# Prescribing Information

## PrVOLTAREN®

(diclofenac sodium)

25 and 50 mg Enteric-Coated Tablets

75 and 100 mg Slow-Release Tablets

50 and 100 mg Suppositories

Anti-inflammatory, Analgesic Agent

Novartis Pharmaceuticals Canada Inc.
385 Bouchard
Dorval, Quebec H9S 1A9

Date Of Preparation:
July 5, 1989

Date Of Revision:
November 2, 1989
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# Prescribing Information

## Name Of Drug

## PrVOLTAREN®

(diclofenac sodium)

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75 and 100 mg Slow-Release Tablets

50 and 100 mg Suppositories

## Therapeutic Classification

Anti-inflammatory, Analgesic Agent

## Actions And Clinical Pharmacology

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The mode of action is not fully known but it does not act through the pituitary-adrenal axis. Diclofenac sodium inhibits prostaglandin synthesis by interfering with the action of prostaglandin synthetase. This inhibitory effect may partially explain its actions.

From a clinical efficacy standpoint, diclofenac sodium 75 mg is similar to 3.6 g of acetylsalicylic acid.

Diclofenac sodium is similar in activity to equivalent dosages of indomethacin (75-150 mg daily), and causes less central nervous system side effects at these doses.

Although VOLTAREN does not alter the course of the underlying disease, it has been found to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders of the types listed.

### Pharmacokinetics and Metabolism

**Absorption**: In humans, orally-administered diclofenac sodium is rapidly and almost completely absorbed and distributed to blood, liver, and kidneys. The plasma concentrations show a linear relationship to the amount of drug administered. No accumulation occurs provided the recommended dosage intervals are observed.

Enteric coating may delay the onset of absorption from 25 and 50 mg tablets. Absorption occurs more rapidly when the drug is administered on an empty stomach ($T_{max}$ 2.5 hours), than with meals ($T_{max}$ 6 hours). The bioavailability remains the same under both conditions. The mean peak plasma concentration of 1.5 μg/mL (5 μmol/L) is attained, on average, 2 hours after ingestion of one 50 mg enteric-coated tablet.

Following administration of slow-release (SR) diclofenac sodium, $C_{max}$ is reached at approximately 4 hours or later. Significant drug plasma concentrations persist when levels would have dropped almost to baseline values following enteric-coated tablet administration. Mean plasma concentrations of 13 ng/mL (40 nmol/L) were

produced 24 hours after VOLTAREN SR 100 mg, or 16 hours after VOLTAREN SR 75 mg (single dose). Trough levels are approximately 22-25 ng/mL (70-80 nmol/L) during treatment with VOLTAREN SR 100 once daily or VOLTAREN SR 75 twice daily. In pharmacokinetic studies no accumulation of diclofenac sodium was found following repeated once daily administration of VOLTAREN SR 100 mg tablets or repeated twice daily administration of VOLTAREN SR 75 mg tablets.

Suppositories have a more rapid onset, but slower rate of absorption than oral enteric-coated tablets. $C_{max}$ is approximately 2/3 of that produced by an equivalent 50 mg enteric-coated tablet oral dose. $T_{max}$ occurs within 1 hour. The unchanged diclofenac plasma AUC values for rectal administration are within the range of values produced by equivalent oral enteric-coated tablet doses. Since about half the active substance is metabolised during its first passage through the liver ("first pass" effect), the area under the concentration curve (AUC) following oral or rectal administration is about half as large as it is following a parenteral dose of equal size.

**Distribution**: Diclofenac sodium is extensively bound (99%) to serum albumin. The apparent volume of distribution is 0.12 to 0.17 L/kg. Single-dose (P.O. or I.M). studies in rheumatoid patients with joint effusions have shown that diclofenac is distributed to the synovial fluid, where $T_{max}$ occurs 2 to 4 hours after plasma $T_{max}$. Synovial fluid concentrations exceed plasma levels within 4 to 6 hours of administration. This elevation above plasma concentrations can be maintained for up to 12 hours. The synovial fluid elimination half-life is at least 3 times greater than that for plasma.

**Biotransformation**: Diclofenac undergoes single and multiple hydroxylation and methoxylation, producing 3'-, 4'-, 5-hydroxy, 4'- 5-hydroxy and 3'-hydroxy-4'-methoxy derivatives of diclofenac. These phenolic metabolites are largely inactive, and (along with the parent compound) are mostly converted to glucuronide conjugates.

**Elimination**: Plasma clearance of diclofenac is 263 ± 56 mL/min. The mean terminal drug half-life in plasma is 1.8 hour after oral doses. In humans about 60% of the drug and its metabolites are eliminated in the urine and the balance through bile in the feces. More than 90% of an oral dose is accounted for in elimination products within 72 hours. About 1% of an oral dose is excreted unchanged in urine.

