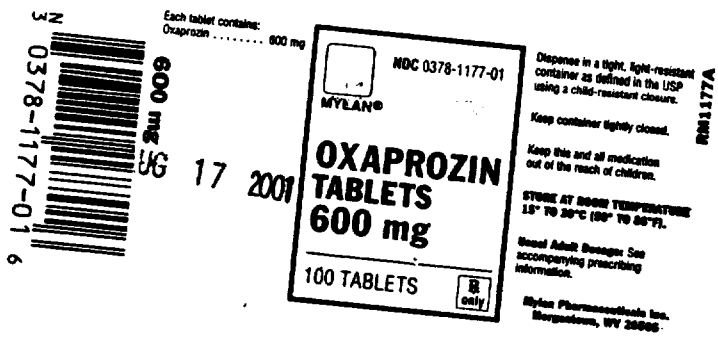
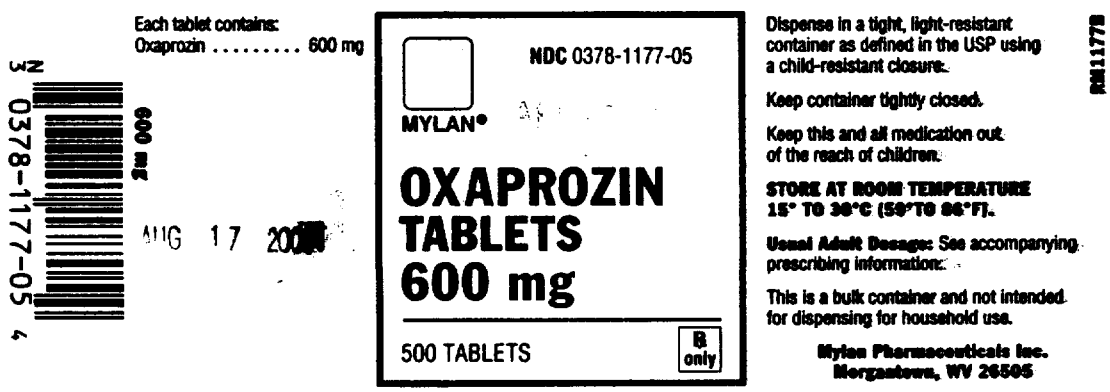
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-851

APPROVED DRAFT LABELING


Each tablet contains:
Oxaprozin ..... 600 mg
NDC 0378-1177-01
MYLAN®
OXAPROZIN
TABLETS
600 mg
100 TABLETS
℞ only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F).
Usual Adult Dosage: See accompanying prescribing information.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1177A
600 mg
AUG 17 2001
0378-1177-01


Each tablet contains:
Oxaprozin ..... 600 mg
NDC 0378-1177-05
MYLAN®
OXAPROZIN
TABLETS
600 mg
500 TABLETS
℞ only
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT ROOM TEMPERATURE 15° TO 30°C (59°TO 86°F).
Usual Adult Dosage: See accompanying prescribing information.
This is a bulk container and not intended for dispensing for household use.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM1177B
600 mg
AUG 17 2001
0378-1177-05

OXAP:R1

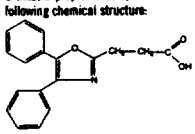
AUG 17 2001

APPROVED

OXAPROZIN TABLETS 600 mg

℞ only

DESCRIPTION: Oxaprozin 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 is $C_{18}H_{15}NO_3$, and the molecular weight is 293. Oxaprozin is a white to off-white powder with a slight odor and a melting point of 162°C to 163°C. It is slightly soluble in alcohol and insoluble in water, with an octanol/water partition coefficient of 4.8 at physiologic pH (7.4). The pK_a in water is 4.3.

