

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DAYPRO ALTA safely and effectively. See full prescribing information for DAYPRO ALTA.

DAYPRO ALTA™ (oxaprozin potassium) tablets, for oral use  
Initial U.S. Approval: 1992

### WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (5.1)**
- **DAYPRO ALTA is contraindicated in the setting of coronary artery bypass graft (CABG) surgery (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events (5.2)**

### INDICATIONS AND USAGE

DAYPRO ALTA is a non-steroidal anti-inflammatory drug indicated for

- Relief of the signs and symptoms of osteoarthritis (1)
- Relief of the signs and symptoms of rheumatoid arthritis (1)

### DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals (2.1)
- OA: 1200 mg (two 600 mg tablets) given orally once a day (2.2, 14.1)
- RA: 1200 mg (two 600 mg tablets) given orally once a day (2.3, 14.2)

### DOSAGE FORMS AND STRENGTHS

DAYPRO ALTA (oxaprozin potassium) tablets: 600 mg (3)

### CONTRAINDICATIONS

- Known hypersensitivity to oxaprozin potassium or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

### WARNINGS AND PRECAUTIONS

- **Hepatotoxicity:** Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop (5.3)
- **Hypertension:** Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure (5.4, 7)
- **Heart Failure and Edema:** Avoid use of DAYPRO ALTA in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure (5.5)

- **Renal Toxicity:** Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of DAYPRO ALTA in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function (5.6)
- **Anaphylactic Reactions:** Seek emergency help if an anaphylactic reaction occurs (5.7)
- **Exacerbation of Asthma Related to Aspirin Sensitivity:** DAYPRO ALTA is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity) (5.8)
- **Serious Skin Reactions:** Discontinue DAYPRO ALTA at first appearance of skin rash or other signs of hypersensitivity (5.9)
- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** Discontinue and evaluate clinically (5.10)
- **Fetal Toxicity:** Limit use of NSAIDs, including DAYPRO ALTA, between about 20 to 30 weeks in pregnancy due to the risk of oligohydramnios/fetal renal dysfunction. Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/fetal renal dysfunction and premature closure of the fetal ductus arteriosus (5.11, 8.1)
- **Hematologic Toxicity:** Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia (5.12, 7)

### ADVERSE REACTIONS

Most common adverse reactions (incidence >3%) are: constipation, diarrhea, dyspepsia, nausea, rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- **Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, selective serotonin reuptake inhibitors [SSRIs]/serotonin norepinephrine reuptake inhibitors [SNRIs]):** Monitor patients for bleeding who are concomitantly taking DAYPRO ALTA with drugs that interfere with hemostasis. Concomitant use of DAYPRO ALTA and analgesic doses of aspirin is not generally recommended (7)
- **Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers:** Concomitant use with DAYPRO ALTA may diminish the antihypertensive effect of these drugs. Monitor blood pressure (7)
- **ACE Inhibitors and ARBs:** Concomitant use with DAYPRO ALTA in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function (7)
- **Diuretics:** NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects (7)
- **Digoxin:** Concomitant use with DAYPRO ALTA can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels (7)

### USE IN SPECIFIC POPULATIONS

**Infertility:** NSAIDs are associated with reversible infertility. Consider withdrawal of DAYPRO ALTA in women who have difficulties conceiving (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2022

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## FULL PRESCRIBING INFORMATION

### **WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS**

#### **Cardiovascular Thrombotic Events**

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use [see *Warnings and Precautions (5.1)*].**
- **DAYPRO ALTA™ is contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications (4)* and *Warnings and Precautions (5.1)*].**

#### **Gastrointestinal Bleeding, Ulceration, and Perforation**

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) 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 and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [see *Warnings and Precautions (5.2)*].**

## **1 INDICATIONS AND USAGE**

DAYPRO ALTA is indicated:

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

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 General Dosing Instructions**

Carefully consider the potential benefits and risks of DAYPRO ALTA and other treatment options before deciding to use DAYPRO ALTA. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5)*].