### Special Populations

**Renal impairment**: A single dose pharmacokinetic study in patients with varying degrees of renal dysfunction (creatinine clearance rates ranging from 3 mL/min to 42 mL/min (0.05 mL/s to 0.7 mL/s)), suggests that moderate renal impairment does not affect the elimination rate of unchanged diclofenac from plasma but that it may reduce the elimination rate of the metabolites of the drug. In one patient with a creatinine clearance of <10 mL/min, the theoretical steady-state plasma levels of metabolites (normally devoid of pharmacological activity) were about 4 times higher than those in normal subjects, with metabolites cleared through the bile. Although no accumulation of pharmacologically active substance seems to occur, caution is advised while administering VOLTAREN to patients with impaired kidney function.

**Hepatic impairment**: The kinetics and metabolism of diclofenac, as revealed in a study of ten patients with impaired hepatic function (chronic hepatitis and non-decompensated cirrhosis) receiving a single oral dose of 100 mg, were the same as in patients without liver disease.

**Elderly**: The ability of elderly subjects to absorb, metabolize and excrete VOLTAREN does not appear to differ significantly from those of young subjects.

## Indications And Clinical Use

VOLTAREN (diclofenac sodium) is indicated for the symptomatic treatment of rheumatoid arthritis and osteoarthritis, including degenerative joint disease of the hip.

## Contraindications

Voltaren (diclofenac sodium) should not be used in patients with a history of recurrent ulceration, active or recent history of, inflammatory diseases of the gastrointestinal tract such as:

- peptic ulcer
- regional ulcer
- gastritis
- ulcerative colitis

Known or suspected hypersensitivity to diclofenac or other non-steroidal anti-inflammatory drugs. Since cross-sensitivity has been demonstrated, VOLTAREN should not be given to patients with the complete or partial syndrome of nasal polyps or in whom acetylsalicylic acid or other non-steroidal anti-inflammatory agents (NSAIDs) have induced asthma, anaphylaxis, rhinitis, urticaria or other allergic manifestations. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical problems are at risk of a severe reaction even if they have taken NSAIDS in the past without any adverse effects.

Significant hepatic impairment or active liver disease.

Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min (0.5 mL/s)). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

VOLTAREN is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

Suppositories are contraindicated in patients with any inflammatory lesions of rectum or anus and in patients with recent history of rectal or anal bleeding.

## Warnings

**Gastrointestinal system (GI)**

Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal, can occur at any time, with or without symptoms in patients treated with non-steroidal anti-inflammatory drugs (NSAIDs) including diclofenac.

Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 4% of patients treated for one year. The risk continues beyond one year and possibly increases.

The incidence of these complications increases with increasing dose.

VOLTAREN should be given under close medical supervision to patients prone to gastrointestinal tract irritation, particularly those with a history of peptic ulcer, melena, diverticulosis or other inflammatory disease of the gastrointestinal tract (such as ulcerative colitis or Crohn's disease). In these cases the physician must weigh the benefits of treatment against the possible hazards (see **Contraindications And Adverse Reactions**).

Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

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

No studies, to date, have identified any group of patients not at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagulant use have been associated with increased risk.

Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

VOLTAREN is not recommended for routine use with other NSAIDs because of the potential for additive side effects **(see drug interactions)**.

### Use in Pregnancy and Lactation:

Diclofenac sodium readily crosses the placental barrier. The safety of VOLTAREN in pregnancy and lactation has not been established and its use is therefore not recommended. It should only be used during pregnancy for the most compelling reasons, and then only at the lowest effective dose. As with other prostaglandin inhibitors, this applies particularly to the last 3 months of pregnancy, because of the possibility of uterine inertia and/or premature closing of the ductus arteriosus.

The highest diclofenac level observed in the breast milk of six patients receiving oral diclofenac sodium doses of 3x50 mg day 1, followed by 2x50 mg day 2, was smaller than 5 ng/g. By extrapolation, an infant of 3 kg, consuming 500 g/day (with a maximum concentration of 5 ng/g) of breast milk, would receive less than 0.83 µg/kg/day of VOLTAREN. On the other hand, in one patient on long-term treatment with VOLTAREN 150 mg daily, a level of 100 ng/mL (100 ng/g) was measured in breast milk; by extrapolation, an infant of 3 kg consuming 500 g/day of breast milk would receive less than 17 µg/kg/day of VOLTAREN.

### Use in the Elderly, Frail and Debilitated:

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

For such patients, the dosage should be reduced to the lowest level providing control of symptoms, adjusted when necessary and closely supervised **(See Dosage and Administration)**.

### Use in Children:

VOLTAREN is not recommended in children under 16 years of age. Safety and dosages for the pediatric age group have not been established.

### Cross-sensitivity:

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

### Aseptic Meningitis:

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

## Precautions

**Diclofenac sodium should not be used concomitantly with diclofenac potassium ($^{Pr}$VOLTAREN RAPIDE®) since both exist in plasma as the same active organic ion.**

### Gastrointestinal System:

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

### Hematology:

Caution should be exercised in patients with a history of blood dyscrasias or coagulation disorders since drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees (see **Adverse Reactions**).

Patients on long-term VOLTAREN treatment should have their hemopoietic system evaluated periodically. Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of non-steroidal anti-inflammatory drugs are rare, but could occur with severe consequences. Periodic hematologic examinations (CBC and blood film examination) can detect anemias or blood dyscrasias secondary to possible gastrointestinal tract or bone marrow toxicity.

