PRODUCT MONOGRAPH

DAYPRO*

Oxaprozin

600 mg Caplets

Nonsteroidal anti-inflammatory drug (NSAID)

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Caplet / 600 mg	None are clinically relevant. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Daypro (oxaprozin) is indicated for acute and chronic use in the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

For patients with an increased risk of developing CV and/or GI adverse events, other management strategies that do NOT include the use of NSAIDs should be considered first. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

Use of Daypro should be limited to the lowest effective dose for the shortest possible duration of treatment in order to minimize the potential risk for cardiovascular or gastrointestinal adverse events. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS)

Daypro, as a NSAID, does NOT treat clinical disease or prevent its progression.

Daypro, as a NSAID, only relieves symptoms and decreases inflammation for as long as the patient continues to take it.

Geriatrics (>65 years of age):
Evidence from clinical studies and postmarket experience suggests that use in geriatric patients is associated with differences in safety or effectiveness (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Pediatrics (<18 years of age):
Safety and efficacy have not been established in pediatric patients (see **CONTRAINDICATIONS**).

CONTRAINDICATIONS

Daypro (oxaprozin) is contraindicated in:

- The peri-operative setting of coronary artery bypass graft surgery (CABG). Although Daypro has NOT been studied in this patient population, a selective COX-2 inhibitor NSAID studied in such a setting has led to an increased incidence of cardiovascular/thromboembolic events, deep surgical infections and sternal wound complications.
- The third trimester of pregnancy, because of risk of premature closure of the ductus arteriosus and prolonged parturition.
- Women who are breastfeeding, because of the potential for serious adverse reactions in nursing infants.
- Severe uncontrolled heart failure.
- Known or suspected hypersensitivity to oxaprozin or to any of the components/excipients.
- History of asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs (i.e. complete or partial syndrome of ASA-intolerance - rhinosinusitis, urticaria/angioedema, nasal polyps, asthma). Fatal anaphylactoid reactions have occurred in such individuals. Individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects. The potential for cross-reactivity between different NSAIDs must be kept in mind (see **WARNINGS AND PRECAUTIONS – Hypersensitivity Reactions –** ***Anaphylactoid Reactions***).
- Active gastric / duodenal / peptic ulcer, active GI bleeding, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.
- Cerebrovascular bleeding or other bleeding disorders.
- Inflammatory bowel disease.
- Significant hepatic impairment or active liver disease.
- Severely impaired (creatinine clearance <30 mL/min or <0.5mL/sec) or deteriorating renal function (individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored) (see **WARNINGS AND PRECAUTIONS – Renal**).
- Known hyperkalemia (see **WARNINGS AND PRECAUTIONS – Renal -** ***Fluid and Electrolyte Balance***)
- Daypro is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects (see **DRUG INTERACTIONS**).
- Children and adolescents less than 18 years of age.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Risk of Cardiovascular (CV) Adverse Events: Ischemic Heart Disease, Cerebrovascular Disease, Congestive Heart Failure (NYHA II-IV) (See WARNINGS AND PRECAUTIONS – Cardiovascular)

Daypro is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing Daypro to any patient with ischemic heart disease (including but NOT limited to acute myocardial infarction, history of myocardial infarction and/or angina), cerebrovascular disease (including but NOT limited to stroke, cerebrovascular accident, transient ischemic attacks and/or amaurosis fugax) and/or congestive heart failure (NYHA II-IV).

Use of NSAIDs, such as Daypro, can promote sodium retention in a dose-dependent manner, through a renal mechanism, which can result in increased blood pressure and/or exacerbation of congestive heart failure (see also WARNINGS AND PRECAUTIONS – Renal – *Fluid and Electrolyte Balance*)

Randomized clinical trials with Daypro have not been designed to detect differences in cardiovascular events in a chronic setting. Therefore, caution should be exercised when prescribing Daypro.

Risk of Gastrointestinal (GI) Adverse Events (see WARNINGS AND PRECAUTIONS – Gastrointestinal)

Use of NSAIDs, such as Daypro, is associated with an increased incidence of gastrointestinal adverse events (such as peptic/duodenal ulceration, perforation, obstruction and gastrointestinal bleeding).

General

Frail or debilitated patients may tolerate side effects less well and therefore special care should be taken in treating this population. **To minimize the potential risk for an adverse event, the lowest effective dose should be used for the shortest possible duration.** As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Daypro is NOT recommended for use with other NSAIDs, with the exception of low-dose ASA for cardiovascular prophylaxis, because of the absence of any evidence demonstrating

synergistic benefits and the potential for additive adverse reactions. (see **DRUG INTERACTIONS – Drug/Drug Interactions –** ***Acetylsalicylic acid (ASA) or other NSAIDs)***

Carcinogenesis and Mutagenesis:

(See **TOXICOLOGY**)

Cardiovascular

Daypro is a non-steroidal anti-inflammatory drug (NSAID). Use of some NSAIDs is associated with an increased incidence of cardiovascular adverse events (such as myocardial infarction, stroke or thrombotic events) which can be fatal. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Caution should be exercised in prescribing Daypro to patients with risk factors for cardiovascular disease, cerebrovascular disease or renal disease, such as any of the following (NOT an exhaustive list):

- **Hypertension**
- **Dyslipidemia / Hyperlipidemia**
- **Diabetes Mellitus**
- **Congestive Heart Failure (NYHA I)**
- **Coronary Artery Disease (Atherosclerosis)**
- **Peripheral Arterial Disease**
- **Smoking**
- **Creatinine Clearance < 60 mL/min or 1 mL/sec**

For patients with a high risk of developing an adverse CV event, other management strategies that do NOT include the use of NSAIDs should be considered first. **To minimize the potential risk for an adverse CV event, the lowest effective dose should be used for the shortest possible duration.**

Cardiovascular Thrombotic Events:

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 ASA mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of ASA and an NSAID does increase the risk of serious GI events (see **WARNINGS AND PRECAUTIONS - Gastrointestinal*)***.

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 patients treated with Daypro. Therefore, as with many other nonsteroidal anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. Daypro should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention. (See **WARNINGS AND PRECAUTIONS – Renal – *Fluid and Electrolyte Balance***).

Endocrine and Metabolism

With nonsteroidal anti-inflammatory treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

Corticosteroids:

Daypro (oxaprozin) is NOT a substitute for corticosteroids. It does NOT treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids. (see **DRUG INTERACTIONS – Drug-Drug Interactions – *Glucocorticoids)***

Gastrointestinal

Serious GI toxicity (sometimes fatal), such as peptic / duodenal ulceration, inflammation, perforation, obstruction and gastrointestinal bleeding, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, such as Daypro. Minor upper GI problems, such as dyspepsia, commonly occur at any time. Physicians should remain alert for ulceration and bleeding in patients treated with Daypro, even in the absence of previous GI tract symptoms. 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. (see **WARNINGS AND PRECAUTIONS – Special Population – *Geriatrics*)**

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to discontinue using Daypro and seek emergency medical attention if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding. The utility of periodic laboratory monitoring has NOT been

demonstrated, nor has it been adequately assessed. Most patients who develop a serious upper GI adverse event on NSAID therapy have no symptoms. In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation 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. Even short-term therapy has its risks.

