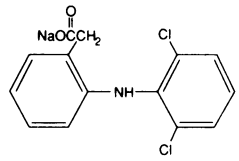
Voltaren®
diclofenac sodium

Enteric-Coated Tablets

Prescribing Information

DESCRIPTION
Voltaren, diclofenac sodium, is a nonsteroidal, anti-inflammatory phenylacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, monosodium salt. The structural formula of diclofenac sodium is:



Diclofenac sodium is a faintly yellow-white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1N hydrochloric acid. Its molecular weight is 318.14. In water, diclofenac sodium has a single dissociation constant (pKa) of 4.0.

Voltaren is available as enteric-coated tablets of 25 mg, 50 mg, and 75 mg for oral administration.

Inactive Ingredients. Cellulose acetate phthalate, colloidal silicon dioxide (25-mg and 50-mg enteric-coated tablets only), diethyl phthalate, hydroxypropyl methylcellulose, iron oxide (25-mg and 50-mg enteric-coated tablets only), lactose, magnesium stearate, microcrystalline cellulose, povidone, shellac, sodium starch glycolate (75-mg enteric-coated tablets only), starch (25-mg and 50-mg enteric-coated tablets only), talc (75-mg enteric-coated tablets only), titanium dioxide.

CLINICAL PHARMACOLOGY
Pharmacology
In pharmacologic studies, Voltaren has shown anti-inflammatory, analgesic, and antipyretic activity. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacokinetics
Voltaren is completely absorbed from the gastrointestinal tract after fasting oral administration, with peak plasma levels occurring in 2-3 hours. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. The mean terminal half-life in plasma is approximately 2 hours, but early elimination is much more rapid. Area under the plasma concentration curve (AUC) is dose-proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.0, 1.5, and 2 mcg/ml for 25-mg, 50-mg, and 75-mg doses, respectively. It should be noted that the administration of several individual tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is due to the uncertainty of complete gastric emptying of all tablets at once to the duodenum. Clearance and volume of distribution were about 350 ml/min and 550 ml/kg, respectively. After repeated oral administration of 50 mg b.i.d., Voltaren did not accumulate in plasma. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity. More than 99% of diclofenac is reversibly bound to human plasma albumin.

Voltaren is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of the principal metabolite, 4'-hydroxy-diclofenac, account for 20-30% of the dose excreted in the urine and for 10-20% of the dose excreted in the bile. Conjugates of three other metabolites (5-hydroxy-,3'-hydroxy-, and 4',5-dihydroxy-diclofenac) together account for 10-20% of the dose excreted in the urine and for small amounts excreted in the bile. Conjugates of unchanged diclofenac account for 5-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. It is not known whether there is genetic polymorphism in the enzymes responsible for metabolism of diclofenac.

The extent of absorption of Voltaren is not significantly affected when the drug is taken with food; however, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients. There is also a reduction in peak plasma levels.

A 4-week study comparing plasma level profiles of diclofenac (50 mg b.i.d.) in younger (26-46) versus older (66-81) adults did not show differences between age groups (10 patients per age group).

Single-dose studies of the effects of renal function impairment (50 mg intravenously) or hepatic impairment (100 mg oral solution) have been performed in small numbers of patients. To date no differences in the pharmacokinetics of diclofenac have been detected in patients with renal or hepatic impairment.

In patients with renal impairment (N = 5, creatinine clearance 3 to 42 ml/min), AUC values and elimination rates were comparable to those in healthy subjects.

In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N = 10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Voltaren diffuses into and out of the synovial fluid. Diffusion into the joint occurs during the first 4 hours following a dose, while plasma levels are higher than those in synovial fluid, after which the process reverses and synovial fluid levels are slightly higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of Voltaren.

In healthy subjects, the daily administration of 150 mg of Voltaren for 3 weeks resulted in a mean fecal blood loss less than that observed with 3.0 g of aspirin daily. In repeated-dose studies, mean fecal blood loss with 150 mg of Voltaren was also less than that observed with 750 mg of naproxen or 150 mg of indomethacin. Repeated-dose endoscopic studies in normal volunteers showed that daily doses of 75 mg or 100 mg of Voltaren for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those which occurred following 500 mg daily doses of naproxen. The clinical significance of these findings is unknown since there is no evidence available to indicate that diclofenac is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.

In patients with rheumatoid arthritis, Voltaren has been administered safely in combination with gold or corticosteroids.

INDICATIONS AND USAGE
Voltaren is indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

CONTRAINDICATIONS
Voltaren is contraindicated in patients with hypersensitivity to it. Voltaren should not be given to patients in whom Voltaren, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions because severe, rarely fatal, anaphylactic-like reactions to Voltaren have been reported in such patients.

WARNINGS
Gastrointestinal Effects
Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving Voltaren. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac sodium, even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac sodium possible consistent with achieving a satisfactory therapeutic response.

Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper G.I. ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious G.I. toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. 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, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

Hepatic Effects
As with other nonsteroidal anti-inflammatory drugs, elevations of one or more liver tests may occur during Voltaren therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., 1.2-3 times the upper limit of normal [ULN]), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. The SGPT (ALT) test is probably the most sensitive indicator of liver injury. In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of SGOT (SGPT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during Voltaren treatment. In a large, open, controlled trial, meaningful elevations of SGOT and/or SGPT occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a lower incidence of borderline (1.2-3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of SGOT or SGPT was observed in patients randomized to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

Transaminase elevations were reversible on cessation of therapy, and among 51 patients in all studies with marked elevations, signs and symptoms of liver disease occurred in only 3 cases, and only 1 patient developed jaundice. Most patients with borderline elevations did not have therapy interrupted; transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms, physicians should measure transaminases periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), which involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action to take should these signs and symptoms appear.

PRECAUTIONS
General
Allergic Reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions including anaphylaxis, have been reported with Voltaren. Specific allergic manifestations consisting of swelling of eyelids, lips, pharynx and larynx, urticaria, asthma, and bronchospasm, sometimes with a concomitant fall in blood pressure (severe at times) have been observed in clinical trials and/or the foreign marketing experience with Voltaren. Anaphylaxis has been reported rarely from foreign sources; in U.S. clinical trials with Voltaren in over 6000 patients, 1 case of anaphylaxis was reported. In controlled clinical trials, allergic reactions have been observed at an incidence of 0.5%. These reactions can occur without prior exposure to the drug.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking Voltaren. Therefore, as with other nonsteroidal anti-inflammatory drugs, Voltaren should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Renal Effects: As a class, nonsteroidal anti-inflammatory drugs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. Papillary necrosis was observed only in 1 animal study with diclofenac, a 4-week study in baboons in which the drug was administered intramuscularly. In oral studies some evidence of renal toxicity was noted but papillary necrosis was not reported.