After observing the response to initial therapy with DAYPRO ALTA, the dose and frequency should be adjusted to suit an individual patient's needs.

Divided doses may be tried in patients unable to tolerate single doses. For osteoarthritis patients of low body weight or 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.

### **2.2 Osteoarthritis**

For OA, the dosage is 1200 mg (two 600 mg tablets) given orally once a day.

## 2.3 Rheumatoid Arthritis

For RA, the dosage is 1200 mg (two 600 mg tablets) given orally once a day.

## 3 DOSAGE FORMS AND STRENGTHS

DAYPRO ALTA (oxaprozin potassium) tablets: 600 mg tablets, blue, capsule-shaped, film-coated, with Searle 1391 printed on one side.

## 4 CONTRAINDICATIONS

DAYPRO ALTA is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to oxaprozin potassium or any components of the drug product [*see Warnings and Precautions (5.7,5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7,5.8)*]
- In the setting of CABG surgery [*see Warnings and Precautions (5.1)*]

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Cardiovascular Thrombotic Events

Clinical trials of several cyclooxygenase-2 (COX-2) selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the 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, such as oxaprozin, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

### Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

### Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death,

and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of DAYPRO ALTA in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If DAYPRO ALTA is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

## **5.2 Gastrointestinal Bleeding, Ulceration, and Perforation**

NSAIDs, including DAYPRO ALTA cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, 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 occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

### Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, antiplatelet drugs (such as aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

### Strategies to Minimize the GI Risks in NSAID-Treated Patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue DAYPRO ALTA until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [*see Drug Interactions (7)*].

## **5.3 Hepatotoxicity**

Elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated

patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including oxaprozin potassium.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash), discontinue DAYPRO ALTA immediately, and perform a clinical evaluation of the patient.

#### **5.4 Hypertension**

NSAIDs, including DAYPRO ALTA, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [*see Drug Interactions (7)*].

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

#### **5.5 Heart Failure and Edema**

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of oxaprozin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [*see Drug Interactions (7)*].

Avoid the use of DAYPRO ALTA in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If DAYPRO ALTA is used in patients with severe heart failure, monitor patients for signs of worsening heart failure

#### **5.6 Renal Toxicity and Hyperkalemia**

##### Renal Toxicity

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 an NSAID 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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of DAYPRO ALTA in patients with advanced renal disease. The renal effects of DAYPRO ALTA may hasten the progression of renal dysfunction in patients with preexisting renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating DAYPRO ALTA. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of DAYPRO ALTA [*see Drug Interactions (7)*]. Avoid the use of DAYPRO ALTA in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If DAYPRO ALTA is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

### Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

### **5.7 Anaphylactic Reactions**

Oxaprozin potassium has been associated with anaphylactic reactions in patients with and without known hypersensitivity to oxaprozin and in patients with aspirin-sensitive asthma [*see Contraindications (4) and Warnings and Precautions (5.8)*].

Seek emergency help if an anaphylactic reaction occurs.

### **5.8 Exacerbation of Asthma Related to Aspirin Sensitivity**

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, DAYPRO ALTA is contraindicated in patients with this form of aspirin sensitivity [*see Contraindications (4)*]. When DAYPRO ALTA is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

### **5.9 Serious Skin Reactions**

NSAIDs, including oxaprozin potassium, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of DAYPRO ALTA at the first appearance of skin rash or any other sign of hypersensitivity. DAYPRO ALTA is contraindicated in patients with previous serious skin reactions to NSAIDs [*see Contraindications (4)*].

### **5.10 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as DAYPRO ALTA. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue DAYPRO ALTA and evaluate the patient immediately.

### **5.11 Fetal Toxicity**

#### Premature Closure of Fetal Ductus Arteriosus

Avoid use of NSAIDs, including DAYPRO ALTA, in pregnant women at about 30 weeks gestation and later. NSAIDs, including DAYPRO ALTA, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

#### Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs, including DAYPRO ALTA, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit DAYPRO ALTA use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if DAYPRO ALTA treatment extends beyond 48 hours. Discontinue DAYPRO ALTA if oligohydramnios occurs and follow up according to clinical practice [*see Use in Specific Populations (8.1)*].