The incidence of these complications increases with increasing dose.

Caution should be taken if prescribing Daypro to patients with a prior history of peptic / duodenal ulcer disease or gastrointestinal bleeding as these individuals have a greater than 10-fold higher risk for developing a GI bleed when taking a NSAID than patients with neither of these risk factors. Other risk factors for GI ulceration and bleeding include the following: *Helicobacter pylori* infection, increased age, prolonged use of NSAID therapy, excess alcohol intake, smoking, female gender, poor general health status, history of diverticulosis, ulcerative colitis, or Crohn's disease, or concomitant therapy with any of the following:

- Anti-coagulants (e.g. warfarin)
- Anti-platelet agents (e.g. ASA, clopidogrel)
- Oral corticosteroids (e.g. prednisone)
- Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)

If ulceration is suspected or confirmed, or if GI bleeding occurs, Daypro should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding.

There is no definitive evidence that the concomitant administration of sucralfate, histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of Daypro therapy when and if these adverse reactions appear.

Genitourinary

Some NSAIDs are associated with persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with Daypro should be stopped to ascertain if symptoms disappear. This should be done before any urological investigations or treatments are carried out.

Hematologic

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action such as those on anti-coagulants or suffering from haemophilia or platelet disorders should be carefully observed

when Daypro is administered.

Anti-coagulants:

Numerous studies have shown that the concomitant use of NSAIDs and anti-coagulants increases the risk of bleeding. Concurrent therapy of Daypro with warfarin requires close monitoring of the international normalized ratio (INR).

Even with therapeutic INR monitoring, increased bleeding may occur.

Anti-platelet Effects:

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike acetylsalicyclic acid (ASA), their effect on platelet function is quantitatively less, or of shorter duration, and is reversible.

Daypro and other NSAIDs have no proven efficacy as anti-platelet agents and should NOT be used as a substitute for ASA or other anti-platelet agents for prophylaxis of cardiovascular thromboembolic diseases. Anti-platelet therapies (e.g. ASA) should NOT be discontinued. There is some evidence that use of NSAIDs with ASA can markedly attenuate the cardioprotective effects of ASA. (see **DRUG INTERACTIONS – Drug-Drug Interactions – *Acetylsalicylic Acid (ASA) or other NSAIDs)***

Concomitant administration of Daypro with low dose ASA increases the risk of GI ulceration and associated complications.

Blood dyscrasias:

Blood dyscrasias (such as neutropenia, leucopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

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

Hepatic/Biliary/Pancreatic

As with other NSAIDs, borderline elevations of one or more liver function tests (AST, ALT, alkaline phosphatase) may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with nonsteroidal anti-inflammatory drugs.

Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop (e.g. jaundice etc.), or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If there is a need to prescribe this drug in the presence of impaired liver function, it must be done under strict observation.

Hypersensitivity Reactions

Anaphylactoid Reactions:

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to Daypro. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving Daypro. Daypro should NOT be given to patients with the ASA-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 ASA or other NSAIDs (see **CONTRAINDICATIONS**).

ASA-Intolerance:

Daypro should NOT be given to patients with complete or partial syndrome of ASA-intolerance (rhinosinusitis, urticaria/angioedema, nasal polyps, asthma) in whom asthma, anaphylaxis, urticaria/angioedema, rhinitis or other allergic manifestations are precipitated by ASA or other NSAIDs. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse reaction (see **CONTRAINDICATIONS**).

Cross-sensitivity:

Patients sensitive to one NSAID may be sensitive to any of the other NSAIDs as well.

Serious skin reactions:

(See **WARNINGS AND PRECAUTIONS – Skin**)

Immune

(See **WARNINGS AND PRECAUTIONS – Infection – *Aseptic Meningitis***)

Infection

Daypro, in common with other NSAIDs, may mask signs and symptoms of an underlying infectious disease.

Aseptic Meningitis:

Rarely, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissue diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the health care provider must be vigilant to the development of this complication.

Neurologic

Some patients may experience drowsiness, dizziness, blurred vision, vertigo, tinnitus, hearing loss ~~or~~ insomnia or depression with the use of NSAIDs, such as Daypro. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Ophthalmologic

Blurred and/or diminished vision have been reported with the use of Daypro and other nonsteroidal anti-inflammatory drugs. If such symptoms develop, Daypro should be discontinued and an ophthalmologic examination performed; ophthalmologic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Peri-Operative Considerations:

See **CONTRAINDICATIONS** – Coronary Artery Bypass Graft Surgery)

Psychiatric

Some patients may experience depression with the use of Daypro. (see **WARNINGS AND PRECAUTIONS – Neurologic**)

Renal

Long-term administration of nonsteroidal anti-inflammatory drugs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, low grade proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion and glomerular filtration rate (GFR). In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with pre-existing renal insufficiency (GFR <60 mL/min or 1 mL/s), dehydrated patients, patients on salt restricted diets, those with congestive heart failure, cirrhosis, liver dysfunction, those taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, cyclosporin, diuretics, and the elderly. Serious or life-threatening renal failure has been reported in patients with normal or impaired renal function after short term therapy with NSAIDs. Even patients at risk who demonstrated the ability to tolerate a NSAID under stable conditions may decompensate during periods of added stress (e.g. dehydration due to gastroenteritis). Discontinuation of NSAIDs is usually followed by recovery to the pre-treatment state.

Caution should be used when initiating treatment with NSAIDs, such as Daypro, in patients with considerable dehydration. Such patients should be rehydrated prior to initiation of therapy. Daypro and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with impaired renal function. In these cases, utilization of lower doses of Daypro should be considered and patients carefully monitored.

During long-term therapy, kidney function should be monitored periodically.

Advanced Renal Disease:

(see **CONTRAINDICATIONS**).

Fluid and Electrolyte Balance:

Use of NSAIDs, such as Daypro, can promote sodium retention in a dose-dependent manner, which can lead to fluid retention and edema, and consequences of increased blood pressure and exacerbation of congestive heart failure. Thus, caution should be exercised in prescribing Daypro in patients with a history of congestive heart failure, compromised cardiac function, hypertension, increased age or other conditions predisposing to fluid retention (see **WARNINGS AND PRECAUTIONS – Cardiovascular**).

Use of NSAIDs, such as Daypro, can increase the risk of hyperkalemia, especially in patients with diabetes mellitus, renal failure, increased age, or those receiving concomitant therapy with adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, cyclosporin, or some diuretics.

Electrolytes should be monitored periodically (see **CONTRAINDICATIONS**).

Respiratory

ASA-induced asthma is an uncommon but very important indication of ASA and NSAID sensitivity. It occurs more frequently in patients with asthma who have nasal polyps.

Sexual Function / Reproduction

The use of Daypro, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of Daypro should be considered.