A second form of renal toxicity generally associated with nonsteroidal anti-inflammatory drugs is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in clinical trials during which serum creatinines and BUNs were followed serially. There were only 7 patients (0.18%) whose serum creatinines and concurrent serum BUNs were greater than 2.0 mg/dl and 40 mg/dl, respectively, while on diclofenac (mean rise in the 7 patients: creatinine 1.5 mg/dl and BUN 20 mg/dl). It is not yet clear whether this low incidence of renal impairment in clinical trials, plus the observation of less renal toxicity than is usual in rodents, will translate into a significant reduction of the risk of renal failure in susceptible patients in widespread use.

Since Voltaren metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, 1 patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA, demonstrated in rats).

Information for Patients
Voltaren, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious G.I. 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 (see WARNINGS, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy*).

Drug Interactions

Aspirin: Concomitant administration of Voltaren and aspirin is not recommended because Voltaren is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

Anticoagulants: While studies have not shown Voltaren to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including Voltaren, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Voltaren, like other NSAIDs, through effects on renal prostaglandins, may cause increased toxicity of certain drugs. Digoxin and methotrexate serum levels may be elevated as well as cyclosporine's nephrotoxicity. Patients receiving these drugs who are started on, or are given increased doses of, Voltaren or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs. In the case of digoxin, serum levels should be monitored.

Lithium: Voltaren decreases lithium renal clearance and increases lithium plasma levels. In patients taking Voltaren and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Voltaren does not alter glucose metabolism in normal subjects nor are the effects of oral hypoglycemic agents altered by the concomitant administration of Voltaren. There are rare reports, however, from postmarketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac which necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Voltaren and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of Voltaren.

Protein Binding

In vitro, Voltaren interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence in vitro on the protein binding of Voltaren in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Voltaren increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Voltaren is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given Voltaren up to 2 mg/kg/day (approximately the human dose) have revealed no significant increases in tumor incidence.

There was a slight increase in benign mammary fibroadenomas in mid-dose females (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. Voltaren did not show mutagenic potential in various mutagenicity studies including the Ames test. Voltaren administered to male and female rats at 4 mg/kg/day did not affect fertility. A 2-year mouse carcinogenicity study is underway.

Teratogenic Effects

Pregnancy Category B: Reproduction studies have been performed in mice given Voltaren (up to 20 mg/kg/day) and in rats and rabbits given Voltaren (up to 10 mg/kg/day), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Voltaren has been shown to cross the placental barrier in mice and rats.

There are no adequate and well-controlled studies in pregnant women. Voltaren should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of Voltaren during late pregnancy should be avoided.

Labor and Delivery

The effects of Voltaren on labor and delivery in pregnant women are unknown. However, as with other nonsteroidal anti-inflammatory drugs, it is possible that Voltaren may inhibit uterine contraction.

Nursing Mothers

Voltaren has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Voltaren is not recommended for use in nursing women.

Pediatric Use

Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded-controlled and open-label clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally impossible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in less than 1% of approximately 1800 patients during their first 3 months of diclofenac treatment and in less than 2% of approximately 800 patients followed for 1 year. The only control group with sufficient patients for comparison received aspirin and only for the first 30 days of treatment. Comparative rates were 0.2% for peptic ulcer or G.I. bleeding in approximately 2000 diclofenac-treated patients and 0.6% in approximately 600 aspirin-treated patients.

In double-blind trials there were fewer minor gastrointestinal complaints in 1227 patients treated with Voltaren than in 721 patients treated with aspirin, 22% vs 33% (compared to 13% on placebo).

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred at an overall rate of about 2% during the first 2 months of Voltaren treatment. Unlike aspirin, where elevations occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the upper limit of normal) were seen in about 1% of patients treated for 2-6 months (see WARNINGS).

The following adverse reactions were reported in patients treated with Voltaren:

Incidence Greater Than 1% (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps*, headache*, fluid retention, abdominal distention.

Digestive: Diarrhea*, indigestion*, nausea*, constipation*, flatulence, liver test abnormalities, PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special senses: Tinnitus.

*Incidence, 3% to 9% (incidence of unmarked reactions is 1-3%)

Incidence Less Than 1%—Causal Relationship Probable (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia, aplastic anemia, agranulocytosis,* purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major,* angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome,* proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure*.

Incidence Less Than 1%—Causal Relationship Unknown (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing,* tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination,* convulsions, *disorientation, psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE

Worldwide reports on overdosage with diclofenac cover 27 cases. In 10 of these 27 cases, diclofenac was the only drug taken; all of these patients recovered. The highest dose of diclofenac was 2.5 g in a 20-year-old male who suffered acute renal failure as a consequence, and who was treated with three dialysis sessions and recovered in 2 days. The next highest dose was 2.35 g in a 17-year-old girl who experienced vomiting and drowsiness. A dose of 2.0 g of diclofenac was taken by a woman of unspecified age who remained asymptomatic.

Animal LD_{50}'s show a wide range of susceptibilities to acute overdosage with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg—rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of Voltaren (99% protein bound, see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of Voltaren.

DOSAGE AND ADMINISTRATION

Voltaren may be administered as 25-mg, 50-mg, and 75-mg enteric-coated tablets. Patients should be generally maintained on the lowest dosage of Voltaren consistent with achieving a satisfactory therapeutic response.

In osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d., or 75 mg b.i.d. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

In rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d., or 75 mg b.i.d. Dosages above 200 mg/day have not been studied in patients with rheumatoid arthritis.

In ankylosing spondylitis, the recommended dosage is 100-125 mg/day, administered as 25 mg q.i.d., with an extra 25 mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

HOW SUPPLIED

Enteric-Coated Tablets 25 mg—yellow, round, biconvex with beveled edges (imprinted VOLTAREN 25)

Bottles of 60	NDC 0028-0058-60
Bottles of 100	NDC 0028-0058-01
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0058-61

Enteric-Coated Tablets 50 mg—light brown, round, biconvex with beveled edges (imprinted VOLTAREN 50)

Bottles of 60	NDC 0028-0162-60
Bottles of 100	NDC 0028-0162-01
Bottles of 1000	NDC 0028-0162-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0162-61

Enteric-Coated Tablets 75 mg—white, round, biconvex with beveled edges (imprinted VOLTAREN 75)

Bottles of 60	NDC 0028-0164-60
Bottles of 100	NDC 0028-0164-01
Bottles of 1000	NDC 0028-0164-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0164-61

Samples, when available, are identified by the word *SAMPLE* appearing on each enteric-coated tablet.