Oxaprozin tablets, for oral administration, contain 600 mg of oxaprozin. In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, povidone, sodium lauryl sulfate, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY: Oxaprozin is a nonsteroidal anti-inflammatory drug (NSAID) that has been shown to have anti-inflammatory, analgesic, and antipyretic properties in animal models. As with other nonsteroidal anti-inflammatory agents, all of the modes of action of oxaprozin are not fully established. Oxaprozin is an inhibitor of several steps along the arachidonic acid pathway of prostaglandin synthesis, and one of its modes of action is presumed to be due to the inhibition of prostaglandin synthesis at the site of inflammation.

Pharmacodynamics: Acute analgesic effects are demonstrable in humans after a single 1200 mg dose of oxaprozin, but anti-inflammatory effects are not reliably achieved after a single dose. Because of the long half-life of oxaprozin, it takes several days of dosing to reach steady state (see Pharmacokinetics).

Pharmacokinetics: The pharmacokinetics of oxaprozin have been evaluated in approximately 400 individuals, which have included patients with rheumatoid arthritis, osteoarthritis, healthy elderly volunteers, and patients with cardiac, renal, and hepatic disease.

Oxaprozin demonstrates high oral bioavailability (95%), with peak plasma concentrations occurring between 3 and 5 hours after dosing. Food may reduce the rate of absorption of oxaprozin, but the extent of absorption is unchanged. Antacids have no effect on the rate or extent of oxaprozin absorption.

As is true for most NSAIDs, approximately 99.9% of the oxaprozin present in plasma is bound to albumin. The fraction of the drug present in the tissues across the therapeutic dosage range ranges between 40% and 60%

PHARMACOLOGY

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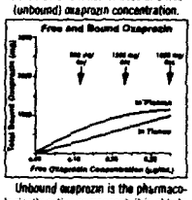
As is true for most NSAIDs, approximately 99.9% of the oxaprozin present in plasma is bound to albumin. The fraction of the drug present in the tissues across the therapeutic dosage range ranges between 40% and 60% of the total drug in the body and is proportional to dose, since the tissue sites are not saturated with the usual clinical doses.

Figure 1 shows the amount of oxaprozin in the plasma and in the tissue as a function of dose and the concentration of the free drug.

Figure 1.

Amount of oxaprozin in plasma and tissue as a function of dose and free (unbound) oxaprozin concentration.



Unbound oxaprozin is the pharmacologically active component; it is able to distribute into tissues and to be cleared from the body. The average unbound concentration is a function of the tissue-bound and plasma-bound drug, and it increases proportionally with dose.

As the amount of oxaprozin in the tissues increases at higher dose, the plasma concentration of oxaprozin is limited by saturation of plasma protein binding. In addition, the increase in free (unbound) oxaprozin results in an increase in clearance. Both of these contribute to the total plasma concentration of oxaprozin increasing less than proportionately with dose.

Oxaprozin kinetics were modeled using a two-compartment model with first-order absorption and protein binding that becomes saturable in the clinical dosage range. As the dose is increased from 600 to 1200 mg daily, the steady state clearance of total oxaprozin increases from 0.25 to 0.34 L/hr, the steady state apparent volume of distribution increases from 10 to 12.5 L, and the accumulation half-life decreases from 25 to 21 hours. The terminal elimination half-life is approximately twice as long as the accumulation half-life because of the increased binding and decreased clearance at lower concentrations. Steady state concentrations in clinical usage are achieved in 4 to 7 days.

Plasma levels of total oxaprozin (free and bound drug) in studies of patients taking 600 to 1200 mg/day for several months ranged from 98 to 230 mcg/mL, corresponding to estimated levels of free drug ranging from about 0.10 to 0.40 mcg/mL.

Oxaprozin is primarily metabolized in the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). A small amount (< 5%) of active phenolic metabolites is produced, but the contribution to overall activity is minimal. All conjugated metabolites are inactive.

Biliary excretion of unchanged oxaprozin is a minor elimination pathway, and enterohepatic recycling of oxaprozin is insignificant. The glucuronide metabolites can be recovered from the urine (65%) and feces (35%), while unchanged oxaprozin is poorly excreted.