#### **5.12 Hematologic Toxicity**

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with DAYPRO ALTA has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including DAYPRO ALTA, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders or concomitant use of warfarin, other anticoagulants, antiplatelet drugs (e.g., aspirin), SSRIs, and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding [*see Drug Interactions (7)*].

#### **5.13 Masking of Inflammation and Fever**

The pharmacological activity of DAYPRO ALTA in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

#### **5.14 Laboratory Monitoring**

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a complete blood count (CBC) and a chemistry profile periodically [*see Warnings and Precautions (5.2, 5.3, 5.6)*].

#### **5.15 Photosensitivity**

Oxaprozin has been associated with rash and/or mild photosensitivity in dermatologic testing. An increased incidence of rash on sun-exposed skin was seen in some patients in the clinical trials.

### **6 ADVERSE REACTIONS**

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [*see Warnings and Precautions (5.1)*]
- GI Bleeding, Ulceration and Perforation [*see Warnings and Precautions (5.2)*]
- Hepatotoxicity [*see Warnings and Precautions (5.3)*]
- Hypertension [*see Warnings and Precautions (5.4)*]



- Heart Failure and Edema [*see Warnings and Precautions (5.5)*]
- Renal Toxicity and Hyperkalemia [*see Warnings and Precautions (5.6)*]
- Anaphylactic Reactions [*see Warnings and Precautions (5.7)*]
- Serious Skin Reactions [*see Warnings and Precautions (5.9)*]
- Hematologic Toxicity [*see Warnings and Precautions (5.12)*]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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% to 10% of patients [*see Clinical Studies (14)*]:

Gastrointestinal experiences including: 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's syndrome), 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.

## 7 DRUG INTERACTIONS

See Table 1 for clinically significant drug interactions with oxaprozin potassium [see *Clinical Pharmacology* (12.3)].

**Table 1: Clinically Significant Drug Interactions with Oxaprozin Potassium**

<b>Drugs That Interfere with Hemostasis</b>	
<i>Clinical Impact:</i>	<ul style="list-style-type: none"> <li>• Oxaprozin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of oxaprozin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.</li> <li>• Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.</li> </ul>
<i>Intervention:</i>	Monitor patients with concomitant use of DAYPRO ALTA with anticoagulants (e.g., warfarin), antiplatelet drugs (e.g., aspirin), SSRIs, and SNRIs for signs of bleeding [see <i>Warnings and Precautions</i> (5.12)].
<b>Aspirin</b>	
<i>Clinical Impact:</i>	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see <i>Warnings and Precautions</i> (5.2)].
<i>Intervention:</i>	Concomitant use of DAYPRO ALTA and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see <i>Warnings and Precautions</i> (5.12)].  DAYPRO ALTA is not a substitute for low dose aspirin for cardiovascular protection.
<b>ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers</b>	
<i>Clinical Impact:</i>	<ul style="list-style-type: none"> <li>• NSAIDs may diminish the antihypertensive effect of ACE inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol).</li> <li>• In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.</li> </ul>
<i>Intervention:</i>	<ul style="list-style-type: none"> <li>• During concomitant use of DAYPRO ALTA and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.</li> <li>• During concomitant use of DAYPRO ALTA and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see <i>Warnings and Precautions</i> (5.6)].</li> <li>• When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.</li> </ul>
<b>Diuretics</b>	
<i>Clinical Impact:</i>	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some

	patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects [see <i>Warnings and Precautions (5.6)</i> ].
<b>Digoxin</b>	
<i>Clinical Impact:</i>	The concomitant use of oxaprozin potassium with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA and digoxin, monitor serum digoxin levels.
<b>Lithium</b>	
<i>Clinical Impact:</i>	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA and lithium, monitor patients for signs of lithium toxicity.
<b>Methotrexate</b>	
<i>Clinical Impact:</i>	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction) because NSAID administration may result in increased plasma levels of methotrexate, especially in patients receiving high doses of methotrexate.
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA and methotrexate, monitor patients for methotrexate toxicity.
<b>Cyclosporine</b>	
<i>Clinical Impact:</i>	Concomitant use of DAYPRO ALTA and cyclosporine may increase cyclosporine's nephrotoxicity.
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA and cyclosporine, monitor patients for signs of worsening renal function.
<b>NSAIDs and Salicylates</b>	
<i>Clinical Impact:</i>	Concomitant use of oxaprozin potassium with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy [see <i>Warnings and Precautions (5.2)</i> ].
<i>Intervention:</i>	The concomitant use of oxaprozin potassium with other NSAIDs or salicylates is not recommended.
<b>Pemetrexed</b>	
<i>Clinical Impact:</i>	Concomitant use of DAYPRO ALTA and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
<i>Intervention:</i>	During concomitant use of DAYPRO ALTA and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity.  NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed.  In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
<b>Corticosteroids</b>	
<i>Clinical Impact:</i>	Concomitant use of corticosteroids with DAYPRO ALTA may increase the risk of GI ulceration or bleeding.

<i>Intervention:</i>	Monitor patients with concomitant use of DAYPRO ALTA with corticosteroids for signs of bleeding [ <i>see Warnings and Precautions (5.2)</i> ].
<b>Glyburide</b>	
<i>Clinical Impact:</i>	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.
<i>Intervention</i>	During concomitant use of DAYPRO ALTA and glyburide, monitor patients' blood glucose in the beginning phase of cotherapy.

### Laboratory Test Interactions

False-positive urine immunoassay screening tests for benzodiazepines have been reported in patients taking oxaprozin. This is due to lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of oxaprozin therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish oxaprozin from benzodiazepines.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Use of NSAIDs, including DAYPRO ALTA, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of DAYPRO ALTA use between about 20 and 30 weeks of gestation, and avoid DAYPRO ALTA use at about 30 weeks of gestation and later in pregnancy (*see Clinical Considerations, Data*).

#### *Premature Closure of Fetal Ductus Arteriosus*

Use of NSAIDs, including DAYPRO ALTA, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

#### *Oligohydramnios/Neonatal Renal Impairment*

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies, oral administration of oxaprozin to pregnant rabbits at doses 0.1-times the maximum daily human dose (based on body surface area) resulted in evidence of teratogenicity; however, oral administration of oxaprozin to pregnant mice and rats during organogenesis at doses equivalent to the maximum recommended human dose (MRHD) revealed no evidence of teratogenicity or embryotoxicity. In rat reproduction studies in which oxaprozin was administered through late gestation failure to deliver and a reduction in live birth index was observed at doses equivalent to the MRHD. Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as oxaprozin potassium, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In

the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

## Clinical Considerations

### *Fetal/Neonatal Adverse Reactions*

#### Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including DAYPRO ALTA, can cause premature closure of the fetal ductus arteriosus (*see Data*).

#### Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If DAYPRO ALTA treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue DAYPRO ALTA and follow up according to clinical practice (*see Data*).

### *Labor or Delivery*

There are no studies on the effects of DAYPRO ALTA during labor or delivery. In animal studies, NSAIDs, including oxaprozin potassium, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

## Data

### *Human Data*

#### Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

#### Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

### *Animal data*

Teratology studies with oxaprozin potassium were performed in mice, rats, and rabbits in pregnant animals administered oral doses up to 200 mg/kg/day, 200 mg/kg/day, and 30 mg/kg/day, respectively, during the period of organogenesis. In rabbits, malformations were observed at doses greater than or

equal to 7.5 mg/kg/day of oxaprozin (0.1-times the MRHD of 1800 mg based on body surface area). However, in mice and rats, no drug-related developmental abnormalities or embryo-fetal toxicity were observed at doses up to 50 and 200 mg/kg/day of oxaprozin, respectively (0.1-times and 1.1-times the MRHD based on body surface area, respectively).

