 to 16 years of age is also supported by the following pediatric studies.

The pharmacokinetic profile and tolerability of oxaprozin were assessed in JRA patients relative to adult rheumatoid arthritis patients in a 14 day multiple dose pharmacokinetic study. Apparent clearance of unbound oxaprozin in JRA patients was reduced compared to adult rheumatoid arthritis patients, but this reduction could be accounted for by differences in body weight *[see Clinical Pharmacology (12.3)]*. No pharmacokinetic data are available for pediatric patients under 6 years. Adverse events were reported by approximately 45% of JRA patients versus an approximate 30% incidence of adverse events in the adult rheumatoid arthritis patient cohort. Most of the adverse events were related to the gastrointestinal tract and were mild to moderate.

In a 3 month open label study, 10 to 20 mg/kg/day of oxaprozin were administered to 59 JRA patients. Adverse events were reported by 58% of JRA patients. Most of those reported were generally mild to moderate, tolerated by the patients, and did not interfere with continuing treatment. Gastrointestinal symptoms were the most frequently reported adverse effects and occurred at a higher incidence than those historically seen in controlled studies in adults. Fifty-two patients completed 3 months of treatment with a mean daily dose of 20 mg/kg. Of 30 patients who continued treatment (19 to 48 week range total treatment duration), nine (30%) experienced rash on sun-exposed areas of the skin and 5 of those discontinued treatment. Controlled clinical trials with oxaprozin in pediatric patients have not been conducted.

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)]*.

No adjustment of the dose of oxaprozin is necessary in the elderly, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging *[see Clinical Pharmacology (12.3)]*.

Of the total number of subjects evaluated in four placebo controlled clinical studies of oxaprozin, 39% were 65 and over, and 11% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses

between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Although selected elderly patients in controlled clinical trials tolerated oxaprozin as well as younger patients, caution should be exercised in treating the elderly.

Oxaprozin is substantially excreted by the kidney, and the risk of toxic reactions to oxaprozin may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Warnings and Precautions (5.6)]*.

10 OVERDOSAGE

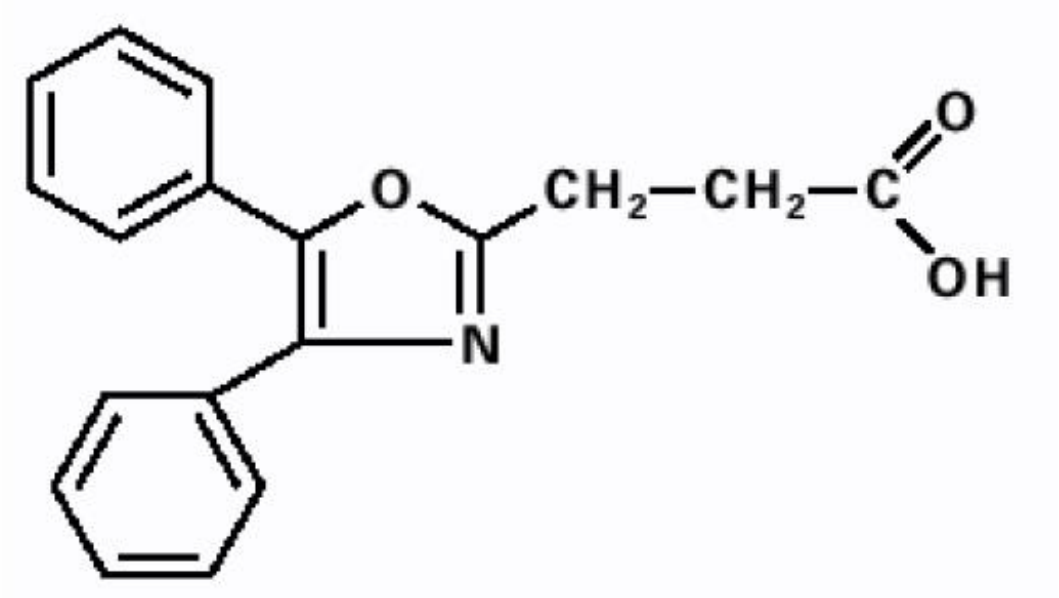
Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma 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 acute NSAID overdosage. There are no specific antidotes. It is advisable to contact a poison control center (1-800-222-1222) to determine the latest recommendations because strategies for the management of overdose are continually evolving.