Do not store above 86°F Protect from moisture.

Dispense in tight container (USP).

Printed in U.S.A. C91-8 (Rev. 4/91)

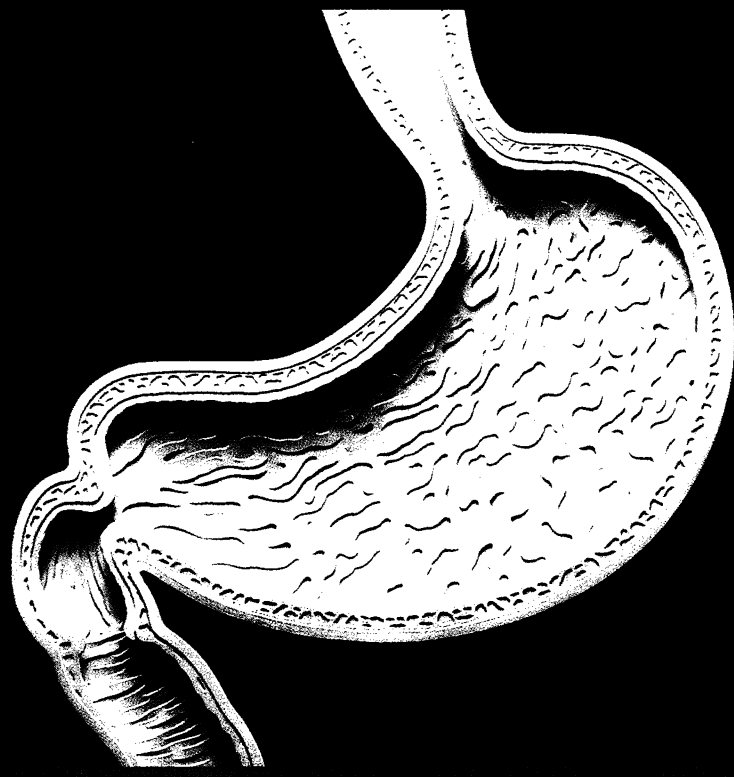
Geigy GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

388-10742-A

In arthritis therapy:

Because you're concerned about G.I. reactions...

NSAIDs may adversely affect the hematologic, hepatic, renal, and gastrointestinal systems, although G.I. reactions occur most frequently.



Voltaren
diclofenac sodium

An established record of G.I. tolerability.*

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*Contraindicated in patients hypersensitive to aspirin, other NSAIDs, or Voltaren. As with other NSAIDs, the most frequent complaints relate to the G.I. tract. In patients treated chronically with NSAID therapy, serious G.I. toxicity such as bleeding, ulceration, and perforation can occur. Elevations of SGOT and/or SGPT, some significant, have been reported in association with Voltaren treatment; cases of severe hepatic reactions have rarely been reported.

Please see complete Prescribing Information preceding this advertisement.

388-10742-A

Voltaren®
diclofenac sodium

Enteric-Coated Tablets

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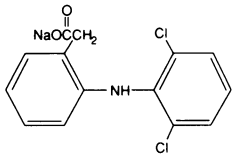


Diclofenac sodium is a faintly yellow-white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1N hydrochloric acid. Its molecular weight is 318.14. In water, diclofenac sodium has a single dissociation constant (pKa) of 4.0.

Voltaren is available as enteric-coated tablets of 25 mg, 50 mg, and 75 mg for oral administration.

Inactive Ingredients. Cellulose acetate phthalate, colloidal silicon dioxide (25-mg and 50-mg enteric-coated tablets only), diethyl phthalate, hydroxypropyl methylcellulose, iron oxide (25-mg and 50-mg enteric-coated tablets only), lactose, magnesium stearate, microcrystalline cellulose, povidone, shellac, sodium starch glycolate (75-mg enteric-coated tablets only), starch (25-mg and 50-mg enteric-coated tablets only), talc (75-mg enteric-coated tablets only), titanium dioxide.

CLINICAL PHARMACOLOGY
Pharmacology
In pharmacologic studies, Voltaren has shown anti-inflammatory, analgesic, and antipyretic activity. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacokinetics
Voltaren is completely absorbed from the gastrointestinal tract after fasting oral administration, with peak plasma levels occurring in 2-3 hours. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. The mean terminal half-life in plasma is approximately 2 hours, but early elimination is much more rapid. Area under the plasma concentration curve (AUC) is dose-proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.0, 1.5, and 2 mcg/ml for 25-mg, 50-mg, and 75-mg doses, respectively. It should be noted that the administration of several individual tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is due to the uncertainty of complete gastric emptying of all tablets at once to the duodenum. Clearance and volume of distribution were about 350 ml/min and 550 ml/kg, respectively. After repeated oral administration of 50 mg b.i.d., Voltaren did not accumulate in plasma. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity. More than 99% of diclofenac is reversibly bound to human plasma albumin.

Voltaren is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of the principal metabolite, 4'-hydroxy-diclofenac, account for 20-30% of the dose excreted in the urine and for 10-20% of the dose excreted in the bile. Conjugates of three other metabolites (5-hydroxy-,3'-hydroxy-, and 4',5-dihydroxy-diclofenac) together account for 10-20% of the dose excreted in the urine and for small amounts excreted in the bile. Conjugates of unchanged diclofenac account for 5-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. It is not known whether there is genetic polymorphism in the enzymes responsible for metabolism of diclofenac.

The extent of absorption of Voltaren is not significantly affected when the drug is taken with food; however, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients. There is also a reduction in peak plasma levels.

A 4-week study comparing plasma level profiles of diclofenac (50 mg b.i.d.) in younger (26-46) versus older (66-81) adults did not show differences between age groups (10 patients per age group).

Single-dose studies of the effects of renal function impairment (50 mg intravenously) or hepatic impairment (100 mg oral solution) have been performed in small numbers of patients. To date no differences in the pharmacokinetics of diclofenac have been detected in patients with renal or hepatic impairment.

In patients with renal impairment (N = 5, creatinine clearance 3 to 42 ml/min), AUC values and elimination rates were comparable to those in healthy subjects.

In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N = 10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Voltaren diffuses into and out of the synovial fluid. Diffusion into the joint occurs during the first 4 hours following a dose, while plasma levels are higher than those in synovial fluid, after which the process reverses and synovial fluid levels are slightly higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of Voltaren.