### Fluid And Electrolyte Balance:

As with many other non-steroidal anti-inflammatory drugs (NSAIDs), fluid retention and edema have been reported with VOLTAREN. Therefore the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. VOLTAREN should be used with caution in patients with cardiac decompensation, heart failure, hypertension, renal diseases and in those recovering from surgical operations under general anesthesia and other conditions predisposing to fluid retention.

There is a risk of potential hyperkalemia with NSAID treatment. Patients most at risk are: the elderly, those having conditions such as diabetes mellitus or renal failure, or those receiving concomitant therapy with ß-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

### Renal Function:

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

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow. Renal prostaglandins have a supportive role in the maintenance of renal perfusion. Administration of NSAIDs may precipitate overt renal decompensation due to a dose-dependent reduction in prostaglandin formation. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Recovery to the pre-treatment state usually follows discontinuation of NSAID therapy.

VOLTAREN and its metabolites are eliminated primarily (60%) by the kidneys; therefore, the drug should be used with great caution in patients with impaired renal function (**see Clinical Pharmacology**). In these cases, utilization of lower doses of VOLTAREN should be considered. Urine output, serum urea, and serum creatinine should be carefully monitored.

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

### Genitourinary tract:

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

### Hepatic Function:

As with other NSAIDs, borderline elevations of one or more liver function tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Patients manifesting abnormal liver function test results, or signs or symptoms that suggest liver dysfunction, should be evaluated for evidence of progression to a more severe hepatic reaction, while on therapy with VOLTAREN. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with NSAIDs. Although such reactions are rare, if abnormal liver function tests persist or worsen, or if systemic manifestations (e.g. eosinophilia, rash etc) or clinical signs consistent with liver disease develop, discontinue VOLTAREN treatment. Liver function should be monitored during long-term treatment with this drug. Minimize hepatic injury risk by informing patients of hepatotoxicity symptoms. Patients will then be alerted that nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms, are signs of possible liver injury.

If this drug is to be used in the presence of impaired liver function, it must be done under strict observation. Caution is called for when using VOLTAREN in patients with hepatic porphyria, since VOLTAREN may trigger an attack.

### Infection:

The anti-inflammatory, antipyretic, and analgesic effects of VOLTAREN may mask the usual signs of infection. Physicians should be alert to the development of infection in patients receiving the drug.

### Ophthalmology:

Blurred and/or diminished vision has been reported with the use of VOLTAREN and with other NSAIDs. If such symptoms develop, this drug should be discontinued and an ophthalmologic examination performed. Ophthalmic

examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

### Central Nervous System:

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of VOLTAREN. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

### Hypersensitivity Reactions:

As with other NSAIDs, allergic reactions, including anaphylactic / anaphylactoid reactions, can occur without prior exposure to drug. Careful questioning for patient history of asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs is important before starting therapy.

### Drug Interactions:

**Alcohol**: there may be an increased risk of gastrointestinal side effects, including ulceration or hemorrhage, when administered concomitantly with NSAIDs.

**Digoxin**: diclofenac may increase the plasma concentration of digoxin. Dosage adjustment may be required.

**Lithium**: lithium plasma concentrations will increase when administered concomitantly with diclofenac (which affects lithium renal clearance). Dosage adjustment of lithium may be required.

**Antidiabetic agents, oral hypoglycemic drugs**: pharmacodynamic studies have shown no potentiation of effect with concurrent administration with diclofenac; however, there are isolated reports of both hypoglycemic and hyperglycemic effects in the presence of diclofenac, which necessitated changes in the dosage of hypoglycemic agents.

**Anticoagulants, heparin, thrombolytic agents and other platelet aggregation inhibitors**: although clinical investigations would appear to indicate that diclofenac has no influence on the effect of anticoagulant, numerous studies have shown that the concurrent use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding. Special caution is therefore recommended and frequent laboratory tests should be performed to check that the desired response to the anticoagulant is being maintained. Although diclofenac, as with other NSAIDs, is an inhibitor of induced platelet aggregation *in vitro* and *in vivo*; it has little effect on spontaneous platelet aggregation at usual therapeutic dosages. However, because prostaglandins play an important role in hemostasis, and NSAIDs affect platelet function, concurrent therapy of VOLTAREN with anticoagulants requires close monitoring to be certain that no change in anticoagulant dosage is necessary.

**Diuretics**: NSAIDs have been reported to decrease the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium, thus making it necessary to monitor levels.

**Glucocorticoids**: numerous studies have shown that concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

**Acetominophen**: there may be an increased risk of adverse renal effects when administered concomitantly with NSAIDs.

**Acetylsalicyclic Acid (ASA) or other NSAIDs**: concurrent oral treatment with two or more NSAIDs, including those over the counter ones (such as ASA and Ibuprofen) is not recommended due to the possibility of additive side effects (**see Warnings**).

