OXAPROZIN- oxaprozin tablet
DIRECT RX

OXAPROZIN

BOXED WARNING SECTION

Cardiovascular Risk

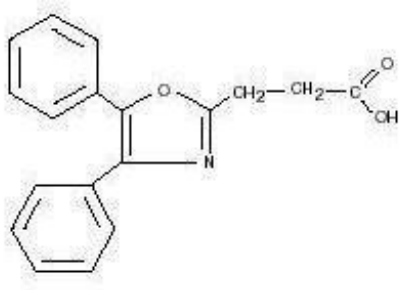
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see WARNINGS).
- Oxaprozin Tablet, USP, 600 mg is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).

DESCRIPTION SECTION

Oxaprozin, USP is a nonsteroidal anti-inflammatory drug (NSAID), chemically designated as 4,5-diphenyl-2-oxazole-propionic acid, and has the following chemical structure:



The empirical formula for oxaprozin, USP is C18H15NO3, and the molecular weight is 293. 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 pKa in water is 4.3.

Oxaprozin oral tablets contain 600 mg of oxaprozin, USP.

Inactive ingredients in oxaprozin tablets, USP are microcrystalline cellulose, methylcellulose, magnesium stearate, starch, sodium starch glycolate, polyethylene glycol, polysorbate 80 and titanium dioxide.

CLINICAL PHARMACOLOGY SECTION

Pharmacodynamics

Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic properties in animal models. The mechanism of action of oxaprozin like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics

(see Table 1)

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.

Table 1 Oxaprozin Pharmacokinetic Parameters [Mean (%CV)](1200 mg)

	Healthy Adults (19-78 years)			
	Total Drug		**Unbound Drug**	
	Single N=35	**Multiple N=12**	**Single N=35**	**Multiple N=12**
Tmax (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)	6230 (28)	2420 (38)
Elimination Half-life (hr)	54.9 (49)	41.4 (27)	27.8 (34)	19.5 (15)

Distribution: In dose proportionality studies utilizing 600, 1200 and 1800 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 and not an increase in the half-life. This phenomenon is considered to have minimal impact on drug accumulation upon multiple dosing.

The apparent volume of distribution (Vd/F) of total oxaprozin is approximately 11-17 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 repetitive 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.

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

Oxaprozin is primarily metabolized by 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 metabolite. 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.

Special Populations

Pediatric patients: 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 (AUC0-24) to unbound oxaprozin in JRA patients relative to adult rheumatoid arthritis patients suggest dose to body weight range relationships as shown in Table 2. No pharmacokinetic data are available for pediatric patients under 6 years of age (see PRECAUTIONS, Pediatric use).

Table 2 Dose to body weight range to achieve similar steady-state exposure (AUC 0-24 hr) to unbound oxaprozin in JRA patients relative to 70 kg adult rheumatoid arthritis patients administered oxaprozin 1200 mg QD1

Dose (mg)	Body Weight Range (kg)
600	22 - 31
900	32 - 54
1200	≥ 55

1Model-based nomogram derived from unbound oxaprozin steady state drug plasma concentrations of JRA patients weighing 22.1-42.7 kg or ≥45.0 kg administered oxaprozin 600 mg or 1200 mg QD for 14 days, respectively.

Geriatric: As with any NSAID, caution should be exercised in treating the elderly (65 years and older). No dosage adjustment is necessary in the elderly for pharmacokinetics reasons, although many elderly may need a reduced dose due to low body weight or disorders associated with aging.

A multiple dose study comparing the pharmacokinetics of oxaprozin (1200 mg QD) in 20 young (21 -44 years) adults and 20 elderly (64-83 years) adults, did not show any statistically significant differences between age groups.

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

Hepatic insufficiency: 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, caution should be observed in patients with severe hepatic dysfunction.

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

Renal insufficiency: The pharmacokinetics of oxaprozin have been investigated in patients with renal insufficiency. Oxaprozin's renal clearance decreased proportionally with creatinine clearance (CrCl), but since only about 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, Renal effects).

CLINICAL STUDIES SECTION

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 1800 mg/day and was found to be comparable to 2600 to 3900 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 1200 mg in most of the clinical trials, but larger doses (up to 26 mg/kg or 1800 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, Individualization of dosage).

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 1200 mg/day) and in fixed (1200 mg/day) dosing schedules in either single or divided doses. In these trials, oxaprozin was found to be comparable to 2600 to 3200 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, Individualization of dosage).