In healthy subjects, the daily administration of 150 mg of Voltaren for 3 weeks resulted in a mean fecal blood loss less than that observed with 3.0 g of aspirin daily. In repeated-dose studies, mean fecal blood loss with 150 mg of Voltaren was also less than that observed with 750 mg of naproxen or 150 mg of indomethacin. Repeated-dose endoscopic studies in normal volunteers showed that daily doses of 75 mg or 100 mg of Voltaren for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those which occurred following 500 mg daily doses of naproxen. The clinical significance of these findings is unknown since there is no evidence available to indicate that diclofenac is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.

In patients with rheumatoid arthritis, Voltaren has been administered safely in combination with gold or corticosteroids.

INDICATIONS AND USAGE
Voltaren is indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

CONTRAINDICATIONS
Voltaren is contraindicated in patients with hypersensitivity to it. Voltaren should not be given to patients in whom Voltaren, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions because severe, rarely fatal, anaphylactic-like reactions to Voltaren have been reported in such patients.

WARNINGS
Gastrointestinal Effects
Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving Voltaren. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac sodium, even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac sodium possible consistent with achieving a satisfactory therapeutic response.

Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper G.I. ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious G.I. toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. 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, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

Hepatic Effects
As with other nonsteroidal anti-inflammatory drugs, elevations of one or more liver tests may occur during Voltaren therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., 1.2-3 times the upper limit of normal (ULN)), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. The SGPT (ALT) test is probably the most sensitive indicator of liver injury. In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of SGOT (SGPT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during Voltaren treatment. In a large, open, controlled trial, meaningful elevations of SGOT and/or SGPT occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a lower incidence of borderline (1.2-3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of SGOT or SGPT was observed in patients randomized to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

Transaminase elevations were reversible on cessation of therapy, and among 51 patients in all studies with marked elevations, signs and symptoms of liver disease occurred in only 3 cases, and only 1 patient developed jaundice. Most patients with borderline elevations did not have therapy interrupted; transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms, physicians should measure transaminases periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), which involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action to take should these signs and symptoms appear.

PRECAUTIONS
General
Allergic Reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions including anaphylaxis, have been reported with Voltaren. Specific allergic manifestations consisting of swelling of eyelids, lips, pharynx and larynx, urticaria, asthma, and bronchospasm, sometimes with a concomitant fall in blood pressure (severe at times) have been observed in clinical trials and/or the foreign marketing experience with Voltaren. Anaphylaxis has been reported rarely from foreign sources; in U.S. clinical trials with Voltaren in over 6000 patients, 1 case of anaphylaxis was reported. In controlled clinical trials, allergic reactions have been observed at an incidence of 0.5%. These reactions can occur without prior exposure to the drug.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking Voltaren. Therefore, as with other nonsteroidal anti-inflammatory drugs, Voltaren should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Renal Effects: As a class, nonsteroidal anti-inflammatory drugs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. Papillary necrosis was observed only in 1 animal study with diclofenac, a 4-week study in baboons in which the drug was administered intramuscularly. In oral studies some evidence of renal toxicity was noted but papillary necrosis was not reported.

A second form of renal toxicity generally associated with nonsteroidal anti-inflammatory drugs is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in clinical trials during which serum creatinines and BUNs were followed serially. There were only 7 patients (0.18%) whose serum creatinines and concurrent serum BUNs were greater than 2.0 mg/dl and 40 mg/dl, respectively, while on diclofenac (mean rise in the 7 patients: creatinine 1.5 mg/dl and BUN 20 mg/dl). It is not yet clear whether this low incidence of renal impairment in clinical trials, plus the observation of less renal toxicity than is usual in rodents, will translate into a significant reduction of the risk of renal failure in susceptible patients in widespread use.

Since Voltaren metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, 1 patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA, demonstrated in rats).

Information for Patients
Voltaren, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious G.I. 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 (see WARNINGS, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy*).

Drug Interactions

Aspirin: Concomitant administration of Voltaren and aspirin is not recommended because Voltaren is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

Anticoagulants: While studies have not shown Voltaren to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including Voltaren, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Voltaren, like other NSAIDs, through effects on renal prostaglandins, may cause increased toxicity of certain drugs. Digoxin and methotrexate serum levels may be elevated as well as cyclosporine's nephrotoxicity. Patients receiving these drugs who are started on, or are given increased doses of, Voltaren or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs. In the case of digoxin, serum levels should be monitored.

Lithium: Voltaren decreases lithium renal clearance and increases lithium plasma levels. In patients taking Voltaren and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Voltaren does not alter glucose metabolism in normal subjects nor are the effects of oral hypoglycemic agents altered by the concomitant administration of Voltaren. There are rare reports, however, from postmarketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac which necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Voltaren and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of Voltaren.

Protein Binding

In vitro, Voltaren interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence in vitro on the protein binding of Voltaren in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Voltaren increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Voltaren is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given Voltaren up to 2 mg/kg/day (approximately the human dose) have revealed no significant increases in tumor incidence.

There was a slight increase in benign mammary fibroadenomas in mid-dose females (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. Voltaren did not show mutagenic potential in various mutagenicity studies including the Ames test. Voltaren administered to male and female rats at 4 mg/kg/day did not affect fertility. A 2-year mouse carcinogenicity study is underway.

Teratogenic Effects

Pregnancy Category B: Reproduction studies have been performed in mice given Voltaren (up to 20 mg/kg/day) and in rats and rabbits given Voltaren (up to 10 mg/kg/day), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Voltaren has been shown to cross the placental barrier in mice and rats.

There are no adequate and well-controlled studies in pregnant women. Voltaren should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of Voltaren during late pregnancy should be avoided.

Labor and Delivery

The effects of Voltaren on labor and delivery in pregnant women are unknown. However, as with other nonsteroidal anti-inflammatory drugs, it is possible that Voltaren may inhibit uterine contraction.

Nursing Mothers

Voltaren has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Voltaren is not recommended for use in nursing women.

Pediatric Use

Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded-controlled and open-label clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally impossible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in less than 1% of approximately 1800 patients during their first 3 months of diclofenac treatment and in less than 2% of approximately 800 patients followed for 1 year. The only control group with sufficient patients for comparison received aspirin and only for the first 30 days of treatment. Comparative rates were 0.2% for peptic ulcer or G.I. bleeding in approximately 2000 diclofenac-treated patients and 0.6% in approximately 600 aspirin-treated patients.

In double-blind trials there were fewer minor gastrointestinal complaints in 1227 patients treated with Voltaren than in 721 patients treated with aspirin, 22% vs 33% (compared to 13% on placebo).