Skin

In rare cases, serious skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme have been associated with the use of some NSAIDs. Because the rate of these reactions is low, they have usually been noted during post-marketing surveillance in patients taking other medications also associated with the potential development of these serious skin reactions. Thus, causality is NOT clear. These reactions are potentially life-threatening but may be reversible if the causative agent is

discontinued and appropriate treatment instituted. Patients should be advised that if they experience a skin rash they should discontinue their NSAID and contact their physician for assessment and advice, including which additional therapies to discontinue.

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.

Special Populations

Pregnant Women:

Daypro is CONTRAINDICATED for use during the third trimester of pregnancy because of risk of premature closure of the ductus arteriosus and the potential to prolong parturition (see TOXICOLOGY).

Caution should be exercised in prescribing Daypro during the first and second trimesters of pregnancy (see TOXICOLOGY).

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantaion loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

Nursing Women:
Daypro is not recommended for use in nursing mothers, since many nonsteroidal anti-inflammatory drugs have been shown to be partially excreted in breast milk. Oxaprozin has been found in the milk of lactating rats. (see **CONTRAINDICATIONS**)

Pediatrics (<18 years of age):
(See CONTRAINDICATIONS).

Geriatrics (>65 years of age):
Patients older than 65 years (referred to in this document as older or elderly) and frail or debilitated patients are more susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs). The incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal injury including ulceration and bleeding.

For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary, and under close supervision.

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 **ACTION AND 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 AND PRECAUTIONS, Renal**).

Monitoring and Laboratory Tests

Cardiovascular:
Hypertension: Blood pressure should be monitored regularly during therapy with Daypro. (see **WARNINGS AND PRECAUTIONS – Cardiovascular; DRUG INTERACTIONS – Antihypertensives, Beta-blockers**)

Renal:
Renal function (serum creatinine, and serum urea, etc.) should be monitored in high-risk populations, such as the elderly, patients with advanced renal disease, patients with cardiovascular disease and diabetes mellitus, as well as in the setting of concomitant use of diuretics, ACE inhibitors, and methotrexate (see **CONTRAINDICATIONS; DRUG INTERACTIONS – Antihypertensives and methotrexate, WARNINGS AND PRECAUTIONS – Renal - *Fluid and Electrolytes Balance***). If abnormal renal tests persist or

worsen, Daypro should be discontinued.

Patients on long term treatment with NSAIDs, including Daypro, should have their electrolytes such as serum potassium checked regularly if they exhibit any signs or symptoms of renal disease (see **WARNINGS AND PRECAUTIONS – Renal - *Fluid and Electrolytes Balance*)**

Hepatic:
Patient with symptoms and/or signs of liver dysfunction, or in whom an abnormal liver function test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with Daypro. If abnormal liver tests persist or worsen, Daypro should be discontinued (see **WARNINGS AND PRECAUTIONS - Hepatic / Biliary / Pancreatic**).

Hematologic:
Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by NSAIDs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients who have initial hemoglobin values of 10 g/dL or less, and who are to receive long-term therapy, should have hemoglobin values determined periodically.

Concurrent therapy of Daypro with warfarin requires close monitoring of the international normalized ratio (INR), (see **WARNINGS AND PRECAUTIONS – Hematologic - Anticoagulants**).

Plasma Lithium:
When lithium and oxaprozin are concurrently administered, a reduction in lithium dose is recommended and plasma concentrations of lithium should be monitored. Plasma concentrations of lithium should also be monitored when stopping or starting an NSAID (see **DRUG INTERACTIONS – Lithium**).

Blood Glucose:

As oxaprozin does alter the pharmacokinetics of glyburide, it is advisable to monitor patients' blood glucose in the beginning phase of glyburide and oxaprozin cotherapy. (see **DRUG INTERACTIONS – Glyburide**)

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions encountered with nonsteroidal anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred, particularly in the elderly.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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

Listed below are the adverse events and their incidences in the first month of use in clinical trials. Most of the events were seen by this time for common adverse reactions. However, the cumulative incidence can be expected to rise with continued therapy, and some events, such as gastrointestinal bleeding seem to occur at a constant or possibly increasing rising rate over time.

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

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

Incidence of adverse reactions occurring at an incidence of >1%	
Central Nervous System:	CNS inhibition (depression, sedation, somnolence, or confusion)
	disturbance of sleep
Gastrointestinal:	abdominal pain/distress
	anorexia
	constipation*
	diarrhea*
	dyspepsia*
	flatulence
	nausea*
	vomiting
Dermatologic:	rash*
Special Senses:	tinnitus
Urogenital:	dysuria or frequency

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Probable causal relationship: The following adverse reactions were reported in clinical trials at an incidence of less than 1%. The probability of a causal relationship exists between the drug and these adverse reactions.

Allergic:	drug hypersensitivity reactions including anaphylaxis
Cardiovascular:	edema, blood pressure changes
Central Nervous System:	weakness, malaise
Dermatologic:	pruritis, urticaria, photosensitivity
Gastrointestinal:	peptic ulceration and/or GI bleeding, liver function abnormalities including stomatitis, hemorrhoidal or rectal bleeding
Hematologic:	anemia, thrombocytopenia, leukopenia, ecchymoses
Metabolic:	weight gain, weight loss
Respiratory:	symptoms of upper respiratory tract infection
Special Senses:	blurred vision, conjunctivitis
Urogenital:	hematuria, renal insufficiency, decreased menstrual flow

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

Cardiovascular:	palpitations
Dermatologic:	alopecia
Gastrointestinal:	alteration in taste
Respiratory:	sinusitis, pulmonary infections
Special Senses:	hearing decrease
Urogenital:	increase in menstrual flow

Abnormal Hematologic and Clinical Chemistry Findings

Anemia, thrombocytopenia, leucopenia and ecchymoses were reported in clinical trials at an incidence of <1%. [See **ADVERSE REACTIONS, Less Common Clinical Trial Adverse Drug Reactions (<1%)]**

Post-Market Adverse Drug Reactions

Additional reports of serious adverse events temporally associated with Daypro during worldwide post-marketing experience are included below. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Daypro exposure.

Allergic:	serum sickness
Dermatologic:	pseudoporphyria, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome)
Gastrointestinal:	hepatitis, pancreatitis
Hematologic:	agranulocytosis, pancytopenia
Urogenital:	acute interstitial nephritis, nephrotic syndrome, acute renal failure

DRUG INTERACTIONS

Overview

Factors such as excess alcohol intake, smoking, age, female gender and concomitant NSAID and oral steroid or anticoagulant use have been associated with increased risk of GI adverse events such as ulceration and bleeding.

Drug Interactions

Drug-Drug Interactions

Acetaminophen:
The coadministration of oxaprozin and acetaminophen resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies.

Acetylsalicylic Acid (ASA) or other NSAID's:
The use of Daypro in addition to any other NSAID, including over the counter ones (such as ASA and ibuprofen) for analgesic and/or anti-inflammatory effects is NOT recommended because of the absence of any evidence demonstrating synergistic benefits and the potential for additive adverse reactions.