**Methotrexate**: caution should be exercised when NSAIDs are administered less than 24 hours before or after treatment with methotrexate. Elevated blood concentrations of methotrexate may occur, increasing toxicity.

**Cyclosporin**: nephrotoxicity of cyclosporin may be increased because of the effect of NSAIDs on renal prostaglandins.

**Quinolone antibacterials**: there have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

**Probenicid**: may decrease the excretion and increase serum concentrations of NSAIDs possibly enhancing effectiveness and/or increasing potential for toxicity. Concurrent therapy of NSAIDs with probenecid requires close monitoring to be certain that no change in dosage is necessary.

**Antihypertensive agents**: Like other NSAIDs, diclofenac can reduce the antihypertensive effects of propranolol and other ß-blockers, as well as other antihypertensive agents.

### Clinical Laboratory Tests:

Diclofenac 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, and are unlikely to be clinically important.

Persistently abnormal or worsening renal, hepatic or hematological test values should be followed up carefully since they may be related to therapy.

### Information To Be Provided To The Patient:

See **Information For The Consumer**.

## Adverse Reactions

Gastrointestinal, dermatological and CNS adverse reactions are the most commonly seen. The most severe gastrointestinal adverse reactions observed were ulceration and bleeding, while the most severe dermatological albeit rare reactions observed were erythema multiforme (Stevens-Johnson Syndrome and Lyell Syndrome). Fatalities have occurred on occasion, particularly in the elderly.

Adverse reactions reported in clinical trials and spontaneous reports are summarized below.

Frequency estimate: Frequent >10%, Occasional >1-10%, Rare >0.001-1%, Isolated cases <0.001%.

### Gastrointestinal System:

**Occasional**: epigastric, gastric, or abdominal pain, abdominal cramps, nausea, dyspepsia, anorexia, diarrhea, vomiting, flatulence.

**Rare**: gastrointestinal bleeding (bloody diarrhea, melena, hematemesis) gastric and intestinal ulcerations with or without bleeding or perforation.

**Isolated**: lower gut disorders (e.g., non-specific hemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), diaphragm-like intestinal strictures, hyperacidity, stomatitis, glossitis, coated tongue, esophageal lesions, constipation, pancreatitis.

### Central Nervous System:

**Occasional**: dizziness, headache, vertigo.

**Rare**: drowsiness, malaise, impaired concentration, tiredness.

**Isolated**: sensory disturbances including paresthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

### Special senses:

**Isolated**: vision disturbances (blurred vision, diplopia), impaired hearing, tinnitus, taste alteration disorders.

### Cardiovascular System:

**Rare**: palpitation, angina, arrhythmias.

**Isolated**: exacerbation of cardiac failure, hypertension.

### Dermatologic:

**Occasional**: rash, pruritus.

**Rare**: urticaria.

**Isolated**: bullous eruption, erythema, eczema, erythema multiforme, Stevens-Johnson Syndrome, Lyell Syndrome (toxic epidermal necrolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

### Renal System:

**Rare**: edema (facial, general, peripheral).

**Isolated**: acute renal failure, nephrotic syndrome, urinary abnormalities (e.g., hematuria and proteinuria), interstitial nephritis, papillary necrosis.

### Hematologic:

**Isolated**: thrombocytopenia, leukopenia, agranulocytosis, hemolytic anemia, aplastic anemia, anemia secondary to gastrointestinal bleeding.

### Hepatic:

**Occasional**: elevations (≥3 times the upper normal limit) of serum aminotransferase enzymes (SGOT or AST, SGPT or ALT).

**Rare**: liver function disorders including hepatitis with or without jaundice.

**Isolated**: fulminant hepatitis

### Hypersensitivity:

**Rare**: hypersensitivity reactions such as asthma in patients sensitive to ASA e.g., bronchospasm; anaphylactic / anaphylactoid systemic reactions including hypotension.

**Isolated**: vasculitis, pneumonitis.

### Other:

Administration of the suppositories may occasionally give rise to local irritation, rarely local bleeding and exacerbation of hemorrhoids.

## Symptoms And Treatment Of Overdosage

There is no specific antidote for VOLTAREN (diclofenac sodium). In cases of overdosage, absorption should be prevented as soon as possible by the induction of vomiting, gastric lavage or treatment with activated charcoal. Supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression. Measures to accelerate elimination (forced diuresis, hemoperfusion, dialysis) may be considered, but may be of limited use because of the high protein-binding and extensive metabolism.

## Dosage And Administration

### VOLTAREN Tablets 25 mg and 50 mg (enteric-coated)

In rheumatoid arthritic patients, VOLTAREN (diclofenac sodium) treatment should be initiated with 75 mg to 150 mg per day in 3 divided doses, depending on the severity of the condition. For maintenance, the dose should be reduced to the minimum amount that will provide continuous control of symptoms, usually 75 mg to 100 mg daily in 3 divided doses.

In osteoarthritic patients, the starting and maintenance dose is usually 75 mg/day in 3 divided doses. The dose should be adjusted individually to the minimum dose that will provide control of symptoms.

The maximum recommended daily dose is 150 mg.

