DAYPRO®

(oxaprozin) 600mg Caplets

Cardiovascular Risk

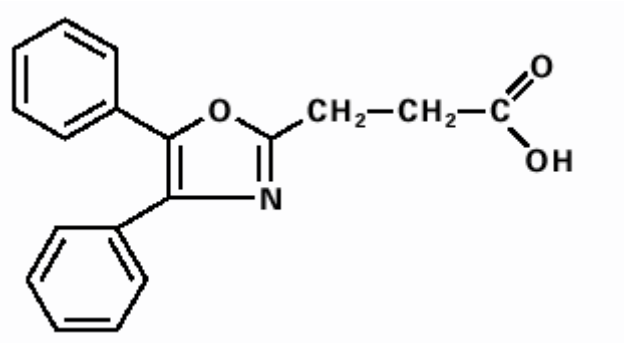
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (see **WARNINGS**)**.**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

Gastrointestinal Risk

- NSAID's 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

DAYPRO (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.

Daypro oral caplets contain 600 mg of oxaprozin.

Inactive ingredients in Daypro oral caplets are microcrystalline cellulose, hypromellose, methylcellulose, magnesium stearate, polacrilin potassium, starch, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

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

Pharmacokinetics (see Table 1)

Absorption: DAYPRO 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 DAYPRO 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
T_{max} (hr)	3.09 (39)	2.44 (40)	3.03 (48)	2.33 (35)
Oral Clearance (L/hr/70 kg)	0.150 (24)	0.301 (29)	136 (24)	102 (45)
Apparent Volume of Distribution at Steady State (Vd/F; L/70 kg)	11.7 (13)	16.7 (14)	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 (AUC_{0-24}) to unbound oxaprozin in JRA patients relative to adult rheumatoid arthritis patients suggest dose to body weight range relationships as shown in Table 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_{0-24hr}) to unbound oxaprozin in JRA patients relative to 70 kg adult rheumatoid arthritis patients administered oxaprozin 1200 mg QD[1]

Dose (mg)	Body WeightRange (kg)
600	22 –31
900	32 –54
1200	≥ 55

[1]Model-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

Rheumatoid arthritis: DAYPRO was evaluated for managing the signs and symptoms of rheumatoid arthritis in placebo and active controlled clinical trials in a total of 646 patients. DAYPRO 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.

DAYPRO 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, DAYPRO may be better tolerated in divided doses. Due to its long half-life, several days of Daypro therapy were needed for the drug to reach its full effect (see **DOSAGE AND ADMINISTRATION, Individualization of dosage**).

Osteoarthritis: DAYPRO 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. Daypro 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 DAYPRO and other treatment options before deciding to use DAYPRO. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals (see **WARNINGS**).

DAYPRO 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

DAYPRO is contraindicated in patients with known hypersensitivity to oxaprozin.

DAYPRO 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**).

DAYPRO is contraindicated for the treatment of peri-operative pain in the setting of coronary artery

bypass graft (CABG) surgery (see **WARNINGS**).

WARNINGS

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 DAYPRO, 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 DAYPRO, 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. DAYPRO should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Effects–Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including DAYPRO, 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.

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 form controlled clinical studies regarding the use of DAYPRO in patients with advanced renal disease. Therefore, treatment with DAYPRO is not recommended in these patients with advanced renal disease. If DAYPRO therapy must be initiated, close monitoring of the patients renal function is advisable.

Anaphylactoid reactions As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to DAYPRO. DAYPRO 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 DAYPRO, 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, DAYPRO should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

DAYPRO 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 DAYPRO 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 DAYPRO. 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 DAYPRO. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), DAYPRO 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 DAYPRO. 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 DAYPRO 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 DAYPRO 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, DAYPRO 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.

- DAYPRO, 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**).

- DAYPRO, 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**).

- DAYPRO, 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, Anaphylactoid reactions**).

- In late pregnancy, as with other NSAIDs, DAYPRO 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 of 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, DAYPRO should be discontinued.

Drug interactions

Aspirin Concomitant administration of DAYPRO 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 AUC_{0-24} and C_{max}) and its active metabolite enalaprilat (significant increase in dose-adjusted AUC_{0-24}). This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Diuretics

Clinical studies, as well as post marketing observations, have shown that DAYPRO 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

DAYPRO, 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.

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 DAYPRO 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 DAYPRO 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 DAYPRO. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of DAYPRO therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish DAYPRO 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/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

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). 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 DAYPRO 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 DAYPRO, 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 DAYPRO 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 DAYPRO 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 DAYPRO 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 DAYPRO 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.

DAYPRO is substantially excreted by the kidney, and the risk of toxic reactions to DAYPRO 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

Adverse reaction data were derived from patients who received DAYPRO 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 DAYPRO 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 DAYPRO 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

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

OVERDOSAGE

No patient experienced either an accidental or intentional overdosage of DAYPRO 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 AND ADMINISTRATION

Carefully consider the potential benefits and risks of DAYPRO and other treatment options before deciding to use DAYPRO. 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 DAYPRO, 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 caplets) 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 caplets) 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 DAYPRO, 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 DAYPRO to minimize adverse effects. The **maximum** recommended total daily dose of DAYPRO 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 allows 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 DAYPRO, although divided doses may be tried in patients unable to tolerate single doses.

SAFETY AND HANDLING

DAYPRO 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

DAYPRO 600-mg caplets are white, capsule-shaped, scored, film-coated, with DAYPRO debossed on one side and 1381 on the other side.

NDC Number	**Size**
0025-1381-31	bottle of 100
0025-1381-51	bottle of 500
0025-1381-34	carton of 100 unit dose

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

℞ only

Distributed by

G.D. Searle LLC
Division of Pfizer Inc, NY, NY 10017

DAYPRO®
oxaprozin caplets

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Medication Guide
for
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
(See the end of this Medication Guide for a list of prescription NSAID medicines.)

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 use 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:	**Other 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	• 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
- skin rash or blisters with fever
- unusual weight gain
- 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.

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
Flurbiprofen	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-Naproxyn, 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) NSAIDs, and is usually used for less than 10 days to treat pain. The OTC NSAID 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.