The exception is the use of low dose ASA for cardiovascular protection, when another NSAID is being used for its analgesic/anti-inflammatory effect, keeping in mind that combination NSAID therapy is associated with additive adverse reactions.

Some NSAIDs (e.g. ibuprofen) may interfere with the anti-platelet effects of low dose ASA,

possibly by competing with ASA for access to the active site of cyclooxygenase-I.

Studies in man have shown that such combined administration produces decreased protein-binding of oxaprozin, with a reduced biological half-life, and increased clearance of oxaprozin.

Because of the long biological half-life of oxaprozin (approximately 50 hours), a clinical study of patients with rheumatoid arthritis was conducted to determine its interactions with ASA, naproxen, ibuprofen, and tolmetin sodium after therapy with Daypro was discontinued and the other drugs were started. In the same manner, patients with osteoarthritis were studied for interactions between Daypro and ASA, naproxen, ibuprofen and indomethacin. No clinically detectable interactions were found.

Antacids:
The coadministration of oxaprozin and antacids resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies.

Anticoagulants:
Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

Because prostaglandins play an important role in hemostatis, and NSAIDs affect platelet function, concurrent therapy of Daypro with warfarin requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

Concomitant warfarin and Daypro therapy did not produce further alterations of prothrombin times or a variety of other clotting factors when administered to normal subjects. Patients stabilized on phenprocoumon showed significant potentiation of the anticoagulation effect after 2.5 weeks of oxaprozin therapy. The values returned to pretreatment levels within one week after stopping oxaprozin. (see **WARNINGS AND PRECAUTIONS – Hematologic – *Anti-coagulants*)**

Antihypertensives:
While oxaprozin does alter the pharmacokinetics of enalapril and its active metabolite enalaprilat, coadministration of oxaprozin to hypertensive patients did not produce significant changes in blood pressure values. However, some NSAIDs have been reported to reduce the antihypertensive effects of Angiotensin Converting Enzyme (ACE) inhibitors.

Combinations of ACE inhibitors, angiotensin-II antagonists, or diuretics with NSAIDs might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and renal function (including electrolytes) should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure.

Anti-platelet Agents (including ASA):

There is an increased risk of bleeding, via inhibition of platelet function, when anti-platelet agents are combined with NSAIDs, such as Daypro (see **WARNINGS AND PRECAUTIONS – Hematologic – *Anti-platelet Effects*)**

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.

Cimetidine/Ranitidine:
Concomitant administration of cimetidine or ranitidine results in a clinically insignificant reduction of oxaprozin clearance. This does not require dosage adjustment.

Conjugated Estrogens:
No interaction was observed when Daypro was administered concomitantly with conjugated estrogens.

Diuretics:
Clinical studies as well as post-marketing observations have shown that NSAIDs can reduce the effect of diuretics, such as thiazide diuretics and potassium-sparing diuretics.

Glucocorticoids:

Some studies have shown that the concomitant use of NSAIDs and oral glucosteroids increases the risk of GI adverse events such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

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.

Gold Salts, Antimalarial Agents, Corticosteroids:
Daypro may be used in combination with gold salts, antimalarial agents, or corticosteroids in the treatment of rheumatoid arthritis in adults.

In patients who received concomitant antimalarial therapy, a significantly higher incidence of muscular cramps/aching/pain, gastrointestinal bleeding, vision disorders and edema of the lower extremities was found. In patients who received concomitant gold therapy, a significantly higher incidence of sedation, skin disorders and ENT disorders or symptoms was found.

Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years old) individuals. In patients who received concomitant steroid therapy, significantly higher incidences of constipation, dyspepsia and alteration in taste were found.

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.

Lithium:
NSAIDs have been reported to increase steady-state plasma lithium concentrations. It is recommended that these concentrations be monitored when initiating, adjusting and discontinuing drug treatment.

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.

Selective Serotonin Reuptake Inhibitors (SSRIs):

Concomitant administration of NSAIDs and SSRIs may increase the risk of gastrointestinal ulceration and bleeding (see **WARNINGS AND PRECAUTIONS – Gastroinestinal)**.

Tacrolimus or cyclosporin:

Although this interaction has not been studied with oxaprozin, co-administration of tacrolimus or cyclosporin and any NSAID may increase the nephrotoxic effect of tacrolimus or cyclosporin due to the NSAID**'**s effect on renal prostaglandins. Renal function should be monitored when oxaprozin and either of these drugs are used in combination.

Other drug interactions:
No drug interaction data are available for Daypro and the co-administration of the following products: alcohol, aminoglycosides, bone marrow depressants, butemide, cholestyramine, colchicine, cyclosporine, digoxin, indapamide, insulin, nephrotoxic agents, potassium supplements, probenecid, valproic acid, zidovudine.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Consideration should be given to reducing the starting dose in elderly patients. In patients with moderate to severe renal impairment, and in those on hemodialysis, a maximum daily dosage of 600 mg administered under careful monitoring is recommended.

Recommended Dose and Dosage Adjustment

Rheumatoid Arthritis: The initial therapy is 1200 mg once daily. This may be decreased or increased depending on the patient's response. The maximum daily dose should not exceed 1800 mg, or 26 mg/kg, whichever is less. Doses larger than 1200 mg/day should be reserved for patients who weigh more than 50 kg, have normal renal and hepatic function, are at low risk of peptic ulcer and whose severity of disease justifies maximal therapy. Physicians should ensure that patients are tolerating lower doses before advancing to the larger doses.

The 1800 mg dose should be divided into two doses (1200 mg in the morning and 600 mg in the evening).

Osteoarthritis: The initial therapy is 1200 mg once daily. This may be decreased to 600 mg once daily depending on the patient's response.

For patients of low body weight or with milder disease, an initial dose of 600 mg once daily may be appropriate.

Missed Dose

The missed dose should be skipped and the next dose taken at the scheduled time.

Administration

In a clinical study in which healthy volunteers were administered Daypro (oxaprozin) after a meal, the extent of absorption was unchanged while the rate of absorption was slightly delayed. Daypro may be administered orally once or twice daily with food or milk, and dosage adjusted for optimal response as described above.

OVERDOSAGE

No patient experienced either an accidental or intentional overdosage of DAYPRO in the clinical trials of the drug. The symptoms of overdosage may include: 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. In the event of overdosage, 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Daypro (oxaprozin) is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties. The modes of action of Daypro, like that of other nonsteroidal anti-inflammatory agents, are not fully established. It is known, however, that it does inhibit prostaglandin synthesis.

Pharmacodynamics

The effects of therapeutic doses of Daypro (1200 mg) and acetylsalicylic acid (3900 mg) on the gastric mucosa and fecal blood were studied in healthy subjects. Daypro produced significantly less submucosal hemorrhage or bleeding than did ASA in a 10-day crossover study utilizing gastroscopic evaluation of the gastric mucosa. The average amount of fecal blood loss that was induced by oxaprozin during a two week study using ^{51}Cr-labelled autologous red blood cells was similar to that caused by placebo during the second week, but was significantly greater during the first week. The fecal blood loss induced by oxaprozin was significantly less than that caused by acetylsalicylic acid throughout the two week study.