In fertility/reproductive studies in rats, 200 mg/kg/day oxaprozin was orally administered to female rats for 14 days prior to mating through lactation day (LD) 2, or from gestation day (GD) 15 through LD 2 and the females were mated with males treated with 200 mg/kg/day oxaprozin for 60 days prior to mating. Oxaprozin administration resulted in failure to deliver and a reduction in live birth index at 200 mg/kg/day (1.1-times the MRHD based on body surface area comparison).

## **8.2 Lactation**

### Risk Summary

Lactation studies have not been conducted with DAYPRO ALTA. It is not known whether DAYPRO ALTA is excreted in human milk. DAYPRO ALTA should be administered to lactating women only if clearly indicated. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DAYPRO ALTA and any potential adverse effects on the breastfed infant from the DAYPRO ALTA or from the underlying maternal condition.

## **8.3 Females and Males of Reproductive Potential**

### Infertility

#### *Females*

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including DAYPRO ALTA, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including DAYPRO ALTA, in women who have difficulties conceiving or who are undergoing investigation of infertility.

#### *Males*

Testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the MRHD based on body surface area) of oxaprozin for 42 days or 6 months [see *Nonclinical Toxicology (13.1)*].

## **8.4 Pediatric Use**

DAYPRO ALTA has not been investigated in patients <16 years of age. Safety and effectiveness of DAYPRO ALTA in pediatric patients have not been established.

## **8.5 Geriatric Use**

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects [see *Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.14)*].

Age was not shown to have an effect on the pharmacokinetics of DAYPRO ALTA following 600 mg, 1200 mg and 1800 mg doses or on the incidence of adverse reactions reported [see *Clinical Pharmacology* (12.3)]. 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 and Precautions* (5.6)].

## 10 OVERDOSAGE

Symptoms following acute NSAID overdoses have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare [see *Warnings and Precautions* (5.1, 5.2, 5.4, 5.6)].

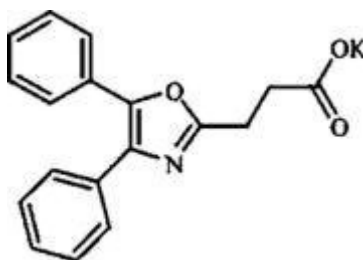
Manage patients with symptomatic and supportive care following an acute NSAID overdose. There are no specific antidotes. It is advisable to contact a poison control center (1-800-222-1222) to determine the latest recommendations because strategies for the management of overdose are continually evolving.

If gastric decontamination may be potentially beneficial to the patient, e.g., short time since ingestion or a large overdose (5 to 10 times the recommended dosage), consider emesis and/or activated charcoal (60 grams to 100 grams in adults, 1 gram to 2 grams per kg of body weight in pediatric patients) and/or an osmotic cathartic in symptomatic patients. Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

## 11 DESCRIPTION

DAYPRO ALTA (oxaprozin potassium) tablet is a member of the propionic acid group of NSAIDs, available as tablets of 600 mg (678 mg of oxaprozin potassium equivalent to 600 mg of oxaprozin) for oral administration. The chemical name for oxaprozin potassium is 4,5-diphenyl-2-oxazolepropionic acid, potassium salt. The molecular weight is 331. Its molecular formula is  $C_{18}H_{14}NO_3K$ , and it has the following chemical structure.

It has the following structural formula:



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.

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

DAYPRO ALTA, the potassium salt of oxaprozin, is a NSAID, which dissociates into the active moiety oxaprozin *in vivo*. Oxaprozin has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of DAYPRO ALTA, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Oxaprozin is a potent inhibitor of prostaglandin synthesis *in vitro*. Oxaprozin concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because oxaprozin potassium is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

### 12.3 Pharmacokinetics

#### General pharmacokinetic characteristics

In dose proportionality studies utilizing 600 mg, 1200 mg and 1800 mg doses, the pharmacokinetics of oxaprozin in healthy subjects demonstrated nonlinear kinetics of both the total and unbound drug in opposite directions, i.e., dose exposure related increase in the clearance of total drug and decrease in the clearance of the unbound drug. 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 pharmacokinetic parameters of oxaprozin in healthy subjects receiving a single dose or multiple once-daily doses of 1200 mg are presented in Table 2.