INDICATIONS AND USAGE

Carefully consider the potential benefits and risks of oxaprozin tablet, USP and other treatment options before deciding to use oxaprozin tablet, USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

Oxaprozin Tablet, USP is 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

CONTRAINDICATIONS SECTION

Oxaprozin tablet, USP is contraindicated in patients with known hyper-sensitivity to oxaprozin.

Oxaprozin tablet, USP should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Preexisting asthma).

Oxaprozin tablet, USP is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

Oxaprozin tablet, USP is contraindicated in patients with active gastrointestinal bleeding (see WARNINGS

WARNINGS SECTION

Cardiovascular Effects

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about the signs and/or symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events (see WARNINGS, Gastrointestinal Effects -Risk of Ulceration, Bleeding and Perforation).

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 (see CONTRAINDICATIONS).

Hypertension

NSAIDs including oxaprozin, can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including oxaprozin, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema

Fluid retention and edema have been observed in some patients taking NSAIDs. oxaprozin should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects- Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including oxaprozin, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

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

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulcerations and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI event is suspected. This should include

discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Oxaprozin tablet, USP is contraindicated in patients with active GI bleeding.

Renal Effects

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 a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced renal disease

No information is available from controlled clinical studies regarding the use of oxaprozin in patients with advanced renal disease. Therefore, treatment with oxaprozin is not recommended in these patients with advanced renal disease. If oxaprozin therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to oxaprozin. Oxaprozin should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Preexisting asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including oxaprozin, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, oxaprozin should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS SECTION

General

Oxaprozin cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

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

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including oxaprozin. These laboratory abnormalities may progress, remain unchanged, or may be

transient with continued therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminate hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

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

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.

Hematological Effects

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

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration, and reversible. Patients receiving oxaprozin who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with the severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, oxaprozin should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

Patients should be informed of the following information before initiating therapy with an NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

- Oxaprozin tablet, USP, like other NSAIDs, may cause CV side effects, such as MI or stroke, which may result in hospitalization and even death. Although serious CV events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, weakness, slurring of speech, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, Cardiovascular Effects).
- Oxaprozin tablet, USP, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative sign or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see WARNINGS, Gastrointestinal Effects, Risk of Ulceration, Bleeding and Perforation).
- Oxaprozin tablet, USP, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs hypersensitivity such as itching, and should ask for medical advice when observing any indicative sign or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

- Patients should promptly report signs or symptoms of unexplained weight gain, or edema to their physicians.
- Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and “flu-like” symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.
- Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (see WARNINGS).
- In late pregnancy, as with other NSAIDs, oxaprozin tablet, USP should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

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

Drug Interactions

Aspirin

Concomitant administration of oxaprozin and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity. As with other NSAIDs, concomitant administration of oxaprozin and aspirin is not generally recommended because of the potential for increased adverse effects.

Methotrexate

NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate. Coadministration of oxaprozin with methotrexate results in approximately a 36% reduction in apparent oral clearance of methotrexate. A reduction in methotrexate dosage may be considered due to the potential for increased methotrexate toxicity associated with the increased exposure.

ACE-inhibitors

Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. Oxaprozin has been shown to alter the pharmacokinetics of enalapril (significant decrease in dose-adjusted AUC0-24 and Cmax) and its active metabolite enalaprilat (significant increase in dose-adjusted AUC0-24). This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, coadministration of NSAIDs, including selective COX-2 inhibitors, with ACE inhibitors, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.

Diuretics

Clinical studies, as well as post marketing observations, have shown that oxaprozin can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS, Renal effects), as well as to assure diuretic efficacy.

Lithium

Oxaprozin like other NSAIDs has produced an elevation of plasma lithium levels and a reduction in

renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the nonsteroidal anti-inflammatory drug. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Glyburide

While oxaprozin does alter the pharmacokinetics of glyburide, coadministration 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. However, it is advisable to monitor patients' blood glucose in the beginning phase of glyburide and oxaprozin cotherapy.

Warfarin

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

H2-receptor antagonists

The total body 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.

Beta-blockers

Subjects receiving 1200 mg oxaprozin QD with 100 mg metoprolol bid exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, as with all NSAIDs, routine blood pressure monitoring should be considered in these patients when starting oxaprozin therapy.

Other drugs

The coadministration 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In oncogenicity studies, 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 rats. The significance of this species-specific finding to man is unknown.

Oxaprozin did not display mutagenic potential. Results from 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, and cell transformation testing in mouse fibroblast all showed no evidence of genetic toxicity or cell-transforming ability.

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m2); the usual human dose is 17 mg/kg/day (629 mg/m2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known.

Pregnancy

Teratogenic Effects—Pregnancy Category C.

Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Animal reproductive studies are not always predictive of human response. There are no adequate or well-controlled studies in pregnant women. Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Nonteratogenic Effects

Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.

Labor and Delivery

In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of oxaprozin on labor and delivery in pregnant women are unknown.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness 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 6-16 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 6-16 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 Pharmacokinetics, Pediatric patients). 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, 10-20 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 (19-48 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.

Geriatric Use

No adjustment of the dose of oxaprozin is necessary in the elderly for pharmacokinetic reasons, although many elderly may need to receive a reduced dose because of low body weight or disorders associated with aging. No significant differences in the pharmacokinetic profile for oxaprozin were seen in studies in the healthy elderly (see CLINICAL PHARMACOLOGY, Special populations).

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 as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

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, Renal effects).

ADVERSE REACTIONS SECTION

Adverse reaction data were derived from patients who received oxaprozin in multidose, controlled, and open-label clinical trials, and from worldwide marketing experience. Rates for events occurring in more than 1% of patients, and for most of the less common events, are based on 2253 patients who took 1200 to 1800 mg oxaprozin per day in clinical trials. Of these, 1721 were treated for at least 1 month, 971 for at least 3 months, and 366 for more than 1 year. Rates for the rarer events and for events reported from worldwide marketing experience are difficult to estimate accurately and are only listed as less than 1%.

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 LESS THAN 1%: The following adverse reactions were reported in clinical trials, from worldwide marketing experience (in italics) or in patients taking other NSAIDs.

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

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 hepatitis, liver failure, stomatitis, hemorrhoidal or rectal bleeding, pancreatitis.

Hematologic system: agranulocytosis, aplastic anemia, ecchymoses, eosinophilia, hemolytic anemia, lymphadenopathy, melena, pancytopenia, 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, pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, sweat, toxic epidermal necrolysis (Lyell's syndrome).

Special senses: blurred vision, conjunctivitis, hearing decrease.

Urogenital: acute interstitial nephritis, cystitis, hematuria, increase in menstrual flow, nephrotic syndrome, oliguria/polyuria, proteinuria, renal insufficiency, acute renal failure, decreased menstrual flow.

DRUG ABUSE AND DEPENDENCE SECTION

Oxaprozin is a non-narcotic drug. Usually reliable animal studies have indicated that oxaprozin has no known addiction potential in humans.

OVERDOSAGE SECTION

No patient experienced either an accidental or intentional overdosage of oxaprozin in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. Gastrointestinal bleeding and coma have occurred following NSAID overdose. Hypertension, acute renal failure, and respiratory depression are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

DOSAGE & ADMINISTRATION SECTION

Carefully consider the potential benefits and risks of oxaprozin tablet, USP and other treatment options before deciding to use oxaprozin tablet, USP. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

After observing the response to initial therapy with oxaprozin tablet, USP, the dose and frequency should be adjusted to suit an individual patient's needs.

Rheumatoid arthritis: For relief of the signs and symptoms of rheumatoid arthritis, the usual recommended dose is 1200 mg (two 600-mg tablets) given orally once a day (see Individualization of dosage).

Osteoarthritis: For relief of the signs and symptoms of osteoarthritis, the usual recommended dose is 1200 mg (two 600-mg tablets) given orally once a day (see Individualization of dosage).

Juvenile rheumatoid arthritis: For the relief of the signs and symptoms of JRA in patients 6-16 years of age, the recommended dose given orally once per day should be based on body weight of the patient as given in Table 3 (see also Individualization of dosage).

Table 3

Body Weight Range (kg)	Dose (mg)
22-31	600
32-54	900
≥55	1200

(see CLINICAL PHARMACOLOGY: Special populations: Pediatric patients)

Individualization of dosage:

As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy with oxaprozin tablet, USP, 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 tablet, USP to minimize adverse effects. The maximum recommended total daily dose of oxaprozin tablet, USP in adults is 1800 mg (26 mg/kg, whichever is lower) in divided doses. In children, doses greater than 1200 mg have not been studied.

Patients of 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 1200 mg, but only with close monitoring (see CLINICAL PHARMACOLOGY, Special populations). In adults, in cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allow therapy to be started with a one-time loading dose of 1200 to 1800 mg (not to exceed 26 mg/kg). Doses larger than 1200 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 to 1200 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 tablet, USP, although divided doses may be tried in patients unable to tolerate single doses.

SAFE HANDLING WARNING SECTION

Oxaprozin tablet, USP is supplied as a solid dosage form in closed containers, is not known to produce contact dermatitis, and poses no known risk to healthcare workers. It may be disposed of in accordance with applicable local regulations governing the disposal of pharmaceuticals.