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred at an overall rate of about 2% during the first 2 months of Voltaren treatment. Unlike aspirin, where elevations occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the upper limit of normal) were seen in about 1% of patients treated for 2-6 months (see WARNINGS).

The following adverse reactions were reported in patients treated with Voltaren:

Incidence Greater Than 1% (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps*, headache*, fluid retention, abdominal distention.

Digestive: Diarrhea*, indigestion*, nausea*, constipation*, flatulence, liver test abnormalities, PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special senses: Tinnitus.

*Incidence, 3% to 9% (incidence of unmarked reactions is 1-3%)

Incidence Less Than 1%—Causal Relationship Probable (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia, aplastic anemia, agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure*.

Incidence Less Than 1%—Causal Relationship Unknown (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination*, convulsions, *disorientation, psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE

Worldwide reports on overdosage with diclofenac cover 27 cases. In 10 of these 27 cases, diclofenac was the only drug taken; all of these patients recovered. The highest dose of diclofenac was 2.5 g in a 20-year-old male who suffered acute renal failure as a consequence, and who was treated with three dialysis sessions and recovered in 2 days. The next highest dose was 2.35 g in a 17-year-old girl who experienced vomiting and drowsiness. A dose of 2.0 g of diclofenac was taken by a woman of unspecified age who remained asymptomatic.

Animal LD_{50}'s show a wide range of susceptibilities to acute overdosage with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg—rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of Voltaren (99% protein bound, see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of Voltaren.

DOSAGE AND ADMINISTRATION

Voltaren may be administered as 25-mg, 50-mg, and 75-mg enteric-coated tablets. Patients should be generally maintained on the lowest dosage of Voltaren consistent with achieving a satisfactory therapeutic response.

In osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d., or 75 mg b.i.d. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

In rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d., or 75 mg b.i.d. Dosages above 200 mg/day have not been studied in patients with rheumatoid arthritis.

In ankylosing spondylitis, the recommended dosage is 100-125 mg/day, administered as 25 mg q.i.d., with an extra 25 mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

HOW SUPPLIED

Enteric-Coated Tablets 25 mg—yellow, round, biconvex with beveled edges (imprinted VOLTAREN 25)

Bottles of 60	NDC 0028-0058-60
Bottles of 100	NDC 0028-0058-01
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0058-61

Enteric-Coated Tablets 50 mg—light brown, round, biconvex with beveled edges (imprinted VOLTAREN 50)

Bottles of 60	NDC 0028-0162-60
Bottles of 100	NDC 0028-0162-01
Bottles of 1000	NDC 0028-0162-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0162-61

Enteric-Coated Tablets 75 mg—white, round, biconvex with beveled edges (imprinted VOLTAREN 75)

Bottles of 60	NDC 0028-0164-60
Bottles of 100	NDC 0028-0164-01
Bottles of 1000	NDC 0028-0164-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0164-61

Samples, when available, are identified by the word *SAMPLE* appearing on each enteric-coated tablet.

Do not store above 86°F. Protect from moisture.

Dispense in tight container (USP).

Printed in U.S.A. C91-8 (Rev. 4/91)

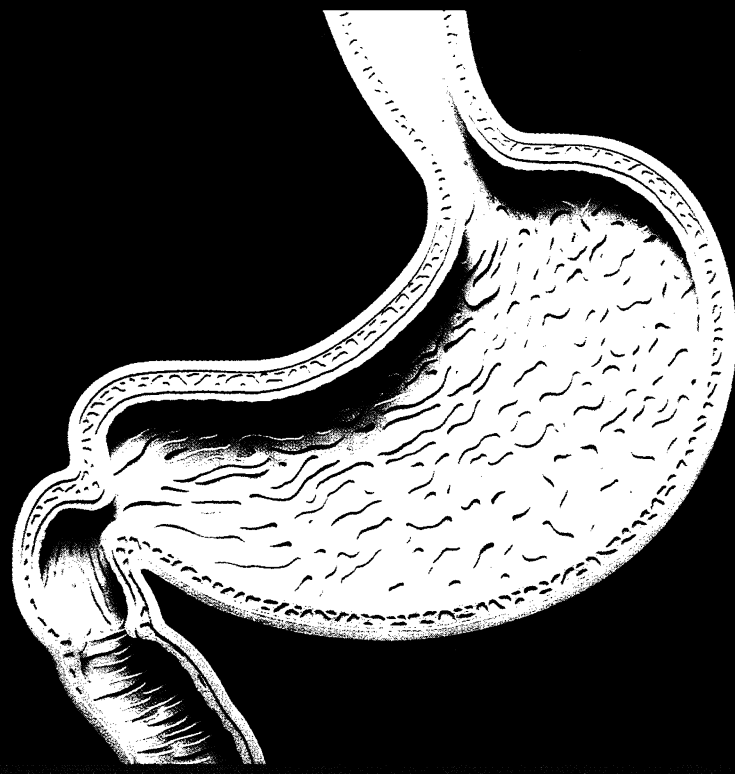
Geigy GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

388-10742-A

In arthritis therapy:

Because you're concerned about G.I. reactions...

NSAIDs may adversely affect the hematologic, hepatic, renal, and gastrointestinal systems, although G.I. reactions occur most frequently.



Voltaren
diclofenac sodium

An established record of G.I. tolerability.*

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*Contraindicated in patients hypersensitive to aspirin, other NSAIDs, or Voltaren. As with other NSAIDs, the most frequent complaints relate to the G.I. tract. In patients treated chronically with NSAID therapy, serious G.I. toxicity such as bleeding, ulceration, and perforation can occur. Elevations of SGOT and/or SGPT, some significant, have been reported in association with Voltaren treatment; cases of severe hepatic reactions have rarely been reported.

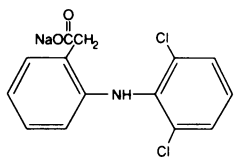
Please see complete Prescribing Information preceding this advertisement. 388-10742-A

Voltaren®
diclofenac sodium

Enteric-Coated Tablets

Prescribing Information

DESCRIPTION
Voltaren, diclofenac sodium, is a nonsteroidal, anti-inflammatory phenylacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino]benzeneacetic acid, monosodium salt. The structural formula of diclofenac sodium is:



Diclofenac sodium is a faintly yellow-white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1N hydrochloric acid. Its molecular weight is 318.14. In water, diclofenac sodium has a single dissociation constant (pKa) of 4.0.

Voltaren is available as enteric-coated tablets of 25 mg, 50 mg, and 75 mg for oral administration.

