In osteoarthritis and adult rheumatoid arthritis

Get

*Usual adult dosage is 1200 mg (two 600-mg caplets) once a day. For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day may be appropriate.

†As with all NSAIDs (nonsteroidal anti-inflammatory drugs), the most frequently reported adverse reactions were related to the GI tract: nausea (8%) and dyspepsia (8%). In patients treated with DAYPRO, as with other NSAIDs in the long-term, serious GI toxicity such as bleeding, ulceration, and perforation can occur and patients should be selected accordingly.

Please see brief summary of prescribing information on last page of this advertisement.

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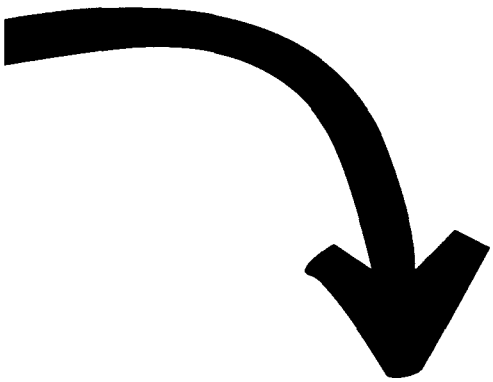

Two caplets, once a day*

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(oxaprozin) 600-mg caplets

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From the same chemical class as naproxen and ibuprofen, but with the extended duration of action of piroxicam[1]

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GI tolerability† without a loss of therapeutic efficacy[1]

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want in an NSAID

Get DAYPRO® (oxaprozin) 600-mg caplets *All you want in an NSAID*

✔ Usual adult dosage is 1200 mg (two 600-mg caplets) once a day*

Experience with NSAIDs has shown that starting therapy with maximal doses in elderly patients or those with CHF, hepatic impairment, or mild-to-moderate renal insufficiency is likely to increase the frequency of adverse events and is not recommended.

*For osteoarthritis patients of low body weight or with milder disease, an initial dosage of one 600-mg caplet once a day may be appropriate.

BRIEF SUMMARY

CONTRAINDICATIONS: Patients with previously demonstrated hypersensitivity to oxaprozin or any of its components or in individuals with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe and occasionally fatal asthmatic and anaphylactic reactions have been reported in patients receiving NSAIDs, and there have been rare reports of anaphylaxis in patients taking oxaprozin.

WARNINGS: RISK OF GASTROINTESTINAL (GI) ULCERATION, BLEEDING, AND PERFORATION WITH NONSTEROIDAL ANTI-INFLAMMATORY DRUG THERAPY: Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials for several months to 2 years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Patients at risk for developing peptic ulceration and bleeding are those with a prior history of serious GI events, alcoholism, smoking, or other factors known to be associated with peptic ulcer disease. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in these populations. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions.