If gastric decontamination may be potentially beneficial to the patient, e.g., short time since ingestion or a large overdosage (5 to 10 times the recommended dosage), consider emesis and/or activated charcoal (60 grams to 100 grams in adults, 1 gram to 2 grams per kg of body weight in pediatric patients) and/or an osmotic cathartic in symptomatic patients. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

11 DESCRIPTION

Oxaprozin is a nonsteroidal anti-inflammatory drug, available as tablets of 600 mg for oral administration. The chemical name is 4,5-diphenyl-2-oxazole-propionic acid. The molecular weight is 293. Its molecular formula is $C_{18}H_{15}NO_3$, and it has the following chemical structure.



Oxaprozin, USP is a white to off-white powder with a slight odor and a melting point of 162°C to 163°C. It is slightly soluble in alcohol and insoluble in water, with an octanol/water partition coefficient of 4.8 at physiologic pH (7.4). The pK_a in water is 4.3.

Oxaprozin oral tablets, USP contain 600 mg of oxaprozin, USP.

The inactive ingredients in oxaprozin tablets, USP are hypromellose, magnesium stearate, methylcellulose, microcrystalline cellulose, polacrilin potassium, polyethylene glycol, pregelatinized starch and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

Oxaprozin is a potent inhibitor of prostaglandin synthesis *in vitro*. Oxaprozin 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 oxaprozin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

In dose proportionality studies utilizing 600 mg, 1,200 mg and 1,800 mg doses, the pharmacokinetics of oxaprozin in healthy subjects demonstrated nonlinear kinetics of both the total and unbound drug in opposite directions, i.e., dose exposure related increase in the clearance of total drug and decrease in the clearance of the unbound drug. Decreased clearance of the unbound drug was related predominantly to a decrease in the volume of distribution of the unbound drug and not an increase in the

elimination half-life. This phenomenon is considered to have minimal impact on drug accumulation upon multiple dosing. The pharmacokinetic parameters of oxaprozin in healthy subjects receiving a single dose or multiple once-daily doses of 1,200 mg are presented in Table 3.

Table 3. Oxaprozin Pharmacokinetic Parameters [Mean (%CV)] (1,200 mg)

	Healthy Adults (19 to 78 years)			
	Total Drug		**Unbound Drug**	
	Single N=35	**Multiple N=12**	**Single N=35**	**Multiple N=12**
T_{max} (hr)	3.09 (39)	2.44 (40)	3.03 (48)	2.33 (35)
Oral Clearance (L/hr/70 kg)	0.150 (24)	0.301 (29)	136 (24)	102 (45)
Apparent Volume of Distribution at Steady-State (Vd/F; L/70 kg)	11.7 (13)	16.7 (14)	6,230 (28)	2,420 (38)
Elimination Half-life (hr)	54.9 (49)	41.4 (27)	27.8 (34)	19.5 (15)
T_{max} = time to reach the maximum plasma concentration of oxaprozin.				

Absorption

Oxaprozin is 95% absorbed after oral administration. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. Antacids do not significantly affect the extent and rate of oxaprozin absorption.

Distribution

The apparent volume of distribution (Vd/F) of total oxaprozin is approximately 11 to 17 L/70 kg. Oxaprozin is 99% bound to plasma proteins, primarily to albumin. At therapeutic drug concentrations, the plasma protein binding of oxaprozin is saturable, resulting in a higher proportion of the free drug as the total drug concentration is increased. With increases in single doses or following multiple once-daily dosing, the apparent volume of distribution and clearance of total drug increased, while that of unbound drug decreased due to the effects of nonlinear protein binding.

Oxaprozin penetrates into synovial tissues of rheumatoid arthritis patients with oxaprozin concentrations 2-fold and 3-fold greater than in plasma and synovial fluid, respectively. Oxaprozin is expected to be excreted in human milk based on its physical-chemical properties; however, the amount of oxaprozin excreted in breast milk has not been evaluated.