Inactive ingredients. Cellulose acetate phthalate, colloidal silicon dioxide (25-mg and 50-mg enteric-coated tablets only), diethyl phthalate, hydroxypropyl methylcellulose, iron oxide (25-mg and 50-mg enteric-coated tablets only), lactose, magnesium stearate, microcrystalline cellulose, povidone, shellac, sodium starch glycolate (75-mg enteric-coated tablets only), starch (25-mg and 50-mg enteric-coated tablets only), talc (75-mg enteric-coated tablets only), titanium dioxide.

CLINICAL PHARMACOLOGY
Pharmacology
In pharmacologic studies, Voltaren has shown anti-inflammatory, analgesic, and antipyretic activity. As with other nonsteroidal anti-inflammatory agents, its mode of action is not known; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacokinetics
Voltaren is completely absorbed from the gastrointestinal tract after fasting oral administration, with peak plasma levels occurring in 2-3 hours. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available. The mean terminal half-life in plasma is approximately 2 hours, but early elimination is much more rapid. Area under the plasma concentration curve (AUC) is dose-proportional within the range of 25 mg to 150 mg. Peak plasma levels are less than dose-proportional and are approximately 1.0, 1.5, and 2 mcg/ml for 25-mg, 50-mg, and 75-mg doses, respectively. It should be noted that the administration of several individual tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is due to the uncertainty of complete gastric emptying of all tablets at once to the duodenum. Clearance and volume of distribution were about 350 ml/min and 550 ml/kg, respectively. After repeated oral administration of 50 mg b.i.d., Voltaren did not accumulate in plasma. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity. More than 99% of diclofenac is reversibly bound to human plasma albumin.

Voltaren is eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulfate conjugates of the metabolites. Approximately 65% of the dose is excreted in the urine, and approximately 35% in the bile.

Conjugates of the principal metabolite, 4'-hydroxy-diclofenac, account for 20-30% of the dose excreted in the urine and for 10-20% of the dose excreted in the bile. Conjugates of three other metabolites (5-hydroxy-,3'-hydroxy-, and 4',5-dihydroxy-diclofenac) together account for 10-20% of the dose excreted in the urine and for small amounts excreted in the bile. Conjugates of unchanged diclofenac account for 5-10% of the dose excreted in the urine and for less than 5% excreted in the bile. Little or no unchanged unconjugated drug is excreted. It is not known whether there is genetic polymorphism in the enzymes responsible for metabolism of diclofenac.

The extent of absorption of Voltaren is not significantly affected when the drug is taken with food; however, there is usually a delay in the onset of absorption of 1 to 4.5 hours, with delays as long as 10 hours in some patients. There is also a reduction in peak plasma levels.

A 4-week study comparing plasma level profiles of diclofenac (50 mg b.i.d.) in younger (26-46) versus older (66-81) adults did not show differences between age groups (10 patients per age group).

Single-dose studies of the effects of renal function impairment (50 mg intravenously) or hepatic impairment (100 mg oral solution) have been performed in small numbers of patients. To date no differences in the pharmacokinetics of diclofenac have been detected in patients with renal or hepatic impairment.

In patients with renal impairment (N = 5, creatinine clearance 3 to 42 ml/min), AUC values and elimination rates were comparable to those in healthy subjects.

In patients with biopsy-confirmed cirrhosis or chronic active hepatitis (variably elevated transaminases and mildly elevated bilirubins, N = 10), diclofenac concentrations and urinary elimination values were comparable to those in healthy subjects.

Voltaren diffuses into and out of the synovial fluid. Diffusion into the joint occurs during the first 4 hours following a dose, while plasma levels are higher than those in synovial fluid, after which the process reverses and synovial fluid levels are slightly higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of Voltaren.

In healthy subjects, the daily administration of 150 mg of Voltaren for 3 weeks resulted in a mean fecal blood loss less than that observed with 3.0 g of aspirin daily. In repeated-dose studies, mean fecal blood loss with 150 mg of Voltaren was also less than that observed with 750 mg of naproxen or 150 mg of indomethacin. Repeated-dose endoscopic studies in normal volunteers showed that daily doses of 75 mg or 100 mg of Voltaren for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those which occurred following 500 mg daily doses of naproxen. The clinical significance of these findings is unknown since there is no evidence available to indicate that diclofenac is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.

In patients with rheumatoid arthritis, Voltaren has been administered safely in combination with gold or corticosteroids.

INDICATIONS AND USAGE
Voltaren is indicated for acute and chronic treatment of the signs and symptoms of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

CONTRAINDICATIONS
Voltaren is contraindicated in patients with hypersensitivity to it. Voltaren should not be given to patients in whom Voltaren, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions because severe, rarely fatal, anaphylactic-like reactions to Voltaren have been reported in such patients.

WARNINGS
Gastrointestinal Effects
Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving Voltaren. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac sodium, even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac sodium possible consistent with achieving a satisfactory therapeutic response.

Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy: Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous G.I. tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper G.I. ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious G.I. toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious G.I. events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal G.I. events are in this population. 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, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of G.I. toxicity.

Hepatic Effects
As with other nonsteroidal anti-inflammatory drugs, elevations of one or more liver tests may occur during Voltaren therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., 1.2-3 times the upper limit of normal [ULN]), or greater elevations of transaminases occurred in about 15% of Voltaren-treated patients. The SGPT (ALT) test is probably the most sensitive indicator of liver injury. In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of SGOT (SGPT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during Voltaren treatment. In a large, open, controlled trial, meaningful elevations of SGOT and/or SGPT occurred in about 4% of 3700 patients treated for 2-6 months, including marked elevations (i.e., more than 8 times the ULN) in about 1% of the 3700 patients. In that open-label study, a lower incidence of borderline (1.2-3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of SGOT or SGPT was observed in patients randomized to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

Transaminase elevations were reversible on cessation of therapy, and among 51 patients in all studies with marked elevations, signs and symptoms of liver disease occurred in only 3 cases, and only 1 patient developed jaundice. Most patients with borderline elevations did not have therapy interrupted; transaminase elevations in most of these cases disappeared or did not progress. There were no identifying features to distinguish those patients who developed marked elevations from those who did not.

In addition to the enzyme elevations seen in clinical trials, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, have been reported.

Because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms, physicians should measure transaminases periodically in patients receiving long-term therapy with Voltaren. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), which involved 3700 patients monitored first at 8 weeks and 1200 patients monitored again at 24 weeks, almost all meaningful elevations in transaminases were detected before patients became symptomatic. In 42 of the 51 patients in all trials who developed marked transaminase elevations, abnormal tests occurred during the first 2 months of therapy with Voltaren. Based on this experience the first transaminase measurement should be made no later than 8 weeks after the start of Voltaren treatment. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), Voltaren should be discontinued.