Renal dysfunction appears to alter oxaprozin binding and to reduce unbound clearance and unbound volume of distribution; dosage reductions should be made (see PRECAUTIONS-

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Age, gender, and well-compensated cardiac failure do not affect the plasma protein binding or the pharmacokinetics of oxaprozin.

Like other NSAIDs exhibiting a high degree of protein binding and a primarily metabolic route of elimination, oxaprozin has the potential for drug-drug interactions (see PRECAUTIONS: Drug Interactions).

CLINICAL STUDIES: 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 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 INDIVIDUALIZATION OF DOSAGE).

INDIVIDUALIZATION OF DOSAGE: Oxaprozin, like other NSAIDs, shows considerable interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Therefore, the dosage for each patient should be individualized according to the patient's response to therapy.

The usual starting dose for most normal weight patients with rheumatoid arthritis is 1200 mg, once a day.

The usual starting dose for normal weight patients with mild to moderate osteoarthritis is 600 mg, once a day.

In cases where a quick onset of action is important, the pharmacokinetics of oxaprozin allow therapy to be started with a <u>one-time</u> loading dose of 1200 to 1800 mg (not to exceed 26 mg/kg).

Doses larger than 1200 mg/day 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.

The maximum recommended total daily dosage is 1800 mg in divided doses.

Most patients will tolerate once-a-day dosing with oxaprozin, although divided doses may be tried in patients unable to tolerate single doses. As with all drugs of this class, the frequency and severity of adverse events will depend on the dose of the drug, the age and physical condition of the patient, any concurrent medical diagnoses, individual vulnerability, and the duration of therapy. In clinical trials of oxaprozin, no clear dose-response relationship was seen for serio-

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 INDIVIDUALIZATION OF DOSAGE).

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Experience with other NSAIDs has shown that starting therapy with maximal doses in patients at increased risk due to renal or hepatic disease, low body weight, advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects is likely to increase the frequency of adverse events and is not recommended (see PRECAUTIONS).

INDICATIONS AND USAGE: Oxaprozin tablets are indicated for acute and long-term use in the management of the signs and symptoms of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS: Oxaprozin tablets should not be used in patients with previously demonstrated hypersensitivity to oxaprozin tablets or any of its components or in individuals with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).

Severe and occasionally fatal asthmatic and anaphylactic reactions have been reported in patients receiving NSAIDs, and there have been rare reports of anaphylaxis in patients taking oxaprozin tablets.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY: Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Although minor upper gastrointestinal problems, such as dyspepsia, are common, and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials for several months to 2 years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Patients at risk for developing peptic ulceration and bleeding are those with a prior history of serious GI events, alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in these populations. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory drugs

5

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PRECAUTIONS: General: ***Hepatic Effects:*** As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or resolve with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGOT (AST) occurred in controlled clinical trials of oxaprozin in just under 1% of patients. 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 more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice have been reported with oxaprozin, and there may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, fever), oxaprozin should be discontinued.

Well-compensated hepatic cirrhosis does not appear to alter the disposition of unbound oxaprozin, so dosage adjustment is not necessary. However, the primary route of elimination of oxaprozin is hepatic metabolism, so caution should be observed in patients with severe hepatic dysfunction.

Renal Effects: Acute interstitial nephritis, hematuria, and proteinuria have been reported with oxaprozin as with other NSAIDs. Long-term administration of some nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. This was not observed with oxaprozin, but the clinical significance of this difference is unknown.

A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow, where the renal prostaglandins have a supportive 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 may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with previously impaired renal function, heart failure, or liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is often followed by recovery to the pretreatment state. Those patients at high risk who chronically take oxaprozin should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, or loss of appetite. As with all NSAID therapy, patients may occasionally

develop some elevation of serum creatinine and BUN levels without any signs or symptoms.

The pharmacokinetics of oxaprozin may be significantly altered in patients with renal insufficiency or in patients who are undergoing hemodialysis. Such patients should be started on doses of 600 mg/day, with cautious dosage increases if the desired effect is not obtained. Oxaprozin is not dialyzed because of its high degree of protein binding.