HOW SUPPLIED SECTION

Oxaprozin tablets, USP, 600 mg are available as: white to off-white, capsule shaped film coated tablets with “391” debossed on one side and scored on the other side in the bottles of 100 (NDC 57664-391-08), 500 (NDC 57664-391-13) and 1000 (NDC 57664-391-18).

Store at controlled room temperature 15°-30°C (59°-86°F). Dispense in tight, light-resistant container as defined in the USP, with child resistant closure.

CARACO PHARMACEUTICAL LABORATORIES, LTD.

DETROIT, MI 48202

C.S.No. 5220T09

Iss. 03/13

SPL MEDGUIDE SECTION

What is the most important information I should know about medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines may increase the chance of a heart attack or stroke that can lead to death. This chance increases:

- with longer use of NSAID medicines
- in people who have heart disease

NSAID medicines should never be used right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

NSAID medicines can cause ulcers and bleeding in the stomach and intestines at any time during treatment. Ulcers and bleeding:

- can happen without warning symptoms
- may cause death

The chance of a person getting an ulcer or bleeding increases with:

- taking medicines called “corticosteroids” and “anticoagulants”
- longer use
- smoking
- drinking alcohol
- older age
- having poor health

NSAID medicines should only be used:

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

What are Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

NSAID medicines 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 a Non-Steroidal Anti-Inflammatory Drug (NSAID)?

Do not take an NSAID medicine:

- if you had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAID medicine
- for pain right before or after heart bypass surgery

Tell your healthcare provider:

- about all of your medical conditions
- about all of the medicines you take. NSAIDs and some other medicines can interact with each other and cause serious side effects. Keep a list of your medicines to show to your healthcare provider and pharmacist.
- if you are pregnant. NSAID medicines should not be used by pregnant women late in their pregnancy
- if you are breastfeeding. Talk to your doctor.

What are the possible side effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)?

Serious side effects include:

- heart attack
- stroke
- high blood pressure
- heart failure from body swelling (fluid retention)
- kidney problems including kidney failure
- bleeding and ulcers in the stomach and intestine
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- liver problems including liver failure
- asthma attacks in people who have asthma

Other side effects include:

- stomach pain
- constipation
- diarrhea
- gas
- heartburn
- nausea
- vomiting
- dizziness

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

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

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

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- 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 and legs, hands and feet

These are not all the side effects with NSAID medicines. Talk to your healthcare provider or pharmacist for more information about NSAID medicines.

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

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

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

NSAID medicines that need a prescription

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

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

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

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL-600 mg (100 Count)

NDC 57664-391-08

Oxaprozin Tablets, USP

600 mg

Rx Only

PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY

100 Tablets

Oxaprozin is 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

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of oxaprozin and other treatment options before deciding to use oxaprozin. 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 1200 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 1200 mg (two 600 mg tablets) given orally once a day [seeDOSAGE 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 [seeDOSAGE AND ADMINISTRATION (2.5)].

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

Body Weight Range (kg)	Dose (mg)
22 to 31	600
32 to 54	900
greater than or equal to 55	1200

2.5 Individualization of Dosage

After observing the response to initial therapy with oxaprozin, 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 to minimize adverse effects. The maximum recommended total daily dose of oxaprozin in adults is 1800 mg (26 mg/kg, whichever is lower) in divided doses. In children, doses greater than 1200 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 1200 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 1200 mg to 1800 mg (not to exceed 26 mg/kg). Doses larger than 1200 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 1200 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, although divided doses may be tried in patients unable to tolerate single doses.

600 mg - White, capsule-shaped, film-coated tablet, debossed with " E 141" on one side and bisected on the other side.

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 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, 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 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 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, etc.), 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. 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 Premature Closure of Fetal Ductus Arteriosus

Oxaprozin may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including oxaprozin, in pregnant women starting at 30 weeks of gestation (third trimester) [see USE IN SPECIFIC POPULATIONS (8.1)].

5.11 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an 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 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)].

5.12 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.

5.13 Laboratory Monitoring

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

5.14 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.

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

Clinical Impact:

•

Oxaprozin and anticoagulants such as warfarin have a synergistic effect 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 agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see WARNINGS AND PRECAUTIONS (5.11)].

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 (5.11)].

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 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 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 mL/min 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, coadministration 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.

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including oxaprozin, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including oxaprozin, in pregnant women starting at 30 of weeks gestation (third trimester).

There are no adequate and well-controlled studies of oxaprozin in pregnant women.

Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. 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.

Clinical Considerations

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

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 1800 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 mg/kg/day and 200 mg/kg/day of oxaprozin, respectively (0.1 times and 1.1 times the maximum recommended human daily dose of 1800 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 1800 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 mg/kg/day 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, 5.13)].

