January 25, 2002

SEARLE

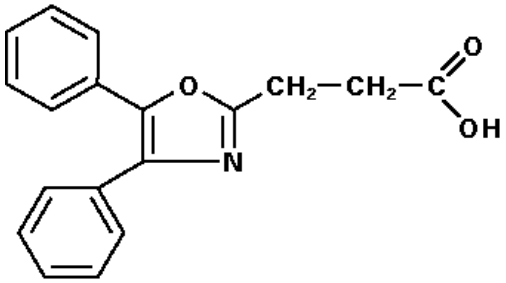
Daypro®

(oxaprozin) Caplets

600 mg

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, hydroxypropyl methylcellulose, 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
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 (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 Weight Range (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 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 **Precautions: *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

Daypro is indicated for relief of the signs and symptoms of osteoarthritis, adult rheumatoid arthritis and 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.**)

WARNINGS

Gastrointestinal (GI) Effects-Risk of GI Ulceration, Bleeding and Perforation

Serious gastrointestinal toxicity, such as inflammation, bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients, who develop a serious upper GI adverse event on NSAID therapy, is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to 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 thus, 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. 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, the lowest effective dose should be used for the shortest possible duration.** For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age and poor general health status.

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.

Advanced Renal Disease In cases with advanced kidney disease, treatment with Daypro is not recommended. If Daypro therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS – Renal Effects).

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.

Renal effects: Caution should be used when initiating treatment with Daypro in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with Daypro. Caution is also recommended in patients with pre-existing kidney disease (see **WARNINGS – Advanced Renal Disease**).

As with other NSAIDs, long-term administration of Daypro has resulted in renal papillary necrosis and other renal medullary changes. Renal toxicity has also been seen in patients in which 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 nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Daypro metabolites are eliminated primarily by the kidneys. The extent to which the metabolites may accumulate in patients with renal failure has not been studied. As with other NSAIDs, metabolites of which are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

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, gastrointestinal 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.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

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. Daypro does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT). 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.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs. Therefore, as with other NSAIDs, Daypro should be used with caution in patients with fluid retention, hypertension, or heart failure.

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: Daypro, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious gastrointestinal 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. Patients should be apprised of the importance of this follow-up (see **WARNINGS, Risk of Gastrointestinal Ulceration, Bleeding and Perforation**).

Patients should report to their physicians the signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, weight gain, or edema.

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 also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see **WARNINGS**).

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

Laboratory Tests 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.

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.

Furosemide: 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 **PRECAUTIONS, Renal Effects**), as well as to assure diuretic efficacy.

Lithium: Coadministration of oxaprozin with lithium carbonate can cause an increase in serum lithium levels. Whenever oxaprozin is added to or removed from patients on lithium therapy, therapeutic drug monitoring of lithium levels should be performed.

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.

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. 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 of Daypro in pediatric patients less than 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 Daypro 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 **PRECAUTIONS *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 or in patients taking other NSAIDs (indicated by double asterisks**), the following adverse reactions occurred at an incidence greater than 1%. Reactions occurring in 3% to 9% of patients treated with Daypro are indicated by an asterisk(*); those reactions occurring in less than 3% of patients are unmarked.

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 (double asterisks**).

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

Cardiovascular system: edema, blood pressure changes, congestive heart failure**, hypertension**, palpitations, tachycardia**, syncope**.

Digestive system: alteration in taste, dry mouth**, esophagitis**, gastritis**, glossitis**, hematemesis**, jaundice**, peptic ulceration and/or GI bleeding (see **WARNINGS**), liver function abnormalities including *hepatitis* (see **PRECAUTIONS**), stomatitis, hemorrhoidal or rectal bleeding, *pancreatitis*.

Hematologic system: *agranulocytosis*, anemia, ecchymoses, eosinophilia**, melena**, *pancytopenia, purpura***, thrombocytopenia, leukopenia.

Metabolic system: weight changes.

Nervous system: anxiety**, asthenia**, confusion**, depression**, dream abnormalities**, drowsiness**, insomnia**, malaise, nervousness**, paresthesia**, somnolence**, tremors**, vertigo**, weakness.

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

Skin: alopecia, angioedema**, pruritus, 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**, dysuria**, 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

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 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 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.

Rx only **(date)**

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