DAYPRO ALTA™
(oxaprozin potassium) 600mg tablets

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. Patient's with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS**).

- Daypro ALTA™ is contraindicated for treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

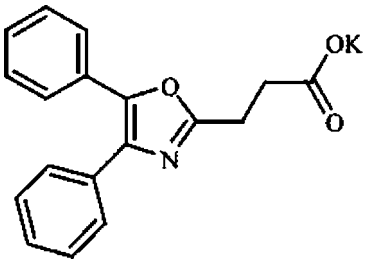
Gastrointestinal Risk

- 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 ALTA (oxaprozin potassium tablets) is a member of the propionic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each blue, capsule-shaped tablet contains oxaprozin potassium (678mg equivalent to 600mg of oxaprozin) for oral administration. The chemical name for oxaprozin potassium is 4,5-diphenyl-2-oxazolepropionic acid, potassium salt. Its empirical formula is $C_{18}H_{14}NO_3K$, and molecular weight is 331. Oxaprozin potassium is a white to off white powder with a melting point of 215°C. It is slightly soluble in alcohol and very soluble in water. The PK in water is 9.7.

It has the following structural formula:



Inactive ingredients in DAYPRO ALTA tablets include microcrystalline cellulose, hydroxypropyl methylcellulose, pregelatinized corn starch, stearic acid, colloidal silicon dioxide, polyethylene glycol, titanium dioxide, FD&C Blue #1 Aluminum Lake, and pharmaceutical glaze.

CLINICAL PHARMACOLOGY

Pharmacodynamics: DAYPRO ALTA, the potassium salt of oxaprozin, is a nonsteroidal anti-inflammatory drug (NSAID), which dissociates into the active moiety oxaprozin *in vivo*. Oxaprozin has been shown to have anti-inflammatory, analgesic, and antipyretic properties in animal models. The

mechanism of action of DAYPRO ALTA, like that of other NSAIDs, is not completely understood but may be related to prostaglandin synthetase inhibition.

Pharmacokinetics: (see Table 1)

Absorption: After oral administration, DAYPRO ALTA dissociates into free oxaprozin which is 95% absorbed. Peak plasma concentration occurs at about 1 hour and 45 minutes after single dose administration (see Table 1). When DAYPRO ALTA is administered with food, the peak concentration of oxaprozin is delayed by about 45 minutes, but the extent of absorption is unchanged. Antacids do not significantly affect the extent and rate of oxaprozin absorption.

Table 1
Oxaprozin Pharmacokinetic Parameters with DAYPRO **ALTA Dosing (1200mg); Mean (%CV)**
Healthy Adults (18-42 years; N= 12-24)

	Total Drug		Unbound Drug	
	Single	Multiple	Single	Multiple
T_{max}(hr)	1.67(65)	2.13 (64)	1.71 (63)	1.59(38)
Oral Clearance (Llhr/70 kg)	0.125 (15)	0.289 (17)	123 (20)	86.7 (33)
Apparent Volume of Distribution at steady state (Vd/T; L/70 kg)	10.14(11)	16.24 (38)	7741 (18)	2067(38)
Elimination Half-life (hr)	57.0(15)	38.0(29)	44.8 (23)	16.4 (11)

Distribution: In dose proportionality studies utilizing 600, 1200 and 1800 mg doses, the pharmacokinetics of oxaprozin in healthy subjects has 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. Concentration dependent changes in the protein binding also resulted in changes in the oxaprozin volume of distribution, which increased for the total drug but decreased for the unbound drug. The apparent volume of distribution (Vd/F) of total oxaprozin is approximately 10-16 L/70 kg. Oxaprozin potassium 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 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 excreted in human urine or feces are considered not to have significant pharmacologic activity. Oxaprozin is primarily metabolized by the liver, by both microsomal oxidation (65%) and glucuronic acid conjugation (35%). Ester and ether glucuronides are the major conjugated metabolites of oxaprozin. A small amount (<5%) of active phenolic metabolites is produced, but the contribution to overall activity is limited.

Excretion: Sixty-five percent (65%) of the dose is excreted into the urine and 35% in the feces as metabolites. Renal elimination of oxaprozin metabolites is a major pathway of elimination. Biliary excretion of unchanged oxaprozin is a minor pathway. After multiple doses of DAYPRO ALTA

(1200mg QD), post-steady state mean elimination half-lives of total oxaprozin and protein unbound oxaprozin were 38.0 and 16.4 hrs, respectively (see Table 1).

Special Populations

Pediatric: DAYPRO ALTA has not been investigated in patients <16 years of age.

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 pharmacokinetic reasons, although many elderly may need a reduced dose due to low body weight or disorders associated with aging.