VOLTAREN should be taken with food and the tablets should be swallowed whole.

### VOLTAREN SR 75 mg and 100 mg (slow-release tablets)

Treatment should be initiated and individual titration carried out using VOLTAREN enteric-coated tablets.

Patients with rheumatoid arthritis or osteoarthritis on a maintenance dose of 75 mg per day may be changed to a once daily dose of VOLTAREN SR 75 mg administered morning or evening.

Patients on a maintenance dose of 100 mg per day may be changed to a once daily dose of VOLTAREN SR 100 mg, administered morning or evening.

Patients on a maintenance dose of 150 mg per day may be changed to a twice daily dose of one VOLTAREN SR 75 mg administered morning and evening.

The maximum daily dose of VOLTAREN should not exceed 150 mg.

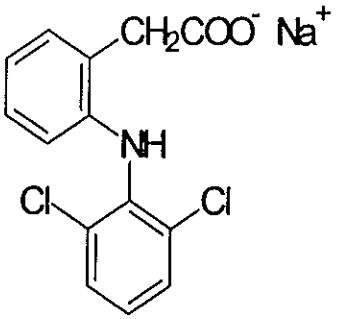
VOLTAREN SR tablets should be swallowed whole with liquid, preferably at mealtime.

### VOLTAREN Suppositories

VOLTAREN suppositories, 50 or 100 mg, may be given as substitute for the last of the 3 oral daily doses, to a total daily dose not greater than 150 mg.

# Pharmaceutical Information

**Drug Substance:**




Diclofenac sodium

| | |
|---|---|
| **Chemical Name**: | Sodium-[o-[(2,6-dichlorophenyl)-amino]-phenyl]-acetate |
| **Molecular Formula**: | $C_{14}H_{10}Cl_2NNaO_2$ |
| **Molecular Weight**: | 318.1 |
| **Description**: | White to off-white powder with a salty bitter taste |
| **Solubility:** | At 25°C, diclofenac sodium is 2% soluble in water (pH 7.7). It is practically insoluble in aqueous acidic solutions |

## Composition:

### VOLTAREN (diclofenac sodium) 25 mg and 50 mg enteric-coated tablets:

Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: black ink, castor oil derivatives, cellulose compound, colloidal silicon dioxide, corn starch, iron oxides, lactose, magnesium stearate, polymethacrylate, povidone, polyethylene glycol, sodium starch glycolate, talc, titanium dioxide.

### VOLTAREN (diclofenac sodium) 75 mg SR tablets and 100 mg SR tablets:

Each tablet contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: black ink, carnauba wax, cellulose compounds, cetyl alcohol, colloidal silicon dioxide, iron oxides, magnesium stearate, povidone, sugar, talc, titanium dioxide.

### VOLTAREN (diclofenac sodium) 50 mg and 100 mg suppositories:

Each suppository contains the medicinal ingredient diclofenac sodium and non-medicinal ingredients: semi-synthetic glycerides.

### Stability And Storage Recommendations:

Protect the tablets from heat (i.e., store below 30°C) and humidity.

Protect suppositories from heat (i.e., store below 30°C).

## Availability Of Dosage Forms

**PrVOLTAREN (diclofenac sodium) 25 mg Tablets:**

Yellow, round, slightly biconvex, enteric-coated tablets.

Printed **VOLTAREN** on one side and **25** on the other.

Available in bottles of 100 tablets.

**PrVOLTAREN (diclofenac sodium) 50 mg Tablets:**

Light brown, round, slightly biconvex, enteric-coated, tablets.

Printed **VOLTAREN** on one side and **50** on the other.

Available in bottles of 100 and 500 tablets.

**PrVOLTAREN (diclofenac sodium) 75 mg Slow-Release Tablets:**

Light pink, triangular, biconvex, film-coated tablets.

Printed **VOLTAREN** on one side and **SR** on the other.

**75**

Available in bottles of 100 and 500 tablets.

**PrVOLTAREN (diclofenac sodium) 100 mg Slow-Release Tablets:**

Pink, round, biconvex, film-coated tablets.

Printed **VOLTAREN SR** on one side and **100** on the other.

Available in bottles of 100 and 250 tablets.

**PrVOLTAREN (diclofenac sodium) 50 mg and 100 mg Suppositories:**

Torpedo-shaped suppositories with smooth surface; yellowish-white in colour.

Available in cartons of 30 suppositories.

## Information For The Consumer

Your doctor has decided to use VOLTAREN (diclofenac sodium) to treat your problem. Here are some things to know about VOLTAREN in order to use it safely, and get the most benefit.

VOLTAREN belongs to a class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are used to treat arthritic (inflammatory) symptoms such as joint pain, swelling, stiffness, relieve pain, inflammation and fever. NSAIDs do not cure arthritis. NSAIDs promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. This medicine will help you only as long as you continue to take it.

You should take VOLTAREN only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient. If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medicine is not causing unwanted effects.

**Stomach upset is one of the most common problems with NSAIDs:**

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

## Identify Your Medication:

You have received one of the following dosage forms:

VOLTAREN 25 mg (enteric-coated) Tablet:

Yellow, round, **VOLTAREN** on one side and **25** on the other.