To minimize the possibility that hepatic injury will become severe between transaminase measurements, physicians should inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms), and the appropriate action to take should these signs and symptoms appear.

PRECAUTIONS
General
Allergic Reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions including anaphylaxis, have been reported with Voltaren. Specific allergic manifestations consisting of swelling of eyelids, lips, pharynx and larynx, urticaria, asthma, and bronchospasm, sometimes with a concomitant fall in blood pressure (severe at times) have been observed in clinical trials and/or the foreign marketing experience with Voltaren. Anaphylaxis has been reported rarely from foreign sources; in U.S. clinical trials with Voltaren in over 6000 patients, 1 case of anaphylaxis was reported. In controlled clinical trials, allergic reactions have been observed at an incidence of 0.5%. These reactions can occur without prior exposure to the drug.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking Voltaren. Therefore, as with other nonsteroidal anti-inflammatory drugs, Voltaren should be used with caution in patients with a history of cardiac decompensation, hypertension, or other conditions predisposing to fluid retention.

Renal Effects: As a class, nonsteroidal anti-inflammatory drugs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. Papillary necrosis was observed only in 1 animal study with diclofenac, a 4-week study in baboons in which the drug was administered intramuscularly. In oral studies some evidence of renal toxicity was noted but papillary necrosis was not reported.

A second form of renal toxicity generally associated with nonsteroidal anti-inflammatory drugs is seen in patients with conditions leading to a reduction in renal blood flow or blood volume, where renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug results in a dose-dependent decrease in prostaglandin synthesis and, secondarily, in a reduction of renal blood flow, which may precipitate overt renal failure. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving Voltaren have been reported from postmarketing experience, but were not observed in over 4,000 patients in clinical trials during which serum creatinines and BUNs were followed serially. There were only 7 patients (0.18%) whose serum creatinines and concurrent serum BUNs were greater than 2.0 mg/dl and 40 mg/dl, respectively, while on diclofenac (mean rise in the 7 patients: creatinine 1.5 mg/dl and BUN 20 mg/dl). It is not yet clear whether this low incidence of renal impairment in clinical trials, plus the observation of less renal toxicity than is usual in rodents, will translate into a significant reduction of the risk of renal failure in susceptible patients in widespread use.

Since Voltaren metabolites are eliminated primarily by the kidneys, patients with significantly impaired renal function should be more closely monitored than subjects with normal renal function.

Porphyria: The use of diclofenac in patients with hepatic porphyria should be avoided. To date, 1 patient has been described in whom diclofenac probably triggered a clinical attack of porphyria. The postulated mechanism for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA, demonstrated in rats).

Information for Patients
Voltaren, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious G.I. 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 (see WARNINGS, *Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy*).

Drug Interactions

Aspirin: Concomitant administration of Voltaren and aspirin is not recommended because Voltaren is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations, peak plasma levels, and AUC values.

Anticoagulants: While studies have not shown Voltaren to interact with anticoagulants of the warfarin type, caution should be exercised, nonetheless, since interactions have been seen with other NSAIDs. Because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function as well, concurrent therapy with all NSAIDs, including Voltaren, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Voltaren, like other NSAIDs, through effects on renal prostaglandins, may cause increased toxicity of certain drugs. Digoxin and methotrexate serum levels may be elevated as well as cyclosporine's nephrotoxicity. Patients receiving these drugs who are started on, or are given increased doses of, Voltaren or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs. In the case of digoxin, serum levels should be monitored.

Lithium: Voltaren decreases lithium renal clearance and increases lithium plasma levels. In patients taking Voltaren and lithium concomitantly, lithium toxicity may develop.

Oral Hypoglycemics: Voltaren does not alter glucose metabolism in normal subjects nor are the effects of oral hypoglycemic agents altered by the concomitant administration of Voltaren. There are rare reports, however, from postmarketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac which necessitated changes in the doses of such agents. Both hypo- and hyperglycemic effects have been reported. A direct causal relationship has not been established, but physicians should consider the possibility that diclofenac may alter a diabetic patient's response to insulin or oral hypoglycemic agents.

Diuretics: Voltaren and other NSAIDs can inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels.

Other Drugs: In small groups of patients (7-10/interaction study), the concomitant administration of azathioprine, gold, chloroquine, D-penicillamine, prednisolone, doxycycline, or digitoxin did not significantly affect the peak levels and AUC values of Voltaren.

Protein Binding

In vitro, Voltaren interferes minimally or not at all with the protein binding of salicylic acid (20% decrease in binding), tolbutamide, prednisolone (10% decrease in binding), or warfarin. Benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole have no influence in vitro on the protein binding of Voltaren in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: Voltaren increases platelet aggregation time but does not affect bleeding time, plasma thrombin clotting time, plasma fibrinogen, or factors V and VII to XII. Statistically significant changes in prothrombin and partial thromboplastin times have been reported in normal volunteers. The mean changes were observed to be less than 1 second in both instances, however, and are unlikely to be clinically important. Voltaren is a prostaglandin synthetase inhibitor, however, and all drugs that inhibit prostaglandin synthesis interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats given Voltaren up to 2 mg/kg/day (approximately the human dose) have revealed no significant increases in tumor incidence.

There was a slight increase in benign mammary fibroadenomas in mid-dose females (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. Voltaren did not show mutagenic potential in various mutagenicity studies including the Ames test. Voltaren administered to male and female rats at 4 mg/kg/day did not affect fertility. A 2-year mouse carcinogenicity study is underway.

Teratogenic Effects

Pregnancy Category B: Reproduction studies have been performed in mice given Voltaren (up to 20 mg/kg/day) and in rats and rabbits given Voltaren (up to 10 mg/kg/day), and have revealed no evidence of teratogenicity despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Voltaren has been shown to cross the placental barrier in mice and rats.

There are no adequate and well-controlled studies in pregnant women. Voltaren should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of Voltaren during late pregnancy should be avoided.

Labor and Delivery

The effects of Voltaren on labor and delivery in pregnant women are unknown. However, as with other nonsteroidal anti-inflammatory drugs, it is possible that Voltaren may inhibit uterine contraction.

Nursing Mothers

Voltaren has been found in the milk of nursing mothers. As with other drugs that are excreted in milk, Voltaren is not recommended for use in nursing women.