Gender: No differences in pharmacokinetic parameters have been observed between male and female subjects in studies of DAYPRO ALTA.

Race: Pharmacokinetic differences due to race have not been identified in studies of DAYPRO ALTA.

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 has been investigated in patients with renal insufficiency. Oxaprozin's renal clearance decreased proportionally with creatinine clearance (CrCl). 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**).

Drug Interactions
(Also see **PRECAUTIONS, Drug Interactions**)

General: 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.

CLINICAL STUDIES
Osteoarthritis: DAYPRO ALTA 1200 mg once daily was evaluated for the relief of the signs and symptoms of osteoarthritis in a 6-month placebo-controlled study versus oxaprozin acid in over 300 patients. In this trial, treatment with DAYPRO ALTA resulted in improvement in WOMAC (Western Ontario and McMaster Universities) osteoarthritis index, a composite of pain, stiffness, and functional measures in OA. DAYPRO ALTA demonstrated significant reduction in joint pain compared to placebo and was found to be comparable to 1200 mg once daily of oxaprozin acid.

With respect to GI events, DAYPRO ALTA appeared to be less well tolerated than oxaprozin acid in this study. The rates for symptomatic ulcers (2.2%) and nausea (13%) for DAYPRO ALTA treated patients were higher than the rates observed with oxaprozin acid (0% and 6%, respectively) (see **ADVERSE REACTIONS**).

Rheumatoid arthritis: Oxaprozin, the active component of DAYPRO ALTA (oxaprozin potassium tablets), was evaluated for the relief of 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.

INDICATIONS AND USAGE

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

DAYPRO ALTA is indicated:

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

CONTRAINDICATIONS

DAYPRO ALTA is contraindicated in patients with known hypersensitivity to oxaprozin potassium.

DAYPRO ALTA 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 – Pre-existing Asthma**).

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

Gastrointestinal Effects - Risk of Ulceration, Bleeding, and Perforation
NSAIDs, including DAYPRO ALTA, 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 from controlled clinical studies regarding the use of DAYPRO ALTA in patients with advanced renal disease. Therefore, treatment with DAYPRO ALTA is not recommended in these patients with advanced renal disease. If DAYPRO ALTA therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to DAYPRO ALTA. DAYPRO ALTA 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 - Pre-existing Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
NSAIDs, including DAYPRO ALTA, 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 an 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 ALTA should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS
General
DAYPRO ALTA should not be used concomitantly with other oxaprozin-containing products, since all such products circulate in the plasma as the oxaprozin anion.

DAYPRO ALTA 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 ALTA 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 ALTA. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing 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 fulminant 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 ALTA. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.). DAYPRO ALTA 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 clinical trials.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including DAYPRO ALTA. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including DAYPRO ALTA, should have their hemoglobin or hematocrit checked 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 ALTA 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 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 ALTA 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 ALTA, 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 ALTA, 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 ALTA, 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 ALTA 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 or 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 ALTA should be discontinued.

Drug Interactions
Aspirin
When DAYPRO ALTA is administered with aspirin, its protein binding is reduced, although the clearance of free DAYPRO ALTA is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of oxaprozin potassium and aspirin is not generally recommended because of the potential of 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% decrease in oral plasma 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. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors. Oxaprozin has been shown to alter the pharmacokinetics of enalapril (significant decrease in dose-adjusted $AUC_{0\text{-}24hr}$ and C_{max}) and its active metabolite enalaprilat (significant increase in dose-adjusted $AUC_{0\text{-}24}$).

Diuretics
Clinical studies, as well as post-marketing observations, have shown that DAYPRO ALTA 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 patients should be observed closely for signs of renal failure (see **WARNINGS**, **Renal Effects**), as well as to assure diuretic efficacy.

Lithium
DAYPRO ALTA, like other NSAIDs, has produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration was increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by NSAIDs. Thus, when NSAIDs and lithium are administered concurrently, lithium level should be monitored and subjects should be observed carefully for signs of lithium toxicity.

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

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 or the magnitude or duration of control. However, it is advisable to monitor patients' blood glucose in the beginning phase of glyburide and oxaprozin co-therapy.

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 once daily with 100 mg metoprolol twice daily exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days. Therefore, routine blood pressure monitoring should be considered in these patients when starting oxaprozin therapy.

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

maybe expected for several days following discontinuation of oxaprozin therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish oxaprozin from benzodiazepines.

Carcinogenesis, mutagenesis, impairment of fertility

In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown.

Oxaprozin did not display mutagenic potential. No evidence of genetic toxicity or cell-transforming ability was found in test 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, or cell transformation testing in mouse fibroblast.