VOLTAREN 50 mg (enteric-coated) Tablet:

Light brown, round, **VOLTAREN** on one side and **50** on the other.

VOLTAREN enteric coated tablets should be swallowed with a meal or food.

VOLTAREN 75 mg Slow Release Tablet:

Light pink, triangular, **VOLTAREN** on one side and **SR** on the other.

**75**

VOLTAREN 100 mg Slow Release Tablet:

Pink, round, **VOLTAREN SR** on one side and **100** on the other.

VOLTAREN Slow Release tablets should be swallowed whole with liquid, preferably at mealtime.

VOLTAREN 50 mg and 100 mg Suppositories:

Torpedo-shaped with smooth surface, yellowish-white colour.

Do not take suppositories by mouth.

Check with your pharmacist if the identifying markings or colour appear different.

## Using VOLTAREN Safely:

Whether you have been prescribed oral tablets and/or rectal suppositories make sure that you do not take more than a total of 150 mg per day.

## What Does Your Doctor, Pharmacist And Dentist Need To Know About You?

To decide whether you can take VOLTAREN safely, your doctor must know whether you have certain medical conditions. Before taking VOLTAREN, make sure your doctor knows if you :

- or a family member are allergic to or have had a reaction to VOLTAREN (diclofenac sodium) or other anti-inflammatory drugs (such as acetylsalicylic acid (ASA), diflunisal, fenoprofen, fluriprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, tiaprofenic acid, tolmetin, nabumetone, or tenoxicam)

manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse),

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives)
- had any side effects from medicines for arthritis, rheumatism or sore joints that you have taken in the past,
- have a history of stomach upset, or ulcers,
- liver disease
- kidney disease
- have blood or urine abnormalities,
- have high blood pressure,
- have diabetes,
- are on any special diet, such as a low-sodium or low-sugar diet,
- are taking any other medication (either prescription or non-prescription) such as NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin,
- have any other medical problems(s) such as alcohol abuse, bleeding problems, etc..

**While taking this medication:**

If you see another doctor, pharmacist or a dentist while taking VOLTAREN, be sure they know you are taking it.

Be aware that VOLTAREN can make some people feel drowsy, dizzy, or lightheaded. Should you experience these symptoms, avoid driving and other activities that require alertness.

Check with your doctor if you are not getting any relief of your arthritis or if any problems develop.

Report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.

Stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication.

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

Some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration, or vision changes. If you have a reaction from the sun, check with your doctor.

Check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication.

Your regular medical checkups are essential.

If you are pregnant, or intend to become pregnant, tell your doctor. VOLTAREN is generally not recommended during pregnancy, especially during the final three months. Similarly, since VOLTAREN can pass into breast milk, it is not recommended that it be taken while breast-feeding. However, your doctor will decide the most appropriate use of VOLTAREN should you need it.

## What About Taking Other Drugs At The Same Time?

It is important to tell your doctor, dentist and pharmacist if you are taking other medication, as combining drugs can sometimes result in changing expected drug effects or cause harmful effects.

While taking VOLTAREN, do not take ASA (acetylsalicylic acid), ASA containing compounds, ibuprofen, VOLTAREN RAPIDE®, or other drugs that are used to relieve pain, arthritis or inflammation symptoms, unless your doctor directs otherwise.

## What Are The Side Effects?

Like any other medication, VOLTAREN can produce side effects especially when used for a long time or in large doses. It is wise to be aware of them, especially if you are getting on in years. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects.

There are some side effects that cause only mild discomfort, but are important for your doctor to know about, should you have any of them. Tell your doctor as soon as possible if any one of the side effects listed below occur. Although not all of them are common, when they occur they may require medical attention:

- bloody or black, tarry stools,
- stomach pain, nausea, vomiting or persistent indigestion, diarrhea, rectal itching or bleeding,
- yellow discolouration of skin or eyes,
- "flu-like" symptoms,
- tenderness just under your ribs on your right side,
- itching, rash, hives, swelling,
- shortness of breath, wheezing, troubled breathing, or tightness in chest,
- swelling of feet or lower legs,
- blurred vision or any visual disturbance or hearing problem,
- changes in the amount or colour of your urine (such as dark, red or brown),
- mental confusion, depression, headache, dizziness, light-headedness,
- any pain or difficulty experienced while urinating,
- malaise, fatigue, loss of appetite

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor. The above is a **partial** list of unwanted effects that can occur while taking VOLTAREN or other NSAID medications. A more detailed list is provided in the Product Monograph, available on request.

## Visits To Your Doctor

Anyone who takes VOLTAREN for more than 2 to 3 weeks should routinely contact their doctor to make sure that no unnoticed unwanted effects are occurring.

## How To Take Your Medication

In order to receive optimum benefits from VOLTAREN it is essential that you take VOLTAREN regularly as directed by your doctor. Take only the amount of medication at the time intervals and for as long as your doctor

has prescribed. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

The **maximum** daily dosage for any form or combination of VOLTAREN is 150 mg. A lower daily dosage may have been prescribed for you. Harmful effects or a lack of benefit can result if you do not follow instructions carefully.

