



## INFORMATION FOR AUTHORS

The *Cleveland Clinic Journal of Medicine* is an indexed, peer-reviewed journal published by the Cleveland Clinic Educational Foundation as part of its program of medical education and scientific communication. It is issued six times yearly. The publication's objective is to disseminate scientific and clinically significant information to the medical community, especially physicians in practice. Therefore, manuscripts on topics of clinical relevance will be given high priority.

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### SUBMISSION OF MANUSCRIPTS

Unsolicited manuscripts are welcome and will be given careful consideration. Manuscripts and related correspondence should be addressed to the Editor, *Cleveland Clinic Journal of Medicine*, E37, 9500 Euclid Avenue, Cleveland, OH 44195 (phone 216/444-2661; fax 216/444-9385).

Submissions should include the original manuscript, two copies, and three complete sets of figures. Manuscripts should be accompanied by a letter that designates one author as correspondent and provides a complete address and telephone number. Manuscripts are considered with the understanding that they are original, have not been previously published, and are not under consideration for publication elsewhere.

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### TYPES OF ARTICLES

The *Cleveland Clinic Journal of Medicine* publishes various types of articles to address the need of its readers for up-to-date information. Most articles fit into one of the categories described below.

**Contribution:** Report of original clinical and clinically relevant basic investigative study.

**Comprehensive review:** In-depth analysis of subject relevant to medical practice, such as diagnosis and treatment of disease, and clinical implications of research.

**Brief review:** Article that addresses discrete clinical problems and that reflects the author's expertise.

**Editorial:** Brief, substantiated commentary on controversial clinical or socioeconomic issue, either freestanding or related to a simultaneously published article.

**Case report:** Atypical or uncommon characteristics of a known entity; new information on pathogenesis; an apparently unique case that represents a previously undescribed syndrome.

**Letter to the editor:** Correspondence is welcome and will be published as space permits.

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### MANUSCRIPT PREPARATION

These guidelines are in accordance with the "Uniform requirements for manuscripts submitted to medical journals" (N Engl J Med 1991; 324:424-428). The submitted manuscript should include an abstract of 200 words or less, references, tables, and legends for illustrations. It should be typed double-spaced. Tables and illustrations should be cited within the article.

**Organization:** A manuscript that describes observational or experimental studies typically includes these sections: Introduction, Materials and Methods, Results, and Discussion. Sources of outside funding should be acknowledged.

**References:** Pertinent references should be cited and numbered in the order in which they are mentioned in the text. Periodicals should be abbreviated as in *Index Medicus*. If a citation has six or fewer authors, all author names should be listed; if a citation has seven or more authors, then "et al" should be used after the third name. Authors are responsible for the accuracy of references; a photostat of the first page of any article referenced should be furnished if requested.

**Figures:** Three sets of figures should accompany the manuscript. If a figure has been published elsewhere, a permission letter from the publisher must be provided even if it is from the author's own work. Figures should be identified by labels placed on the back. Drawings, graphs, and charts should be professionally rendered. Color figures should be submitted as transparencies. Legends for photomicrographs should include the stain type and magnification.

Patient's identity must be masked, and written consent to publish the photograph must accompany the manuscript.

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### PEER REVIEW

Manuscripts are subject to peer review. Authors are usually notified within 6 weeks about the acceptability of a manuscript, but longer intervals are sometimes unavoidable.

All papers accepted for publication will be edited as necessary for clarity and conformity with the *Cleveland Clinic Journal of Medicine* style.

Authors are responsible for all statements made in their work, including any changes made by the copy editor and authorized by the corresponding author.

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**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 erythropoiesis. 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<sup>2</sup>); the usual human dose is 17 mg/kg/day (625 mg/m<sup>2</sup>). However, testicular degeneration was observed in beagle dogs treated with 37.5 to 150 mg/kg/day (750 to 3000 mg/m<sup>2</sup>) 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<sup>2</sup>). 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 overdose 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.

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