The effects of oxaprozin on renal function were studied in normal subjects and in patients with impaired renal function. In clearance studies of normal subjects during sustained water diuresis, oxaprozin caused no acute reduction in glomerular filtration rate (GFR), had no effect on overall sodium clearance, and had no long-term effect on serum creatinine, blood urea nitrogen, or serum potassium. In renally impaired patients with a GFR below 30 to 40 mL/min and in patients undergoing hemodialysis, oxaprozin was distributed more extensively because of a reduction in binding to plasma proteins. The mean biological half-life was not altered by renal disease, although urinary excretion of both oxaprozin and its conjugates was greatly reduced. A multiple-dose study in patients undergoing hemodialysis demonstrated no impairment of total or unbound clearance in the disease state.

Pharmacokinetics

Table 1 Summary of Oxaprozin Pharmacokinetic Parameters in Healthy Adults

	C_{max} (mcg/mL)	Clearance (mL/h/kg)	Volume of Distribution (mL/kg)
Single dose (1200 mg)	120	2.5	180
Steady State	190	5.0	300

Absorption:
Oxaprozin is almost completely absorbed from the gastrointestinal (GI) tract, with peak plasma levels attained 2 to 4 hours after administration. The mean peak plasma concentration (C_{max}) is approximately 120 mcg/mL with a single dose of 1200 mg and approximately 190 mcg/mL at steady-state.

One study demonstrated that food had no effect on the extent of absorption of oral doses of Daypro (oxaprozin) in healthy subjects, whereas the rate of absorption was slightly slower. No abnormal drug accumulation occurred in patients treated with multiple doses (1200 mg/day) for up to 6 months.

Distribution:
At therapeutic levels, more than 99% of oxaprozin is bound to plasma proteins, mostly albumin. The apparent volume of distribution rises from 180 to 300 mL/kg from single dose to steady-state. These increases are due to nonlinear protein binding.

Metabolism:
A dual metabolism has been identified for oxaprozin. Approximately 60% of the drug is oxidized to hydroxyoxaprozin I or II and approximately 30% is glucuronidated to form oxaprozin acyl glucuronide. These inactive metabolic products are excreted in the feces (one third) and in the urine (two thirds). About 30% of an oral dose is recovered as conjugates in urine.

Less than 5% is recovered as oxaprozin. Biliary excretion in cholecystectomized humans accounts for 5% of the drug in 5 days. Oxaprozin does not induce its own metabolism.

Excretion:
The mean biological half-life in humans is approximately 50 hours. Total body clearance of oxaprozin rises from 2.5 mL/h/kg after a single 1200 mg dose to 5.0 mL/h/kg at steady-state.

Special Populations and Conditions

Geriatrics:
Oxaprozin disposition during steady-state conditions is not affected by either subject age or sex. However the volume of distribution declined with increasing age (See **DOSAGE AND ADMINISTRATION**).

Congestive Heart Failure:
The elimination half-life, volume of distribution, and total body clearance of unbound oxaprozin following a single dose were similar for patients with congestive heart failure as compared to healthy subjects.

Hepatic Insufficiency:
One study compared the pharmacokinetics of a single dose of oxaprozin in patients with cirrhosis. Elimination half-life, and clearance of unbound drug were unchanged.

Renal Insufficiency:
The pharmacokinetics of oxaprozin in patients with impaired renal function, patients maintained on hemodialysis, and healthy subjects were evaluated following a single 600 mg oral dose. Total body clearance and elimination half-life did not differ substantially among the three groups. In a multiple dose study of subjects and patients with normal albumin levels, who were undergoing hemodialysis, total body clearance and volume of distribution of unbound drug were higher in patients undergoing hemodialysis. Total oxaprozin levels were not affected and there was no evidence of accumulation in subjects or renally impaired patients. Caution should be used when oxaprozin is given to patients with renal impairment (See **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15-25°C. Protect caplets from light. Keep bottles tightly closed.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

Daypro caplets are available in HDPE bottles with plastic caps. Each bottle contains 100 caplets.

Non-medicinal ingredients present in oxaprozin caplets include cellulose, corn starch, hypromellose, magnesium stearate, methylcellulose, polacrilin potassium, polyethylene glycol, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

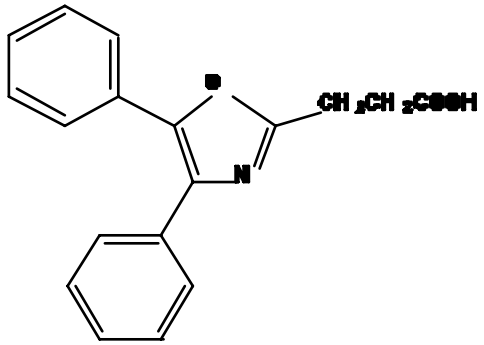
Proper name: Oxaprozin

Chemical name: 4,5-Diphenyl-2-oxazolepropionic acid

Molecular formula: $C_{18}H_{15}NO_3$

Molecular weight: 293.32

Structural formula:
Oxaprozin is a nonsteroidal anti-inflammatory agent of the propionic acid class. It has the following chemical structure:



Physicochemical properties:
Oxaprozin is a white to off-white powder with a slight odour and a melting point of 162-163°C. It is slightly soluble in alcohol and insoluble in water.

CLINICAL TRIALS

Randomized clinical trials with Daypro have NOT been designed to detect differences in cardiovascular adverse events in a chronic setting.

Rheumatoid Arthritis
The safety and efficacy of oxaprozin (*average daily dose of 1200 mg o.d*) in the treatment of rheumatoid arthritis in adults were demonstrated in 2 long-term active (ibuprofen 300 mg q.i.d.; ASA 975 mg q.i.d.) controlled clinical trials. These studies (6 months and 12 months) respectively involved a total of 377 patients of which 188 received oxaprozin.

Osteoarthritis

The safety and efficacy of oxaprozin (*average daily dose ranging between 600 mg and 1200 mg*) in the treatment of osteoarthritis in adults were demonstrated in 2 long-term active (ASA daily dose between 2600 to 3250 mg) controlled clinical trials. These studies (6 months double-blind followed by a 6 months open-label phase) involved a total of 547 patients receiving oxaprozin.

DETAILED PHARMACOLOGY

Oxaprozin has been shown to possess anti-inflammatory, analgesic and antipyretic activity as assessed by a variety of animal test procedures.

Anti-inflammatory Activity: Acute inflammation (induced by injection of carrageenin into the paw of rats) is prevented by 200 mg/kg of oxaprozin given orally. Chronic inflammation (by subcutaneous implantation of cotton pellets in rats) is attenuated by repeated oral administration of 200-500 mg/kg/day. Oxaprozin also protects joints against swelling elicited by subplantar injection of *Mycobacterium butyricum* (rats), systemic administration of 6-sulfanilamidoindazole (rats), and sodium urate crystals (dogs). In the case of adjuvant arthritis (rats) the development of primary as well as secondary arthritic lesions is prevented by oxaprozin (75-500 mg/kg p.o.).