If you are not getting adequate relief from your medication, speak to your doctor before you stop taking it, as you may need up to 2 weeks to feel adequate relief.

To help reduce the possibility of stomach upset you should take a VOLTAREN tablet with a meal or food.

### Taking Slow Release Tablets Once A Day

If you are taking VOLTAREN Slow Release 100 mg tablet or VOLTAREN Slow Release 75 mg tablet **once** a day, it is best to take this tablet at the same time each day unless your doctor has told you differently. If you have not taken this tablet at the prescribed or your regular time you may take it right away, but you should wait at least 12 hours before taking the next dose. You may then continue taking your tablet at the prescribed or your regular time thereafter.

### Taking Slow Release Tablets Twice A Day

VOLTAREN Slow Release 100 mg tablet may **not** be taken more than once a day.

If you are taking a VOLTAREN Slow Release 75 mg tablet **twice** a day, it is best to take this tablet morning and evening, unless your doctor has told you differently. If you have not taken this tablet at the prescribed or your regular time you may take it right away. If a second dose on the same day is necessary, you should wait preferably 12 hours and no less than 6 hours before taking the next dose. You may then continue taking your tablet at the prescribed or your regular time the next day.

VOLTAREN Slow Release tablets should be swallowed whole with liquid, preferably at mealtime.

VOLTAREN suppositories (50 and 100 mg) are wrapped in a plastic film. Make sure that the plastic wrapping is fully removed before inserting the suppository into the rectum. Do not take suppositories by mouth.

### Storage

Protect tablets from heat (i.e., store at temperatures below 30°C) and humidity.

Protect suppositories from heat (i.e., store at temperatures below 30°C).

Keep this and all medication out of the reach of children.

**ALWAYS REMEMBER:**

YOUR DOCTOR HAS PRESCRIBED VOLTAREN FOR YOU AFTER A CAREFUL REVIEW OF YOUR MEDICAL CONDITION. USE IT ONLY AS DIRECTED AND DO NOT GIVE IT TO ANYONE ELSE. IF YOU REQUIRE MORE INFORMATION, CONSULT YOUR DOCTOR OR PHARMACIST. IF YOU SUSPECT YOU ARE EXPERIENCING SIDE EFFECTS, STOP TAKING VOLTAREN, AND NOTIFY YOUR DOCTOR RIGHT AWAY.

VOLTAREN IS NOT RECOMMENDED FOR USE IN PATIENTS UNDER 16 YEARS OF AGE SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED. KEEP THIS AND ALL MEDICATION OUT OF REACH OF CHILDREN.

THE RISKS OF TAKING THIS MEDICATION MUST BE WEIGHED AGAINST THE BENEFITS IT WILL HAVE.

IF YOU REQUIRE MORE INFORMATION ON THIS DRUG, CONSULT YOUR DOCTOR OR PHARMACIST.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER THAN IS NEEDED.

## Pharmacology

Diclofenac sodium is a phenyl-acetic acid derivative possessing anti-inflammatory, analgesic, and antipyretic activities as shown in various pharmacological models.

*In vitro* diclofenac sodium does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in humans.

### Anti-Inflammatory Activity In Rats:

The anti-inflammatory potency was assessed by testing inhibition of paw edema (carrageenin solution and kaolin suspension) and reduction of adjuvant arthritis (Freund's adjuvant).

| Preparation | Inhibition of edema induced by | |
|---|---|---|
| | Carrageenin ($ED_{50}$ mg/kg) P.O.* | Kaolin ($ED_{50}$ mg/kg) P.O.* |
| Diclofenac sodium | 2.1 | 1.2 |

* determined by graphic interpolation from 3 or more doses.

### Analgesic Activity In Mice And Rats:

The antinociceptive effect of diclofenac sodium was assessed by established tests with results as tabulated.

| Preparation | Analgesic potency | | |
|---|---|---|---|
| | Phenyl-p-benzo-quinone test, mouse ($ED_{50}$ mg/kg P.O.) | Acetic acid test, rat ($ED_{50}$ mg/kg P.O.) | Ethacrynic acid test, rat ($ED_{50}$ mg/kg P.O.) |
| Diclofenac sodium | 4.3 | 2.5 | 1.4 |

### Antipyretic Activity In Rats:

Doses of 0.5 mg/kg P.O. diclofenac lowered body temperature by 1.5°C in rats given an I.M. injection of a 15% yeast suspension (10 mL/kg).

### Inhibition Of Prostaglandin:

A close correlation exists between certain febrile reactions and increased prostaglandin levels in the brain. Diclofenac (0.5 µg/mL) reduces prostaglandin $E_2$ formation which parallels antipyresis but does not induce hypothermia in the afebrile animal. The inhibition of prostaglandin synthesis *in vitro* ($IC_{50}$ µM/L) is 1.6.