**Table 2. Oxaprozin Pharmacokinetic Parameters with DAYPRO ALTA Dosing (1200 mg) [Mean (%CV)]**

	Healthy Adults (18-42 years; N=12-24)			
	Total Drug		Unbound Drug	
	Single	Multiple	Single	Multiple
T <sub>max</sub> (hr)	1.67 (65)	2.13 (64)	1.71 (63)	1.59 (38)
Oral Clearance (L/hr/70 kg)	0.125 (15)	0.289 (17)	123 (20)	86.7 (33)
Apparent Volume of Distribution at Steady State (Vd/F; 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)

T<sub>max</sub> = time to reach the maximum plasma concentration of oxaprozin.

#### 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 2). 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.



### Distribution

The apparent volume of distribution (Vd/F) of total oxaprozin is approximately 10 to 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 (1200 mg QD), post-steady state mean elimination half-lives of total oxaprozin and protein unbound oxaprozin were 38.0 and 16.4 hours, respectively [see Table 2].

### Specific 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 Impairment:* 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, monitor patients with severe hepatic dysfunction closely for adverse reactions.

*Renal Impairment:* Oxaprozin's renal clearance decreased proportionally with creatinine clearance (CrCl), but since only about 5% of oxaprozin dose is excreted unchanged in the urine, the decrease in total body clearance becomes clinically important only in those subjects with highly decreased CrCl. Oxaprozin is not significantly removed from the blood in patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) due to its high protein binding. Oxaprozin plasma protein binding may decrease in patients with severe renal deficiency. Dosage adjustment may be necessary in patients with renal impairment [see Warnings and Precautions (5.6)].

*Cardiac Failure:* Well-compensated cardiac failure does not affect the plasma protein binding or the pharmacokinetics of oxaprozin.

### Drug Interaction Studies

*ACE inhibitors (enalapril)*: Oxaprozin potassium has been shown to alter the pharmacokinetics of enalapril (significant decrease in dose-adjusted  $AUC_{0-24}$  and  $C_{max}$ ) and its active metabolite enalaprilat (significant increase in dose-adjusted  $AUC_{0-24}$ ) [see *Drug Interactions (7)*].

*Aspirin*: When oxaprozin was administered with aspirin, the protein binding of oxaprozin was reduced, although the clearance of free oxaprozin was not altered. The clinical significance of this interaction is not known. An *in vitro* study showed that oxaprozin significantly interfered with the anti-platelet activity of aspirin [see *Drug Interactions (7)*].

*Beta-blockers (metoprolol)*: Subjects receiving 1200 mg DAYPRO once daily with 100 mg metoprolol twice daily exhibited statistically significant but transient increases in sitting and standing blood pressures after 14 days [see *Drug Interactions (7)*].

*Glyburide*: Oxaprozin altered the pharmacokinetics of glyburide; however, 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 [see *Drug Interactions (7)*].

*H<sub>2</sub>-receptor antagonists (cimetidine, ranitidine)*: The total 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*: Oxaprozin has produced an elevation in plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20% [see *Drug Interactions (7)*].

*Methotrexate*: Coadministration of oxaprozin with methotrexate resulted in approximately 36% reduction in apparent oral clearance of methotrexate [see *Drug Interactions (7)*].

*Other drugs*: The coadministration of oxaprozin and antacids, acetaminophen, or conjugated estrogens resulted in no statistically significant changes in pharmacokinetic parameters in single- and/or multiple-dose studies. The interaction of oxaprozin with cardiac glycosides has not been studied.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### Carcinogenesis

In carcinogenicity studies in rats and mice, 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 treated with up to 216 mg/kg via the diet (1.2-times the MRHD of 1800 mg based on body surface). The significance of this species-specific finding to man is unknown.