PRECAUTIONS: As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or resolve with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGOT (AST) occurred in controlled clinical trials of Daypro in just under 1% of patients. 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 have been reported with Daypro, and there may be a risk of fatal hepatitis with oxaprozin, such as has been seen with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (eosinophilia, rash, fever), Daypro should be discontinued. Well-compensated hepatic cirrhosis does not appear to alter the disposition of unbound oxaprozin, so dosage adjustment is not necessary. Caution should be observed in patients with severe hepatic dysfunction. Acute interstitial nephritis, hematuria, and proteinuria have been reported with Daypro as with other NSAIDs. Long-term administration of some NSAIDs to animals has resulted in renal papillary necrosis and other abnormal renal pathology. This was not observed with oxaprozin, but the clinical significance of this difference is unknown. A second form of renal toxicity has been seen in patients with preexisting conditions leading to a reduction in renal blood flow, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an 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 previously impaired renal function, heart failure, or liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is often followed by recovery to the pretreatment state. Those patients at high risk who chronically take oxaprozin should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, or loss of appetite. As with all NSAID therapy, patients may occasionally develop some elevation of serum creatinine and BUN levels without any signs or symptoms. The pharmacokinetics of oxaprozin may be significantly altered in patients with renal insufficiency or in patients who are undergoing hemodialysis. Such patients should be started on doses of 600 mg/day, with cautious dosage increases if the desired effect is not obtained. Oxaprozin is not dialyzed because of its high degree of protein binding. Like other NSAIDs, Daypro may worsen fluid retention by the kidneys in patients with uncompensated cardiac failure due to its effect on prostaglandins. It should be used with caution in patients with a history of hypertension, cardiac decompensation, in patients on chronic diuretic therapy, or in those with other conditions predisposing to fluid retention. 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. Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up. Anemia may occur in patients receiving oxaprozin or other NSAIDs. This may be due to fluid retention, gastrointestinal blood loss, or an incompletely described effect upon erythrogenesis. Patients on long-term treatment with Daypro should have their hemoglobin or hematocrit values determined at appropriate intervals as determined by the clinical situation. Oxaprozin, like other NSAIDs, can affect platelet aggregation and prolong bleeding time. Daypro should be used with caution in patients with underlying hemostatic defects or in those who are undergoing surgical procedures where a high degree of hemostasis is needed. The side effects of NSAIDs can cause discomfort and, rarely, serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with their patients the potential risks and likely benefits of Daypro treatment, particularly in less-serious conditions where treatment without Daypro may represent an acceptable alternative to both the patient and the physician. Patients receiving Daypro may benefit from physician instruction in the symptoms of the more common or serious GI, renal, hepatic, hematologic, and dermatologic adverse effects. Daypro is not known to interfere with most common laboratory tests, including tests for drugs of abuse. Concomitant administration of Daypro and aspirin is not recommended because oxaprozin displaces salicylates from plasma protein binding sites. Coadministration would be expected to increase the risk of salicylate toxicity. The anticoagulant effects of warfarin were not affected by the coadministration of 1200 mg/day of Daypro. Nevertheless, caution should be exercised when adding any drug that affects platelet function to the regimen of patients receiving oral anticoagulants. 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. 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. 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 lithium and cardiac glycosides has not been studied. In oncogenicity studies, oxaprozin administration for 2 years was associated with the exacerbation of liver neoplasms (hepatic adenomas and carcinomas) in male CD mice, but not in female CD mice or rats. The significance of this species-specific finding to man is unknown. Oxaprozin did not display mutagenic potential. Oxaprozin administration was not associated with impairment of fertility in male and female rats at oral doses up to 200 mg/kg/day (1180 mg/m^2); the usual human dose is 17 mg/kg/day (629 mg/m^2). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m^2) of oxaprozin for 6 months, or 37.5 mg/kg/day for 42 days, a finding not confirmed in other species. The clinical relevance of this finding is not known. Pregnancy Category C: There are no adequate or well-controlled studies in pregnant women. Teratology studies with oxaprozin were performed in mice, rats, and rabbits. In mice and rats, no drug-related developmental abnormalities were observed at 50 to 200 mg/kg/day of oxaprozin (225 to 900 mg/m^2). However, in rabbits, infrequent malformed fetuses were observed in dams treated with 7.5 to 30 mg/kg/day of oxaprozin (the usual human dosage range). Oxaprozin should be used during pregnancy only if the potential benefits justify the potential risks to the fetus. The effect of oxaprozin in pregnant women is unknown. NSAIDs are known to delay parturition, to accelerate closure of the fetal ductus arteriosus, and to be associated with dystocia. Oxaprozin is known to have caused decreases in pup survival in rat studies. Accordingly, the use of oxaprozin during late pregnancy should be avoided. Studies of oxaprozin excretion in human milk have not been conducted; however, oxaprozin was found in the milk of lactating rats. Since the effects of oxaprozin on infants are not known, caution should be exercised if oxaprozin is administered to nursing women. Safety and effectiveness of Daypro in children have not been established. 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. Although selected elderly patients in controlled clinical trials tolerated Daypro as well as younger patients, caution should be exercised in treating the elderly, and extra care should be taken when choosing a dose. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS: The most frequently reported adverse reactions were related to the GI 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: abdominal pain/distress, anorexia, constipation*, diarrhea*, dyspepsia*, flatulence, nausea*, vomiting, CNS inhibition (depression, sedation, somnolence, or confusion), disturbance of sleep, rash*, tinnitus, dysuria or frequency.

INCIDENCE LESS THAN 1%: ***Probable causal relationship:*** The following adverse reactions were reported in clinical trials at an incidence of less than 1% or were reported from foreign experience. Those reactions reported only from foreign marketing experience are in *italics*. The probability of a causal relationship exists between the drug and these adverse reactions: anaphylaxis, edema, blood pressure changes, peptic ulceration and/or GI bleeding, liver function abnormalities including *hepatitis*, stomatitis, hemorrhoidal or rectal bleeding, anemia, thrombocytopenia, leukopenia, ecchymoses, weight gain, weight loss, weakness, malaise, symptoms of upper respiratory tract infection, pruritus, urticaria, photosensitivity, blurred vision, conjunctivitis, *acute interstitial nephritis*, 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: palpitations, alteration in taste, sinusitis, pulmonary infections, alopecia, hearing decrease, increase in menstrual flow.