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)].

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

Advise patients to stop oxaprozin immediately if they develop any type of rash and to contact their healthcare provider as soon as possible [see WARNINGS AND PRECAUTIONS (5.9)].

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 [see WARNINGS AND PRECAUTIONS (5.10) 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)].

Manufactured by

Sandoz Inc.

Princeton, NJ 08540

Rev. June 2017

MF0141REV06/17

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

for

Oxaprozin Tablets, USP

(OK-ah-proe-zin)

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", "SNRIs"
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age

o
poor health
o
advanced liver disease
o
bleeding problems

NSAIDs should only be used:

o
exactly as prescribed
o
at the lowest dose possible for your treatment
o
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. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 29 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.

For more information, go to www.us.sandoz.com or call 1-800-525-8747.

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

For Medication Guides, please visit www.us.sandoz.com or call 1-800-507-2130.

Manufactured by

Sandoz Inc.

Princeton, NJ 08540

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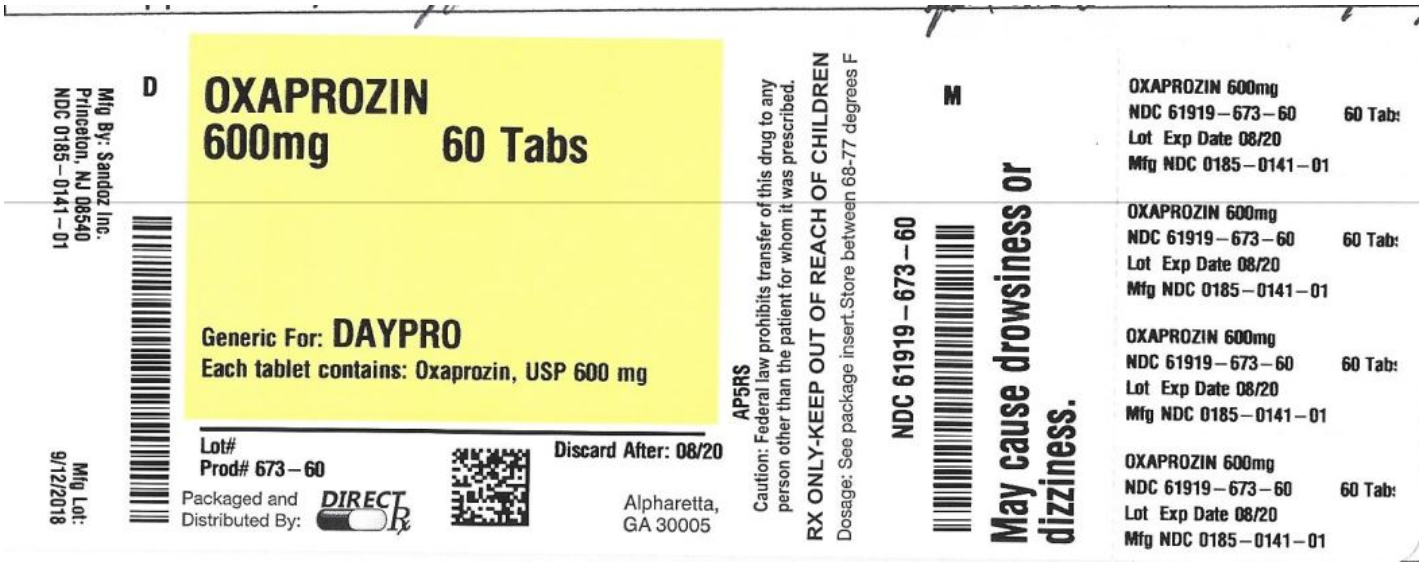
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



OXAPROZIN

oxaprozin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-673(NDC:0185-0141)
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**
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
METHYLCELLULOSE (100 MPA.S) (UNII: 4GFU244C4J)	
POLACRILIN POTASSIUM (UNII: 0BZ5A00FQU)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	E;141
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-673-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	04/19/2019	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075845	04/19/2019	

OXAPROZIN

oxaprozin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:61919-178(NDC:57664-391)
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)	
METHYLCELLULOSE (400 MPA.S) (UNII: O0GN6F9B2Y)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
POLYETHYLENE GLYCOL, UNSPECIFIED (UNII: 3WJQ0SDW1A)	
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	white	**Score**	2 pieces
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	391
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:61919-178-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2015	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075844	01/01/2014	

Labeler - DIRECT RX (079254320)

Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	relabel(61919-178) , repack(61919-178, 61919-673)