Analgesic Activity: Oxaprozin exhibits antinociceptive properties in benzoquinone-induced writhing in mice (10-100 mg/kg p.o.), in the inflamed (Randall-Selitto) rat paw test (ED_{50} 200 mg/kg p.o.) and in the electric foot-shock test in monkeys (5-20 mg/kg p.o.). The failure of oxaprozin to be effective in the rat tail flick test, at oral doses of 100-600 mg/kg, as well as the lack of displacement by oxaprozin of ^{3}H-naloxone, from its opiate binding sites, on rat brain cell membranes, indicates that oxaprozin is a non-narcotic analgesic.

Antipyretic Activity: Fever, precipitated by s.c. injection of brewer's yeast in rats, is dose-dependently reduced by 50-150 mg/kg p.o. of oxaprozin.

Oxaprozin has a rapid onset of action, and a duration of action of several hours, as observed in many different tests and species. The mechanism of action of oxaprozin is not known. Its anti-inflammatory effect is not due to steroid-release from the adrenal gland since the effectiveness persists even after removal of the adrenals.

Whether oxaprozin's inhibition of prostaglandin synthetase *in vitro* plays a role in the mechanism of action is uncertain. However, it does share this property with other nonsteroidal anti-inflammatory agents, e.g., indomethacin and ASA. Moreover, oxaprozin suppresses arachidonic acid-induced diarrhea in mice.

Bradykinin is probably one of many mediators of inflammation. It may, therefore, be relevant that oxaprozin suppresses bradykinin-induced bronchoconstriction although the effect of other potential mediators (e.g., histamine and serotonin) is not altered.

As with phenylbutazone, uricosuric effects could be observed with oxaprozin.

Since arachidonic acid and collagen induced platelet aggregation is inhibited by oxaprozin *in vitro*, the possibility exists that this drug, like many other acidic anti-inflammatory agents, affects normal platelet function and hemostasis.

Oxaprozin, like other nonsteroidal anti-inflammatory drugs is not completely free of gastrointestinal side effects. However, when studied in rats, oxaprozin caused no intestinal ulcers and adhesions in contrast to indomethacin and phenylbutazone. In addition, oxaprozin caused considerably less mucosal bleeding and gastric erosions than ASA, indomethacin and phenylbutazone after equi-effective anti-inflammatory oral doses.

Oxaprozin has no significant cardiovascular or central nervous system activity.

TOXICOLOGY

Single-Dose Toxicity:

Species	**LD_{50} (95% Confidence Limits) mg/kg)**	
	Oral	**I.P.**
Mouse	1144 (939-1395)	316-335
Rat	918 (733-1150)	267 (246-290)

The effects produced in the adult mouse included decreased spontaneous motor activity, ataxia, loss of the righting reflex, body tremors, leg and body twitches, and bradypnea. In the rat, injection of oxaprozin produced a loss of the righting reflex and chromodacryorrhea. Most deaths occurred within forty-eight to seventy-two hours.

In the dog, oxaprozin administered p.o. failed to produce death at doses as high as 600 mg/kg because of the consistent emetic effect of the drug.

Repeat-Dose Toxicity:

Oxaprozin, administered to albino rats for two weeks via gastric intubation, at dose levels of 200, 400 or 600 mg/kg/day, produced the following effects: gastrointestinal irritation, characterized by hemorrhages and erosions; hemorrhagic thymi and enlarged mesenteric lymph nodes; and fatty change, mostly slight, in the liver. When the compound was fed in diet to rats for six months, at doses of 74, 157 or 300 mg/kg/day, the highest dose (300 mg/kg) produced a depression in food consumption and/or body weight gain; no drug-related histopathologic changes were noted at any dose level.

After two years of treatment with 54, 108 or 216 mg/kg/day of oxaprozin in rats, a significant increase in mean serum sodium concentration was noted in all treated male groups, and serum chloride was significantly increased in low- and mid-dose males. No drug-related changes were seen during hematological evaluation.

Common findings in dogs given oxaprozin for periods of two weeks to six months included

emesis, bloody stools and gastrointestinal irritation. At doses of 75, 150 and 300 mg/kg/day in the six-month study, a dose-related incidence of ulcerative gastritis, thymic atrophy, depression of bone marrow and degeneration of the seminiferous tubules were found. Atrophy of lymphoid tissues other than thymus also occurred, but they were less affected. None of these changes were seen in the dogs treated with 37.5 mg/kg except for focal degeneration of seminiferous tubules in one dog and possible thymic atrophy in another animal. During this study, eleven drug-treated dogs (all six animals at 300 mg/kg; three dogs at 150 mg/kg; and one each at 75 and 37.5 mg/kg) died or were sacrificed moribund. Most dogs in the six-month study had a decrease in total serum protein, and serum electrolytes were generally decreased in high dose (300 mg/kg) dogs.

Additionally, blood urea nitrogen was increased and bromsulphalein excretion decreased in several treated dogs. A neutrophilia, an increase in platelets, and a possible impairment of renal concentrative capacity were noted in the six-month study. In another study, drug treatment was initiated when the animals were older (50-90 weeks of age) than those in the previous study. After one year of treatment, histopathological examination revealed moderate chronic gastritis in one treated animal and traces of inflammatory cells within the gastric mucosa of several other high dose (36 mg/kg) dogs; no other drug-related histologic changes were found. In the one-year study, decreased total protein and globulin were found in the high dose (36 mg/kg) female group; total bilirubin was decreased in all drug-treated groups. Early decreases were noted in the red blood cell parameters of drug-treated animals. Toward the end of the one-year study, these values were similar to those of the controls.

Occult blood was found in the stools of monkeys given 75 or 150 mg/kg/day of oxaprozin in a dose-range study. Mucosal reddening with lesions in the stomachs of two of three high dose animals was seen at necropsy. Hemoglobin, hematocrit and red blood cell counts were decreased in monkeys given 75 or 150 mg/kg of oxaprozin. In a one-year study using doses of 18, 36 or 54 mg/kg/day, histopathological examination revealed nonspecific chronic gastritis in some animals from each group including controls; however, in five treated animals, the gastritis was slightly more severe than that observed in controls. No drug-related changes were seen in serum chemistry or urinalysis parameters.

Genotoxicity:

Oxaprozin is not mutagenic; in various assays that included the Ames Test, a forward mutation assay using *Schizosaccharomyces pombe* and Chinese hamster ovary (CHO) cells, an assay to measure DNA damage/repair in *Saccharomyces cerevisiae*, a sister chromatid exchange (SCE) assay using CHO cells, an *in vitro* cytogenetic assay using human lymphocytes and two *in vivo* cytogenetic assays, the first measuring the development of micronuclei in erythrocytes of mice and the second measuring chromosome aberrations in rat bone marrow cells, oxaprozin was devoid of mutagenic activity. Also, oxaprozin was negative in an *in vitro* neoplastic cell transformation assay using Balb/3T3 cells.