Like other NSAIDs, oxaprozin may worsen fluid retention by the kidneys in patients with uncompensated cardiac failure due to its effect on prostaglandins. It should be used with caution in patients with a history of hypertension, cardiac decompensation, in patients on chronic diuretic therapy, or in those with other conditions predisposing to fluid retention.

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.

Recommended Laboratory Testing: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS).

Anemia may occur in patients receiving oxaprozin or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythrogenesis. Patients on long-term treatment with oxaprozin should have their hemoglobin or hematocrit values determined at appropriate intervals as determined by the clinical situation.

Oxaprozin, like other NSAIDs, can affect platelet aggregation and prolong bleeding time. Oxaprozin should be used with caution in patients with underlying hemostatic defects or in those who are undergoing surgical procedures where a high degree of hemostasis is needed.

Information for Patients: Oxaprozin, like other drugs of its class, nonsteroidal anti-inflammatory drugs (NSAIDs), is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis, but they may also be commonly employed for conditions that are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of oxaprozin treatment, particularly in less-serious conditions where treatment without oxaprozin may represent an acceptable alternative to both the patient and the physician.

Patients receiving oxaprozin may benefit from physician instruction in the symptoms of the more common or serious gastrointestinal, renal, hepatic, hematologic, and dermatologic adverse effects.

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.

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.

Oral Anticoagulants: The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of oxaprozin. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants.

H_2-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 moni-

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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 lithium and cardiac glycosides has not been studied.

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/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2) 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:*** There are no adequate or well-controlled studies in pregnant women. 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/m^2). 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). Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Labor and Delivery: The effect of oxaprozin in pregnant women is unknown. NSAIDs are known to delay parturition, to accelerate closure of the fetal ductus arteriosus, and to be associated with dystocia. Oxaprozin is known to have caused decreases in pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided.

Nursing Mothers: Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women.

Pediatric Use: Safety and effectiveness of oxaprozin in pediatric patients have not been established.

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.

Although selected elderly patients in controlled clinical trials tolerated oxaprozin 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.

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ADVERSE REACTIONS: 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%.

The adverse event rates below refer to the incidence in the first month of use. Most of the events were seen by this time for common adverse reactions. However, the cumulative incidence can be expected to rise with continued therapy, and some events, such as gastrointestinal bleeding (see WARNINGS), seem to occur at a constant or possibly increasing rate over time.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were nausea (8%) and dyspepsia (8%).

Incidence Greater Than 1%: In clinical trials the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with oxaprozin are indicated by an asterisk (*); those reactions occurring in less than 3% of patients are unmarked.

Digestive System: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting.

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

Skin and Appendages: rash*.

Special Senses: tinnitus.

Urogenital System: dysuria or frequency.

Incidence Less Than 1%: *Probable Causal Relationship*: The following adverse reactions were reported in clinical trials or from worldwide marketing experience at an incidence of less than 1%. Those reactions reported only from worldwide marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions.

Body as a Whole: drug hypersensitivity reactions including anaphylaxis *and serum sickness*.

Cardiovascular System: edema, blood pressure changes.

Digestive System: peptic ulceration and/or GI bleeding (see WARNINGS), liver function abnormalities including *hepatitis* (see PRECAUTIONS), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis*.

Hematologic System: anemia, thrombocytopenia, leukopenia, ecchymeses, *agranulocytosis, pancytopenia*.

Metabolic System: weight gain, weight loss.

Nervous System: weakness, malaise.

Respiratory System: symptoms of upper respiratory tract infection.

Skin: pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)*.

Special Senses: blurred vision, conjunctivitis.

Urogenital: acute interstitial nephritis, nephrotic syndrome, hematuria, renal insufficiency, *acute renal failure*, decreased menstrual flow.

Causal Relationship Unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circum-

incidence greater than 1% in clinical trials, the following adverse reactions occurred at an incidence greater than 1% and are probably related to treatment. Reactions occurring in 3% to 9% of patients treated with oxaprozin are indicated by an asterisk (*); those reactions occurring in less than 3% of patients are unmarked.