### Platelet Adhesiveness:

At 15 µg/mL, diclofenac reduces collagen-induced aggregation in rabbit platelets by 50%. ADP-induced adhesiveness at the same dosage is similarly affected. At 10 mg/kg P.O., diclofenac protected rabbits against the lethal action of thrombokinase without untoward effects.

### Gastrointestinal Tolerability:

In rats, oral doses of 17 mg/kg diclofenac sodium caused a blood loss of 150 µL in 72 hours, as measured by the administration of $^{51}Cr$-labelled erythrocytes.

# Toxicology

## Acute Toxicity

| Species | Route | $LD_{50}$ mg/kg | 95% Confidence Limits (mg/kg) |
|---|---|---|---|
| Mouse | P.O.<br>I.V. | 389<br>133 | 197 - 595<br>126 - 140 |
| Rat | P.O.<br>I.V. | 173<br>106 | 133 - 213<br>80 - 132 |
| Guinea-pig | P.O.<br>I.V. | 1110<br>127 | 950 - 1270<br>123 - 132 |
| Rabbit | P.O. | 194 | 151 - 259 |

The symptoms included bradycardia and convulsions.

The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequelae.

## Long-Term Toxicity Studies

| SPECIES | PERIOD | DAILY DOSE mg/kg/day P.O. | | |
|---|---|---|---|---|
| | | No signs of intoxication | Reversible signs of toxicity, mainly GI Tract | Minimum lethal dose |
| Rat | 3 months<br>6 months<br>98 weeks | 2<br>1<br>0.25 | -<br>2<br>- | 6<br>4<br>1 |
| Dog | 3 months | - | 0.5 | 2 |
| Rhesus Monkey | 6 months | - | 5-15 | 75 |
| Baboon | 12 months | - | 5 | 10 |

Diclofenac sodium was given orally to male and female rats in doses of 0.25, 1.0 and 2.0 mg/kg/day from 59 weeks (high-dose groups) to 98 weeks (low- and intermediate-dose groups). High dose-related mortality rates resulted in termination of the high-dose administration after 59 weeks; the high mortality rate was caused by severe dose-dependent ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and sequelae. Body-weight gains and feed consumption of the treated groups were close to the controls. Hematologic patterns showing neutrophilic leucocytosis and anemia were seen in the high- and intermediate-dose groups, particularly females at weeks 52 and 98, respectively. Female animals tended to develop enlarged adrenals and eventually experienced depressed glucose and elevated alkaline phosphatase levels. Histology studies carried out on the tissues of the

control, low- and intermediate-dose groups showed drug-related changes including mucosal ulceration of the small intestine, lymphangiectasis, lymphoid hypoplasia, and plasma cell hypoplasia of the mesenteric lymph nodes, foci of hepatocytic hyperplasia, adrenal cortical atrophy and prostatitis. No increase in tumor incidence was observed in the drug-treated groups as compared to the control group.

Diclofenac sodium was administered orally in gelatin capsules once daily to baboons *(Papio spp.)* at dose levels of 0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day for up to 52 weeks. At all dose levels studied, diclofenac caused ulceration of the gastrointestinal tract. Ulceration was confined to the colon in the low-dose group but was present in the stomach and small intestine also in the other two groups. Body weights were below controls. Constipation, with occasional episodes of diarrhea, was a marked feature. In all treated groups, there was a dose-related fall in serum albumin levels. Anemia and an increased ESR were observed in the high-dose group. In the recovery groups (control, low, and intermediate), no intestinal lesions were present. Food consumption and body-weight gains were within normal limits. Hematology parameters were comparable to controls and serum albumin levels returned towards normal values.

## Reproduction Studies

**Rats**: Doses of 2 and 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryotoxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated animals were comparable to those of controls except for slightly retarded growth at the higher dose.

**Mice and Rats**: Teratology studies at oral doses of 2, 3, 10, and 20 mg/kg/day showed no teratogenic effects on fetuses. At the higher doses, pronounced gastrointestinal effects were observed in the dams and a marked toxic effect noted in fetuses (reduced birth weights and increased fetal deaths).

**Rabbits**: Pregnant females treated with oral doses of 5 or 10 mg/animal/day throughout the gestation period showed a dose-dependent increase in resorption rates, diminished fetus weights, and abnormal skeletal findings. Definite embryotoxicity was observed at the highest dose although there was no evidence to suggest teratogenicity.

## Mutagenicity Studies

Mutagenicity studies were carried out *in vitro* using bacteria with, and without microsomal activation, and in mammalian cells. Studies *in vivo* were also performed. Diclofenac sodium was not mutagenic in any of these test systems.

## Carcinogenicity Studies

Long-term carcinogenicity studies in rats given diclofenac sodium up to 2 mg/kg/day have revealed no significant increases in tumor incidence. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats.

In a 2-year mouse study, only controls and animals at the two lower daily doses of 0.1 and 0.3 mg/kg showed survival sufficient for assessment of carcinogenic potential. The two higher daily doses of 1 and 2 mg/kg resulted in a shortening of lifespan, particularly in males, as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to non-steroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. Diclofenac sodium was not carcinogenic to mice under the conditions of this study.

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