Carcinogenicity:

In two-year studies in rats and mice, no evidence of carcinogenicity was seen with oxaprozin at oral doses of up to 225 mg/kg/day. In a two year rat study, interstitial cell adenomas were seen in the testes of males from all groups (0, 54, 108, or 216 mg/kg). The incidence of this tumor

was 5/117, 4/60, 2/58, and 7/58 for the control, low-, mid- and high-dose groups, respectively. In a subsequent two-year rat study consisting of males in control and high-dose groups only, the incidence of testicular interstitial cell adenoma was 5/174 and 13/238 for control and dosed animals, respectively. Tumor incidence in treated groups was not statistically significant when compared to control. In the mouse study, a statistically significant increase in the incidence of hepatic cell carcinoma was found in the high dose males, and an increased incidence of hepatic cell adenoma was found in the mid dose males. These increases represented an exaggerated response of a pre-existing lesion present in the control males.

Reproductive and Developmental Toxicity:

Reproductive Studies

Reproductive studies revealed no impairment of fertility in rats but, like other nonsteroidal anti-inflammatory agents with inhibitory effect on prostaglandin synthesis, oxaprozin had an adverse effect on parturition as evidenced by dystocia and pup retentions in dams treated with 100 or 200 mg/kg/day.

Oxaprozin, at doses of 50, 100 and 200 mg/kg/day was administered to rats. A delay in delivery by one high dose Segment III dam (i.e., females dosed from day 15 post-coitum through day 21 of lactation), and a failure to deliver by two mid-dose and two high-dose Segment I-B dams (i.e., females dosed from day 14 prior to mating through day 21 of lactation) was noted; autopsy revealed dead pups in the uterus or cervix. In a second study, these findings were corroborated as follows:

i. control dams delivered normally with the exception of one dam whose parturition may have been affected by an injury sustained between days 23 and 24;

ii. a percentage of the drug-treated dams failed to deliver all of their pups by gestation day 24;

iii. the "live birth index" in the drug-treated dams was lower than that found in the control dams;

iv. three drug-treated dams died near the time of parturition At autopsy of the rats that died, no gross pathology was found in the dams from Segment I-B. The two dams from Segment III had scattered eroded areas in the stomach and blood in the intestines, indicating stress. All three dams had some or all of their pups in utero at the time of death. After administration of oxaprozin to the parental (P_1) generation, no effect on development, behaviour or reproductive performance of the F_1 generation nor on the development of the F_2 generation was seen.

Teratology Studies

In the mouse and rat at doses of 50, 100 and 200 mg/kg/day, dams tolerated the drug well and the development of their fetuses was normal. In a preliminary teratology study in five rats each at 500, 750 or 1000 mg/kg (20, 31, or 42 times the usual human dose) administered on gestation days 6 through 15, two fetal abnormalities were observed: one fetus from a mid-dose female had a malrotated foot; one fetus from a high-dose female had reduced upper jaw and exencephaly. There were 58 and 37 viable fetuses in the mid- and high-dose groups, respectively.

In a preliminary rabbit study, litter size and mean litter weights were decreased in the 30, 50,

and 70 mg/kg groups, while mean fetal weights were decreased only in the 70 mg/kg dose group. When oxaprozin was administered to twelve Dutch rabbits per group during the period of organogenesis, at doses of 7.5, 15.0 and 30.0 mg/kg/day, no statistically significant differences were found in the mean number of viable fetuses or in the percentage of fetal loss. Two of 72 fetuses from low-dose females were malformed, one with acephaly and the other with cleft palate. No fetuses from mid-dose females were malformed. Three of 70 fetuses from high-dose females were malformed: one had a grossly distended abdomen, enlarged heart, rectal cyst and one kidney embedded in the back musculature; one fetus had exancephaly and gastroschisis; one had gross malformations consisting of craniorachischisis, gastroschisis, open eye, and possible malformations of the forelimbs, hindlimbs and tail. The latter two fetuses were from the same dam.

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PART III: CONSUMER INFORMATION

DAYPRO
(Oxaprozin)

Read this information each time you refill your prescription in case new information has been added.

This leaflet is part III of a three-part "Product Monograph" published when Daypro was approved for sale in Canada and is designed specifically for you to read. It will NOT tell you everything about Daypro. See your health care provider and pharmacist regularly and ask them questions about your health and any medications you take.

ABOUT THIS MEDICATION

What the medication is used for:
Daypro (oxaprozin) which has been prescribed to you by your doctor is used to treat the symptoms of rheumatoid arthritis and osteoarthritis.

What it does:
Daypro (oxaprozin), as a nonsteroidal anti-inflammatory drug (NSAID), helps to relieve joint pain, swelling and stiffness by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. Daypro, does NOT cure arthritis, but it promotes suppression of the inflammation and the tissue damaging effects resulting from this inflammation. Daypro can only relieve pain and reduce swelling as long as you continue to take it.

When it should not be used:
DO NOT TAKE Daypro if you have any of the following medical conditions:

- Heart bypass surgery (planning to have or recently had)
- Severe, uncontrolled heart failure
- Bleeding in the brain or other bleeding disorders
- Current pregnancy (after 28 weeks of pregnancy)
- Currently breastfeeding (or planning to breastfeed)
- Allergy to ASA (Acetylsalicylic Acid) or other NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)
- Ulcer (active)
- Bleeding from the stomach or gut (active)
- Inflammatory bowel disease (Crohn's Disease or Ulcerative Colitis)
- Liver disease (active or severe)
- Kidney disease (severe or worsening)
- High potassium in the blood

Patients who took a drug in the same class as Daypro after a type of heart surgery [coronary artery bypass grafting (CABG)] were more likely to have heart attacks, strokes, blood clots in the leg(s) or lung(s), and infections or other complications than those who did NOT take that drug.

Daypro is not recommended for patients under 18 years of age since safety and effectiveness have not been established.

What the medicinal ingredient is:
Oxaprozin

What the important nonmedicinal ingredients are:
Cellulose, corn starch, hypromellose, magnesium stearate, methylcellulose, polacrilin potassium, polyethylene glycol, titanium dioxide

What dosage forms it comes in:
Caplet 600 mg

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions:
If you have, or previously had, any of the following medical conditions, see your healthcare provider to discuss treatment options other than Daypro:

- **Heart Attack or Angina**
- **Stroke or Mini-stroke**
- **Loss of Vision**
- **Current Pregnancy (less than 28 weeks)**
- **Congestive Heart Failure**

BEFORE you use Daypro talk to your doctor or pharmacist if you have any of the following:

- High blood pressure
- High cholesterol
- Diabetes mellitus or on a low sugar diet
- Atherosclerosis
- Poor circulation to your extremities
- Smoker or ex-smoker
- Kidney disease or urine problems
- Previous ulcer or bleeding from the stomach or gut
- Previous bleeding in the brain
- Bleeding problems
- Family history of allergy to NSAIDs, such as acetylsalicylic acid (ASA), celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, rofecoxib, sulindac, tenoxicam, tiaprofenic acid, tolmetin, or valdecoxib (NOT a complete list)
- Family history of asthma, nasal polyps, long-term swelling of the sinus (chronic sinusitis) or chronic urticaria (hives);
- you are on any special diet, such as a low-sodium or low-sugar diet;
- any other medical problem(s) such as alcohol abuse, etc.