Digestive System: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting.

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

Skin and Appendages: rash*.

Special Senses: tinnitus.

Urogenital System: dysuria or frequency.

Incidence Less Than 1%: *Probable Causal Relationship:* The following adverse reactions were reported in clinical trials or from worldwide marketing experience at an incidence of less than 1%. Those reactions reported only from worldwide marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions.

Body as a Whole: drug hypersensitivity reactions including anaphylaxis *and serum sickness.*

Cardiovascular System: edema, blood pressure changes.

Digestive System: peptic ulceration and/or GI bleeding (see WARNINGS), liver function abnormalities including *hepatitis* (see PRECAUTIONS), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis.*

Hematologic System: anemia, thrombocytopenia, leukopenia, ecchymoses, *agranulocytosis, pancytopenia.*

Metabolic System: weight gain, weight loss.

Nervous System: weakness, malaise.

Respiratory System: symptoms of upper respiratory tract infection.

Skin: pruritus, urticaria, photosensitivity, *pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome).*

Special Senses: blurred vision, conjunctivitis.

Urogenital: acute interstitial nephritis, nephrotic syndrome, hematuria, renal insufficiency, *acute renal failure,* decreased menstrual flow.

Causal Relationship Unknown: The following adverse reactions occurred at an incidence of less than 1% in clinical trials, or were suggested from marketing experience, under circumstances where a causal relationship could not be definitely established. They are listed as alerting information for the physician.

Cardiovascular System: palpitations.

Digestive System: alteration in taste.

Respiratory System: sinusitis, pulmonary infections.

Skin and Appendages: alopecia.

Special Senses: hearing decrease.

Urogenital System: increase in menstrual flow.

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

OVERDOSAGE: 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.

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 AND ADMINISTRATION: Rheumatoid Arthritis: The usual daily dose of oxaprozin tablets in the management of the signs and symptoms of rheumatoid arthritis is 1200 mg (two 600 mg tablets) once a day. Both smaller and larger doses may be required in individual patients (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The usual daily dose of oxaprozin tablets for the management of the signs and symptoms of moderate to severe osteoarthritis is 1200 mg (two 600 mg tablets) once a day. For patients of low body weight or with milder disease, an initial dosage of one 600 mg tablet once a day may be appropriate (see INDIVIDUALIZATION OF DOSAGE).

Regardless of the indication, the dosage should be individualized to the lowest effective dose of oxaprozin

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Forced diuresis, alkalinization of the urine, or hemoperfusion would probably not be useful due to the high degree of protein binding of oxaprozin.

DOSAGE AND ADMINISTRATION: Rheumatoid Arthritis: The usual daily dose of oxaprozin tablets in the management of the signs and symptoms of rheumatoid arthritis is 1200 mg (two 600 mg tablets) once a day. Both smaller and larger doses may be required in individual patients (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The usual daily dose of oxaprozin tablets for the management of the signs and symptoms of moderate to severe osteoarthritis is 1200 mg (two 600 mg tablets) once a day. For patients of low body weight or with milder disease, an initial dosage of one 600 mg tablet once a day may be appropriate (see INDIVIDUALIZATION OF DOSAGE).

Regardless of the indication, the dosage should be individualized to the lowest effective dose of oxaprozin tablets to minimize adverse effects, and the maximum recommended total daily dose is 1800 mg (or 26 mg/kg, whichever is lower) in divided doses.

SAFETY AND HANDLING: Oxaprozin 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: Oxaprozin Tablets are available containing 600 mg of oxaprozin. The tablets are white, film-coated, oval, biconvex, beveled edge tablets debossed with 11 to the left of the score and 77 to the right of the score on one side of the tablet and **MYLAN** on the other side. They are available as follows:

NDC 0378-1177-01
bottles of 100 tablets
NDC 0378-1177-05
bottles of 500 tablets

STORE AT ROOM TEMPERATURE 15° TO 30°C (59° TO 86°F).
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

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