Elimination

Metabolism

Several oxaprozin metabolites have been identified in human urine or feces.

Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). Ester and ether glucuronide are the major conjugated metabolites of oxaprozin. On chronic dosing, metabolites do not accumulate in the plasma of patients with normal renal function. Concentrations of the metabolites in plasma are very low.

Oxaprozin's metabolites do not have significant pharmacologic activity. The major ester and ether glucuronide conjugated metabolites have been evaluated along with oxaprozin in receptor binding studies and *in vivo* animal models and have demonstrated no activity. A small amount (< 5%) of active phenolic metabolites are produced, but the contribution to overall activity is limited.

Excretion

Approximately 5% of the oxaprozin dose is excreted unchanged in the urine. Sixty-five percent (65%) of the dose is excreted in the urine and 35% in the feces as metabolites. Biliary excretion of unchanged oxaprozin is a minor pathway, and enterohepatic recycling of oxaprozin is insignificant. Upon chronic dosing, the accumulation half-life is approximately 22 hours. The elimination half-life is approximately twice the accumulation half-life due to increased binding and decreased clearance at lower concentrations.

Specific Populations

Geriatric: A multiple dose study comparing the pharmacokinetics of oxaprozin (1,200 mg once daily) in 20 young (21 to 44 years) adults and 20 elderly (64 to 83 years) adults did not show any statistically significant differences between age groups.

Pediatric: A population pharmacokinetic study indicated no clinically important age dependent changes in the apparent clearance of unbound oxaprozin between adult rheumatoid arthritis patients (N=40) and juvenile rheumatoid arthritis (JRA) patients (≥ 6 years, N=44) when adjustments were made for differences in body weight between these patient groups. The extent of protein binding of oxaprozin at various therapeutic total plasma concentrations was also similar between the adult and pediatric patient groups. Pharmacokinetic model-based estimates of daily exposure (AUC_{0-24}) to unbound oxaprozin in JRA patients relative to adult rheumatoid arthritis patients suggest dose to body weight range relationships, as shown in Table 4.

Table 4. Dose to Body Weight Range to Achieve Similar Steady-State Exposure (AUC_{0-24hr}) to Unbound Oxaprozin in JRA Patients Relative to 70 kg Adult Rheumatoid Arthritis Patients Administered Oxaprozin 1,200 mg Once Daily[1]

Dose (mg)	Body Weight Range (kg)
600	22 to 31
900	32 to 54
1,200	≥ 55

[1]Model-based nomogram derived from unbound oxaprozin steady-state plasma concentrations in JRA patients weighing 22.1 to 42.7 kg or ≥ 45 kg administered

oxaprozin 600 mg or 1,200 mg once daily for 14 days, respectively.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment: Approximately 95% of oxaprozin is metabolized by the liver. However, patients with well-compensated cirrhosis do not require reduced doses of oxaprozin as compared to patients with normal hepatic function. Nevertheless, monitor patients with severe hepatic dysfunction for adverse reactions.

Renal Impairment: Oxaprozin's renal clearance decreased proportionally with creatinine clearance (CrCL), but since only approximately 5% of oxaprozin dose is excreted unchanged in the urine, the decrease in total body clearance becomes clinically important only in those subjects with highly decreased CrCL. Oxaprozin is not significantly removed from the blood in patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) due to its high protein binding. Oxaprozin plasma protein binding may decrease in patients with severe renal deficiency. Dosage adjustment may be necessary in patients with renal insufficiency *[see Warnings and Precautions (5.6)]*.

Cardiac Failure: Well-compensated cardiac failure does not affect the plasma protein binding or the pharmacokinetics of oxaprozin.

Drug Interaction Studies

ACE inhibitors (enalapril): Oxaprozin has been shown to alter the pharmacokinetics of enalapril (significant decrease in dose-adjusted AUC_{0-24} and C_{max}) and its active metabolite enalaprilat (significant increase in dose-adjusted AUC_{0-24}) *[see Drug Interactions (7)]*.