Also, before taking this medication, tell your healthcare provider if you are planning to get pregnant.

WHILE taking Daypro:

- tell any other doctor, dentist, pharmacist or other healthcare professional that you consult or see, that you are taking this medication, especially if you are planning to have heart surgery;
- do NOT drink alcoholic beverages while taking this medication because you would be more likely to develop stomach problems;
- fertility may be decreased. The use of Daypro is not recommended in women trying to get pregnant. In women who have difficulty conceiving, stopping Daypro should be considered.
- check with your doctor if you are not getting any relief of your arthritis or if any problems develop;
- report any untoward reactions to your doctor; this is very important as it will aid in the early detection and prevention of potential complications.
- your regular medical checkups are essential.

INTERACTIONS WITH THIS MEDICATION

Talk to your healthcare provider and pharmacist if you are taking any other medication (prescription or non-prescription) such as any of the following (NOT a complete list):

- Acetylsalicylic Acid (ASA) or other NSAIDs (e.g. ASA, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen)
- Antidepressants
  - Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g. citalopram, fluoxetine, paroxetine, sertraline)
- Antimalarials
- Beta-blockers
- Blood pressure medications
  - ACE (Angiotensin converting enzyme) inhibitors (e.g. enalapril, lisinopril, perindopril, ramipril)
  - ARBs (angiotensin II receptor blockers) (e.g. candesartan, irbesartan, losartan, valsartan)
- Blood thinners (e.g. warfarin, ASA, clopidogrel)
- Cimetidine/ranitidine
- Corticosteroids (including glucocorticoids) (e.g. prednisone)
- Cyclosporin/tacrolimus
- Diuretics (e.g. furosemide, hydrochlorothiazide)
- Gold salts
- Glyburide
- Lithium
- Methotrexate
- Oral hypoglycemics (diabetes medications)
- Phenytoin

Do not take ASA (acetylsalicylic acid), ASA-containing compounds, or other drugs used to relieve symptoms of arthritis while taking Daypro unless directed to do so by your physician. Your healthcare provider may prescribe low dose ASA (acetylsalicylic acid) as a blood thinner to reduce your risk of having a heart attack or stroke while you are taking Daypro. Take only the amount of ASA prescribed by your healthcare provider. You are more likely to upset or damage your stomach if you take both Daypro and ASA than if you took Daypro alone.

PROPER USE OF THIS MEDICATION

Usual Dose:

Medical Condition	Starting Dose	Maximum Dose (per day)
Rheumatoid arthritis	1200 mg once daily	1800 mg (1200 mg in the morning and 600 mg in the evening)
Osteoarthritis	1200 mg once daily (your doctor may decrease your dose to 600 mg once daily)	1200 mg once daily

Daypro is usually taken once a day, after breakfast or with some food or milk. Some people are told by their doctor to take it twice a day. The first dose is taken in the morning and the second in the evening. When Daypro is taken twice a day, the morning dose may be larger than the evening dose. To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing.

Take Daypro only as directed by your healthcare provider. **Do NOT take more of it, do NOT take it more often and do NOT take it for a longer period of time than your ~~doctor~~ healthcare provider ordered. If possible, you should take the lowest dose of this medication for the shortest time period.** Taking too much Daypro may increase the chance of unwanted and sometimes dangerous side effects, especially if you are an elderly patient, have other disease or take other medications.

If you will be using Daypro for more than 7 days, see your healthcare provider regularly to discuss whether this medicine is working for you and if it causing you any unwanted effects. Be sure to take Daypro regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

This medicine has been prescribed specifically for you. Do NOT give it to anyone else. It may harm them, even if their symptoms seem to be similar to yours.

Daypro is NOT recommended for use in patients under 18 years of age since safety and effectiveness have NOT been established.

Missed Dose:

Skip the missed dose and take the next dose at the scheduled time.

Overdose:
The symptoms of overdose may include lethargy, drowsiness, nausea, vomiting, and stomach pain. If you take more than the prescribed dose, contact your healthcare provider immediately, even if there are no signs of discomfort or poisoning.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Daypro may cause some undesirable reactions especially when used for a long time or in large doses. When these side effects occur, you may require medical attention. Report all symptoms or side effects to your healthcare provider.

Daypro may cause you to become drowsy or tired. Be careful about driving or participating in activities that require you to be alert. If you become drowsy, dizzy or light-headed after Daypro, do NOT drive or operate machinery.

Daypro may cause you to become more sensitive to sunlight. Any exposure to sunlight or sunlamps may cause sunburn, skin blisters, skin rash, redness, itching or discolouration, or vision changes. If you have a reaction from the sun, check with your health care provider.

Check with your healthcare provider IMMEDIATELY if you develop chills, fever, muscle aches or pains, or other flu-like symptoms, especially if they occur before or together with a skin rash. These symptoms may be the first signs of a SERIOUS ALLERGIC REACTION to this medication.

Check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools.

Elderly, frail, or debilitated patients often seem to experience more frequent or more severe side effects.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom	STOP taking Daypro and get emergency medical attention IMMEDIATELY	STOP taking Daypro and talk your doctor or pharmacist
Bloody or black tarry stools	✓	
Shortness of breath, wheezing, any trouble in breathing or tightness in the chest	✓	
Skin rash, hives or swelling, itching	✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom	STOP taking Daypro and get emergency medical attention IMMEDIATELY	STOP taking Daypro and talk your doctor or pharmacist
Blurred vision or any visual disturbance	✓	
Any change in the amount or colour of your urine (red or brown)	✓	
Any pain or difficulty experienced while urinating		✓
Swelling of the feet or lower legs; weight gain		✓
Vomiting or persistent indigestion, nausea, stomach pain or diarrhea		✓
Yellow discoloration of the skin or eyes, with or without itchy skin		✓
Malaise, fatigue, loss of appetite		✓
Headaches, stiff neck		✓
Mental confusion, depression		✓
Dizziness, lightheadedness		✓
Hearing problems		✓

This is not a complete list of side effects. If you develop any other symptoms while taking Daypro, see your healthcare provider..

HOW TO STORE IT

Store at 15-25°C. Protect from light.
Do not keep **outdated medicine or medicine no longer needed**. Any outdated or unused medicine should be returned to your pharmacist.
Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals may be obtained by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001

This leaflet was prepared by
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This Consumer Information section for Daypro was developed from Part I of the Product Monograph, and from the INFORMATION TO THE PATIENT section of the approved Product Monograph (see pages 14-17) and with reference to consumer information for oxaprozin as follows:
http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a693002.html
and
http://yalenewhavenhealth.org/library/healthguide/en-us/drugguide/topic.asp?hwid=d00853a1#d00853a1