Pediatric Use

Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded-controlled and open-label clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally impossible.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks. By far the most common adverse effects were gastrointestinal symptoms, most of them minor, occurring in about 20%, and leading to discontinuation in about 3%, of patients. Peptic ulcer or G.I. bleeding occurred in clinical trials in less than 1% of approximately 1800 patients during their first 3 months of diclofenac treatment and in less than 2% of approximately 800 patients followed for 1 year. The only control group with sufficient patients for comparison received aspirin and only for the first 30 days of treatment. Comparative rates were 0.2% for peptic ulcer or G.I. bleeding in approximately 2000 diclofenac-treated patients and 0.6% in approximately 600 aspirin-treated patients.

In double-blind trials there were fewer minor gastrointestinal complaints in 1227 patients treated with Voltaren than in 721 patients treated with aspirin, 22% vs 33% (compared to 13% on placebo).

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (3%).

Meaningful (exceeding 3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred at an overall rate of about 2% during the first 2 months of Voltaren treatment. Unlike aspirin, where elevations occur more frequently in patients with rheumatoid arthritis, these elevations were more frequently observed in patients with osteoarthritis (2.6%) than in patients with rheumatoid arthritis (0.7%). Marked elevations (exceeding 8 times the upper limit of normal) were seen in about 1% of patients treated for 2-6 months (see WARNINGS).

The following adverse reactions were reported in patients treated with Voltaren:

Incidence Greater Than 1% (All derived from clinical trials.)

Body as a Whole: Abdominal pain or cramps*, headache*, fluid retention, abdominal distention.

Digestive: Diarrhea*, indigestion*, nausea*, constipation*, flatulence, liver test abnormalities, PUB, i.e., peptic ulcer, with or without bleeding and/or perforation, or bleeding without ulcer (see above and also WARNINGS).

Nervous System: Dizziness.

Skin and Appendages: Rash, pruritus.

Special senses: Tinnitus.

*Incidence, 3% to 9% (incidence of unmarked reactions is 1-3%)

Incidence Less Than 1%—Causal Relationship Probable (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Malaise, swelling of lips and tongue, photosensitivity, *anaphylaxis*, anaphylactoid reactions.

Cardiovascular: Hypertension, congestive heart failure.

Digestive: Vomiting, jaundice, melena, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *hemolytic anemia, aplastic anemia, agranulocytosis*, purpura, *allergic purpura*.

Metabolic and Nutritional Disorders: Azotemia.

Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability.

Respiratory: Epistaxis, asthma, laryngeal edema.

Skin and Appendages: Alopecia, urticaria, eczema, dermatitis, *bullous eruption, erythema multiforme major*, angioedema, *Stevens-Johnson syndrome*.

Special Senses: Blurred vision, taste disorder, reversible hearing loss, scotoma.

Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure*.

Incidence Less Than 1%—Causal Relationship Unknown (Adverse reactions reported only in the literature, not seen in clinical trials, are considered rare and are italicized.)

Body as a Whole: Chest pain.

Cardiovascular: Palpitations, *flushing*, tachycardia, premature ventricular contractions, myocardial infarction.

Digestive: Esophageal lesions.

Hemic and Lymphatic: *Bruising*.

Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss*.

Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination*, convulsions, *disorientation, psychotic reaction*.

Respiratory: Dyspnea, hyperventilation, edema of pharynx.

Skin and Appendages: Excess perspiration, *exfoliative dermatitis*.

Special Senses: Vitreous floaters, night blindness, amblyopia.

Urogenital: Urinary frequency, nocturia, hematuria, impotence, vaginal bleeding.

OVERDOSAGE

Worldwide reports on overdosage with diclofenac cover 27 cases. In 10 of these 27 cases, diclofenac was the only drug taken; all of these patients recovered. The highest dose of diclofenac was 2.5 g in a 20-year-old male who suffered acute renal failure as a consequence, and who was treated with three dialysis sessions and recovered in 2 days. The next highest dose was 2.35 g in a 17-year-old girl who experienced vomiting and drowsiness. A dose of 2.0 g of diclofenac was taken by a woman of unspecified age who remained asymptomatic.

Animal LD_{50}'s show a wide range of susceptibilities to acute overdosage with primates being more resistant to acute toxicity than rodents (LD_{50} in mg/kg—rats, 55; dogs, 500; monkeys, 3200).

In case of acute overdosage it is recommended that the stomach be emptied by vomiting or lavage. Forced diuresis may theoretically be beneficial because the drug is excreted in the urine. The effect of dialysis or hemoperfusion in the elimination of Voltaren (99% protein bound, see CLINICAL PHARMACOLOGY) remains unproven. In addition to supportive measures, the use of oral activated charcoal may help to reduce the absorption and reabsorption of Voltaren.

DOSAGE AND ADMINISTRATION

Voltaren may be administered as 25-mg, 50-mg, and 75-mg enteric-coated tablets. Patients should be generally maintained on the lowest dosage of Voltaren consistent with achieving a satisfactory therapeutic response.

In osteoarthritis, the recommended dosage is 100-150 mg/day in divided doses, 50 mg b.i.d. or t.i.d., or 75 mg b.i.d. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

In rheumatoid arthritis, the recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d., or 75 mg b.i.d. Dosages above 200 mg/day have not been studied in patients with rheumatoid arthritis.

In ankylosing spondylitis, the recommended dosage is 100-125 mg/day, administered as 25 mg q.i.d., with an extra 25 mg dose at bedtime if necessary. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

HOW SUPPLIED

Enteric-Coated Tablets 25 mg—yellow, round, biconvex with beveled edges (imprinted VOLTAREN 25)

Bottles of 60	NDC 0028-0058-60
Bottles of 100	NDC 0028-0058-01
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0058-61

Enteric-Coated Tablets 50 mg—light brown, round, biconvex with beveled edges (imprinted VOLTAREN 50)

Bottles of 60	NDC 0028-0162-60
Bottles of 100	NDC 0028-0162-01
Bottles of 1000	NDC 0028-0162-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0162-61

Enteric-Coated Tablets 75 mg—white, round, biconvex with beveled edges (imprinted VOLTAREN 75)

Bottles of 60	NDC 0028-0164-60
Bottles of 100	NDC 0028-0164-01
Bottles of 1000	NDC 0028-0164-10
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0164-61

Samples, when available, are identified by the word *SAMPLE* appearing on each enteric-coated tablet.

Do not store above 86°F. Protect from moisture.

Dispense in tight container (USP).

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In arthritis therapy:

Because you're concerned about G.I. reactions...

NSAIDs may adversely affect the hematologic, hepatic, renal, and gastrointestinal systems, although G.I. reactions occur most frequently.