Aspirin: When oxaprozin was administered with aspirin, the protein binding of oxaprozin was reduced, although the clearance of free oxaprozin was not altered. The clinical significance of this interaction is not known. An *in vitro* study showed that oxaprozin significantly interfered with the anti-platelet activity of aspirin *[see Drug Interactions (7)].*

Beta-blockers (metoprolol): Subjects receiving 1,200 mg oxaprozin once daily with 100 mg metoprolol twice daily exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days *[see Drug Interactions (7)]*.

Glyburide: Oxaprozin altered the pharmacokinetics of glyburide; however, co-administration of oxaprozin to type II non-insulin dependent diabetic patients did not affect the area under the glucose concentration curve nor the magnitude or duration of control *[see Drug Interactions (7)]*.

H_2-receptor antagonists (cimetidine, ranitidine): The total clearance of oxaprozin was reduced by 20% in subjects who concurrently received therapeutic doses of cimetidine or ranitidine; no other pharmacokinetic parameter was affected. A change of clearance of this magnitude lies within the range of normal variation and is unlikely to produce a clinically detectable difference in the outcome of therapy.

Lithium: Oxaprozin has produced an elevation in plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20% *[see Drug Interactions (7)]*.

Methotrexate: Co-administration of oxaprozin with methotrexate resulted in approximately 36% reduction in apparent oral clearance of methotrexate *[see Drug*

Interactions (7)].

Other drugs: The co-administration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies. The interaction of oxaprozin with cardiac glycosides has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In carcinogenicity studies in rats and mice, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or male or female rats treated with up to 216 mg/kg via the diet (1.2-times the maximum daily human dose of 1,800 mg based on body surface area). The significance of this species-specific finding to man is unknown.

Mutagenesis

Oxaprozin was not genotoxic in the Ames test, forward mutation in yeast and Chinese hamster ovary (CHO) cells, DNA repair testing in CHO cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, or cell transformation testing in mouse fibroblast.

Impairment of Fertility

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1.1-times the maximum recommended human daily dose [MRHD] of 1,800 mg based on a body surface area comparison). However, testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the MRHD based on body surface area) of oxaprozin for 42 days or 6 months, a finding not confirmed in other species. The clinical relevance of this finding is not known.

14 CLINICAL STUDIES

14.1 Osteoarthritis

Oxaprozin was evaluated for the management of the signs and symptoms of osteoarthritis in a total of 616 patients in active controlled clinical trials against aspirin (N=464), piroxicam (N=102), and other NSAIDs. Oxaprozin was given both in variable (600 to 1,200 mg/day) and in fixed (1,200 mg/day) dosing schedules in either single or divided doses. In these trials, oxaprozin was found to be comparable to 2,600 to 3,200 mg/day doses of aspirin or 20 mg/day doses of piroxicam. Oxaprozin was effective both in once daily and in divided dosing schedules. In controlled clinical trials several days of oxaprozin therapy were needed for the drug to reach its full effects *[see Dosage and Administration (2.5)]*.

14.2 Rheumatoid Arthritis

Oxaprozin was evaluated for managing the signs and symptoms of rheumatoid arthritis in placebo and active controlled clinical trials in a total of 646 patients. Oxaprozin was given in single or divided daily doses of 600 to 1,800 mg/day and was found to be comparable to 2,600 to 3,900 mg/day of aspirin. At these doses there was a trend (over all trials) for oxaprozin to be more effective and cause fewer gastrointestinal side effects than aspirin.

Oxaprozin was given as a once-a-day dose of 1,200 mg in most of the clinical trials, but larger doses (up to 26 mg/kg or 1,800 mg/day) were used in selected patients. In some patients, oxaprozin may be better tolerated in divided doses. Due to its long half-life, several days of oxaprozin therapy were needed for the drug to reach its full effect *[see Dosage and Administration (2.5)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Oxaprozin Tablets USP, **600 mg** are supplied as white, capsule-shaped, beveled edged, biconvex, film-coated tablets, debossed with “AA59” on one side and scored on the other side.

They are available as follows:

Bottles of 100:	NDC 69238-1120-1
Bottles of 500:	NDC 69238-1120-5

Storage

Keep bottles tightly closed. Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container with a child-resistant closure.