DRUG ABUSE AND DEPENDENCE: Daypro is a non-narcotic drug. Usually reliable animal studies have indicated that Daypro has no known addiction potential in humans.

OVERDOSAGE: No patient experienced either an accidental or intentional overdosage of Daypro in the clinical trials of the drug. Symptoms following acute overdose with other NSAIDs are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain and are generally reversible with supportive care. GI bleeding and coma have occurred following NSAID overdose. Hypertension, acute renal failure, and respiratory depression are rare. 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. 2/2/93 • P93DA7916V

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Morrow JD, Margolies GR, Rowland J, Roberts LJ 2nd. Evidence that histamine is the causative toxin of scombroid-fish poisoning. N Engl J Med 1991; 324:716-20.

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Clinical Experience Network (CEN). A large-scale, office-based study evaluates the use of a new class of nonsedating antihistamines. A report from CEN. J Am Board Fam Pract 1990; 3:241-58.

Book

Rakel RE. Textbook of family practice. 4th ed. Philadelphia: WB Saunders, 1990.

Chapter in Book

Haynes RC Jr. Agents affecting calcification: calcium, parathyroid hormone, calcitonin, vitamin D, and other compounds. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York: Pergamon Press, 1990.

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Schwartz JL. Review and evaluation of smoking cessation methods: the United States and Canada, 1978-1985. Bethesda, MD: Department of Health and Human Services, 1987. (NIH publication no. 87-2940.)

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Nursing Mothers: The effects of ESGIC-PLUS™ on infants of nursing mothers are not known. Barbiturates are excreted in the breast milk of nursing mothers. The serum levels in infants are believed to be insignificant with therapeutic doses.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: The most frequent adverse reactions are drowsiness and dizziness. Less frequent adverse reactions are lightheadedness and gastrointestinal disturbances including nausea, vomiting and flatulence. Mental confusion or depression can occur due to intolerance or overdosage of butalbital.

Several cases of dermatological reactions including toxic epidermal necrolysis and erythema multiforme have been reported.

DRUG ABUSE & DEPENDENCE: Prolonged use of barbiturates can produce drug dependence, characterized by psychic dependence and tolerance. The abuse liability of ESGIC-PLUS™ is similar to that of other barbiturate-containing drug combinations. Caution should be exercised when prescribing medication for patients with a known propensity for taking excessive quantities of drugs, which is not uncommon in patients with chronic tension headache.

OVERDOSAGE: The toxic effects of acute overdosage of ESGIC-PLUS™ are attributable mainly to its barbiturate component, and, to a lesser extent, acetaminophen. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from ESGIC-PLUS™ overdosage is unlikely.

Barbiturate: Signs and Symptoms: Drowsiness, confusion, coma; respiratory depression; hypotension; shock.

Treatment:

1. Maintenance of an adequate airway, with assisted respiration and oxygen administration as necessary.
2. Monitoring of vital signs and fluid balance.
3. If the patient is conscious and has not lost the gag reflex, emesis may be induced with ipecac. Care should be taken to prevent pulmonary aspiration of vomitus. After completion of vomiting, 30 grams of activated charcoal in a glass of water may be administered.
4. If emesis is contraindicated, gastric lavage may be performed with a cuffed endotracheal tube in place with the patient in the facedown position. Activated charcoal may be left in the emptied stomach and a saline cathartic administered.
5. Fluid therapy and other standard treatment for shock, if needed.
6. If renal function is normal, forced diuresis may aid in the elimination of the barbiturate. Alkalinization of the urine increases renal excretion of some barbiturates, especially phenobarbital.
7. Although not recommended as a routine procedure, hemodialysis may be used in severe barbiturate intoxication or if the patient is anuric or in shock.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdosage may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case, within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Oral: One ESGIC-PLUS™ tablet every four hours as needed. Do not exceed six tablets or capsules per day.

HOW SUPPLIED: ESGIC-PLUS™ (Butalbital* 50 mg [*WARNING—May be habit forming], Acetaminophen 500 mg and Caffeine 40 mg) Tablets are white, capsule-shaped, single-scored, and are debossed "FOREST" on the upper side, "678" on one side of the score on the lower side. They are supplied as: Bottles of 100—NDC 0456-0678-01.

Storage: Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Dispense in a tight, light-resistant container with a child-resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by: MIKART, INC., Atlanta, GA 30318

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