#### Mutagenesis

Oxaprozin did not genotoxic in 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.

### Impairment of Fertility

Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1.1-times the MRHD of 1800 mg based on body surface area comparison). However, testicular degeneration was observed in beagle dogs treated with 37.5 mg/kg/day (0.7-times the MRHD based on body surface area) of oxaprozin for 42 days or 6 months, a finding not confirmed in other species. The clinical relevance of this finding is not known.

## 14 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 (6)*].

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.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

<b>NDC Number</b>	<b>Size</b>
0025-5500-01	bottle of 100
0025-5500-03	bottle of 500
0025-5500-02	carton of 100 unit dose

Store at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) (see USP Controlled Room Temperature). Dispense in a tightly-closed container. Protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with DAYPRO ALTA and periodically during the course of ongoing therapy.

### Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [*see Warnings and Precautions (5.1)*].

### Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [*see Warnings and Precautions (5.2)*].

### Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop DAYPRO ALTA and seek immediate medical therapy [*see Warnings and Precautions (5.3)*].

### Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur [*see Warnings and Precautions (5.5)*].

### Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [*see Contraindications (4) and Warnings and Precautions (5.7)*].

### Serious Skin Reactions, including DRESS

Advise patients to stop taking DAYPRO ALTA immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [*see Warnings and Precautions (5.9, 5.10)*].

### Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including DAYPRO ALTA, may be associated with a reversible delay in ovulation [*see Use in Specific Populations (8.3)*].

### Fetal Toxicity

Inform pregnant women to avoid use of DAYPRO ALTA and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with DAYPRO ALTA is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours [*see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)*].

### Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of DAYPRO ALTA with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [*see Warnings and Precautions (5.2) and Drug Interactions (7)*]. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

### Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with DAYPRO ALTA until they talk to their healthcare provider [*see Drug Interactions (7)*].

This product’s labeling may have been updated. For the most recent prescribing information, please visit [www.pfizer.com](http://www.pfizer.com).

For medical information about DAYPRO ALTA, please visit [www.pfizermedinfo.com](http://www.pfizermedinfo.com) or call 1-800-438-1985.



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Division of Pfizer Inc.  
New York, NY 10017

LAB-0279-11.2

## Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

**What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?**

**NSAIDs can cause serious side effects, including:**

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

**Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”**

**Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.**

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death
- **The risk of getting an ulcer or bleeding increases with:**
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called “corticosteroids”, “antiplatelet drugs”, “anticoagulants”, “SSRIs” or “SNRIs”
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems
- **NSAIDs should only be used:**
  - exactly as prescribed
  - at the lowest dose possible for your treatment
  - for the shortest time needed

**What are NSAIDs?**

NSAIDs are used 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 NSAIDs?**

**Do not take NSAIDs:**

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

**Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:**

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Taking NSAIDs at about 20 weeks of pregnancy or later may harm your unborn baby. If you need to take NSAIDs for more than 2 days when you are between 20 and 30 weeks of pregnancy, your healthcare provider may need to monitor the amount of fluid in your womb around your baby. **You should not take NSAIDs after about 30 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

**Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements.** NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

## What are the possible side effects of NSAIDs?

**NSAIDs can cause serious side effects, including:**

**See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?**

- new or worse high blood pressure
- heart failure
- stroke
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- asthma attacks in people who have asthma
- bleeding and ulcers in the stomach and intestine
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

**Get emergency help right away if you get 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 taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:**

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

**If you take too much of your NSAID, call your healthcare provider or get medical help right away.**

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

## Other information about NSAIDs

- Aspirin is an NSAID 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 NSAIDs 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.

## General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

This product's labeling may have been updated. For the most recent prescribing information, please visit [www.pfizer.com](http://www.pfizer.com).



Distributed by  
**Pfizer Labs**  
Division of Pfizer Inc.  
New York, NY 10017

LAB-0790-4.2

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: November 2022