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 oxaprozin 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 health care 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 health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and 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, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop oxaprozin 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 oxaprozin 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 oxaprozin, 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 oxaprozin and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with oxaprozin 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 oxaprozin 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 oxaprozin until they talk to their healthcare provider *[see Drug Interactions (7)]*.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.amneal.com.

Manufactured by:
Amneal Pharmaceuticals Pvt. Ltd.

Oral Solid Dosage Unit
Ahmedabad 382213, INDIA

Distributed by:
Amneal Pharmaceuticals LLC
Bridgewater, NJ 08807

Rev. 12-2024-07

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", "antiplatelet drugs", "anticoagulants", "SSRIs", "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 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
- stroke
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- asthma attacks in people who have asthma
- bleeding and ulcers in the stomach and intestine
- **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.

This product's labeling may have been updated. For the most recent prescribing information, please visit www.amneal.com.

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

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Rev. 06-2023-06

Dispense with Medication Guide available at:
documents.amneal.com/mg/oxaprozin-tablets.pdf

PRINCIPAL DISPLAY PANEL

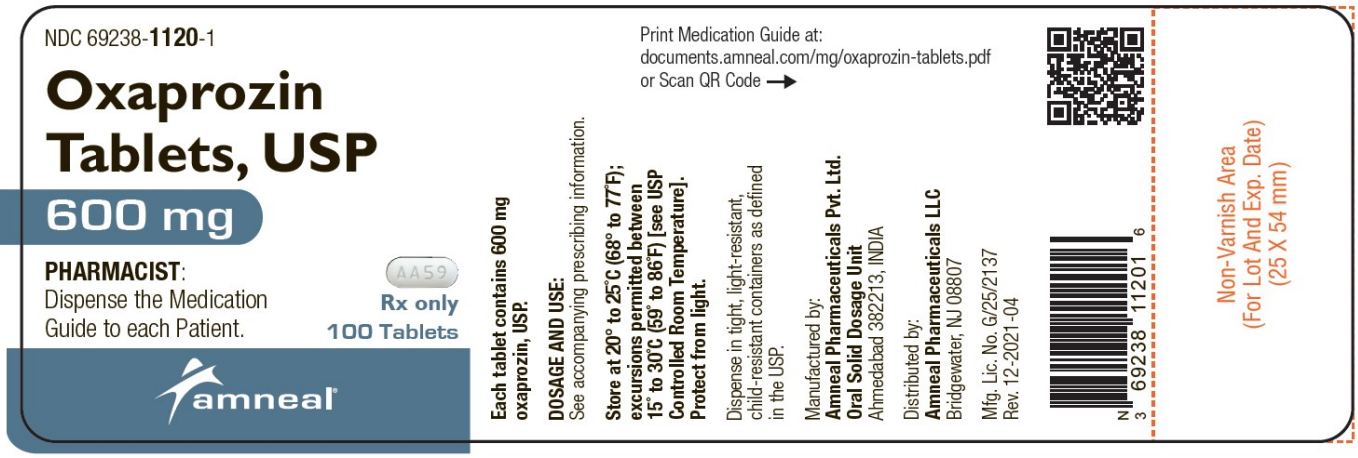
NDC 69238-1120-1

Oxaprozin Tablets USP, 600 mg

Rx only

100 Tablets

Amneal Pharmaceuticals LLC



OXAPROZIN
oxaprozin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:69238-1120
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
OXAPROZIN (UNII: MHJ80W9LRB) (OXAPROZIN - UNII:MHJ80W9LRB)	OXAPROZIN	600 mg

Inactive Ingredients

Ingredient Name	Strength
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
METHYLCELLULOSE (100 CPS) (UNII: 4GFU244C4J)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLACRILIN POTASSIUM (UNII: 0BZ5A00FQU)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WQ0SDW1A)	
STARCH, CORN (UNII: O8232NY3SJ)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white	**Score**	2 pieces
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	AA59
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:69238-1120-1	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/04/2017	
2	NDC:69238-1120-5	500 in 1 BOTTLE; Type 0: Not a Combination Product	05/04/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA208633	05/04/2017	

Labeler - Amneal Pharmaceuticals NY LLC (123797875)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals Private Limited		650762060	analysis(69238-1120) , label(69238-1120) , manufacture(69238-1120) , pack(69238-1120)