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200mg/kg/day (1180 mg/m^2/day); the usual human dose is 17 mg/kg/day, or (629 mg/m^2/day). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2/day) 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 200mg/kg/day of oxaprozin (225 to 900 mg/m^2/day). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30mg/kg/day of oxaprozin (the usual human dosage range). Animal reproduction studies are not always predictive of human response. Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risk 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 ALTA 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 ALTA, 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 ALTA in pediatric patients have not been established.

Geriatric Use

Age was not shown to have an effect on the pharmacokinetics of DAYPRO ALTA following 600,

1200 and 1800 rug doses or on the incidence of adverse reactions reported (see **CLINICAL PHARMACOLOGY**, **Special Populations**). In a controlled 6-month clinical trial of 803 patients (322 of whom received DAYPRO ALTA), about 40% of whom were elderly, there was basically no difference detected in terms of the total number of subjects reporting adverse events with respect to age. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients. Caution should be exercised in treating the elderly (65 years and older), and extra care should be taken when choosing a dose.

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

In patients taking DAYPRO ALTA (oxaprozin potassium tablets), oxaprozin, or other NSAIDs , the following are the most frequently reported adverse experiences occurring in approximately 1-10% of patients (see **CLINICAL STUDIES**, **Osteoarthritis**):

Gastrointestinal experiences including:

~~abdominal~~Abdominal pain, anorexia, constipation, diarrhea, dyspepsia, flatulence, gross gastrointestinal bleeding/perforation, GI ulcers (gastric/duodenal), heartburn, nausea, vomiting.

Non-gastrointestinal experiences including:

abnormal renal function, anemia, confusion, depression, disturbance of sleep, dizziness, dysuria or frequency, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, sedation, somnolence, tinnitus.

Additional adverse experiences reported in less than 1% of patients:

Body as a whole-- anaphylactic reactions, appetite changes, death, fever, infection, sepsis, serum sickness.

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

Digestive system-- alteration in taste, dry mouth, eructation, esophagitis, gastritis, glossitis, hematemesis, hemorrhoidal or rectal bleeding, hepatitis, jaundice, liver failure, pancreatitis, stomatitis.

Hemic and lymphatic system-- agranulocytosis, aplastic anemia, ecchymosis, eosinophilia, hemolytic anemia, leukopenia, lymphadenopathy, melena, pancytopenia, purpura, thrombocytopenia.

Metabolic and nutritional-- 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, pneumonia, pulmonary infections, respiratory depression, sinusitis, symptoms of upper respiratory tract infection.

Skin and appendages-- alopecia. angioedema, increased sweating, photosensitivity, pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis

(Lyell'ssyndrome), urticaria.

Special senses-- blurred vision, conjunctivitis, hearing impairment.

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

OVERDOSAGE

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Hypertension, acute renal failure, respiratory depression and coma may occur, but 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 NSAID overdose, There are no specific antidotes. Emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) and/or osmotic cathartic maybe indicated in patients seen within 4 hours of ingestion with symptoms or following a large overdose (5 to 10 times the usual dose). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

DOSAGE AND ADM1NISTRATION

Carefully consider the potential benefits and risks of DAYPRO ALTA and other treatment options before deciding to use DAYPRO ALTA. 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 ALTA, the dose and frequency should be adjusted to suit an individual patient's needs.

Osteoarthritis and Rheumatoid Arthritis: The recommended dose of DAYPRO ALTA for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis is 1200 mg (two 600 mg tablets) once a day. Divided doses may be tried in patients unable to tolerate single doses. For osteoarthritis patients of low body weight of with milder disease, an initial dose of one 600 mg tablet once a day may be appropriate. The maximum total daily dose is 1200 mg.

HOW SUPPLIED

DAYPRO ALTA 600 mg tablets are blue, capsule-shaped, film-coated, with Searle 1391 printed on one side.

NDC Number	***Size***
0025-5500-01	**bottle of 100**
0025-5500-03	**bottle of 500**
0025-5500-02	**carton of 100** unit **dose**

Store at 25ºC (77ºF); excursions permitted to 15-30ºC (59-86ºF) (see USP Controlled Room Temperature) in tightly-closed container. Protect from moisture.

Rx only

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DAYPRO ALTA™
(oxaprozin potassium tablets)

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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
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- 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-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)
Oxaprozin	Daypro
Piroxicam	Feldene
Sulindac	Clinoril
Tolmetin	Tolectin, Tolectin DS, Tolectin 600

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~~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-Naprosyn, Naprelan, Naprapac (copackaged with lansoprazole)~~

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~~Oxaprozin~~	~~Daypro~~
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~~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.