NOVARTIS

T2000-19
89008901

Cataflam®
diclofenac potassium
Immediate-Release Tablets

Voltaren®
diclofenac sodium
Delayed-Release (enteric-coated) Tablets

Voltaren®-XR
diclofenac sodium
Extended-Release Tablets

Rx only

Prescribing Information

DESCRIPTION

Diclofenac, as the sodium or potassium salt, is a benzeneacetic acid derivative, designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium or monopotassium salt. The structural formula is shown in Figure 1.

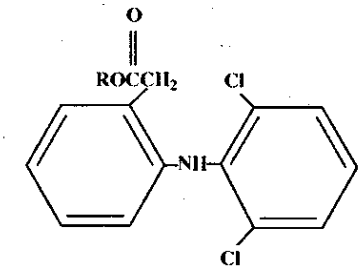

Figure 1

R = K: Cataflam®, diclofenac potassium
R = Na: Voltaren® or Voltaren®-XR, diclofenac sodium

Diclofenac, as the sodium or potassium salt, is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. Molecular weights of the sodium and potassium salts are 318.14 and 334.25, respectively. It is freely soluble in methanol, soluble in ethanol, and practically insoluble in chloroform and in dilute acid. Diclofenac sodium is sparingly soluble in water while diclofenac potassium is soluble in water. The n-octanol/water partition coefficient is, for both diclofenac salts, 13.4 at pH 7.4 and 1545 at pH 5.2. Both salts have a single dissociation constant (pKa) of 4.0 ± 0.2 at 25°C in water.

Diclofenac potassium is available as **Cataflam Immediate-Release Tablets** of 50 mg for oral administration.

CATAFLAM Inactive Ingredients: Calcium phosphate, colloidal silicon dioxide, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, starch, sucrose, talc, titanium dioxide.

Diclofenac sodium is available as **VOLTAREN Delayed-Release (enteric-coated) Tablets** of 25 mg, 50 mg, and 75 mg for oral administration, and **VOLTAREN-XR Extended-Release Tablets** of 100 mg.

VOLTAREN Inactive Ingredients: Hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide, D&C Yellow No. 10 Aluminum Lake (25-mg tablet only), FD&C Blue No. 1 Aluminum Lake (50-mg tablet only).

VOLTAREN-XR Inactive Ingredients: Cetyl alcohol, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, polysorbate, povidone, silicon dioxide, sucrose, talc, titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Diclofenac, the anion in Cataflam, Voltaren, and Voltaren-XR, is a nonsteroidal anti-inflammatory drug (NSAID). In pharmacologic studies, diclofenac has shown anti-inflammatory, analgesic, and antipyretic activity. As with other NSAIDs, its mode of action is not known; its ability to inhibit prostaglandin synthesis, however, may be involved in its anti-inflammatory activity, as well as contribute to its efficacy in relieving pain related to inflammation and primary dysmenorrhea. With regard to its analgesic effect, diclofenac is not a narcotic.

Pharmacokinetics

Cataflam Immediate-Release Tablets, Voltaren Delayed-Release Tablets, and Voltaren-XR Extended-Release Tablets, contain the same therapeutic moiety, diclofenac. They differ in the cationic portion of the salt (see DESCRIPTION), as well as in their release characteristics. Cataflam Immediate-Release Tablets are formulated to release diclofenac in the stomach.

Voltaren Delayed-Release (enteric-coated) Tablets are in a pharmaceutical formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH-environment of the duodenum. Conversely, Voltaren-XR Extended-Release Tablets are formulated to release drug over a prolonged period. The primary pharmacokinetic difference between the three products is in the pattern of drug release and absorption, as described below and shown in Table 1.

Table 1
Mean (% CV) Pharmacokinetics of Diclofenac Following Single Oral Doses of CATAFLAM, VOLTAREN Delayed-Release, and VOLTAREN-XR

Drug	Dose (mg)	AUC (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
Cataflam	50	1309 (21.7%)	1312 (44.1%)	1.00 (74.6%)
Voltaren	50	1429 (38.4%)	1417 (22.4%)	2.22 (49.8%)
Voltaren-XR	100	2079 (33.7%)	417 (40.7%)	5.25 (28.3%)

For this reason, separate sections are provided below to describe the different absorption profiles of Cataflam Immediate-Release Tablets, Voltaren Delayed-Release Tablets, and Voltaren-XR Extended-Release Tablets.

Absorption

Under fasting condition, diclofenac is completely absorbed from the gastrointestinal tract. However, due to first-pass metabolism, only about 50% of the absorbed dose is systemically available.

Cataflam Immediate-Release Tablets: In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing with Cataflam. Peak plasma levels are achieved in approximately 1 hour in fasting normal volunteers, with a range from 0.33 to 2 hours.

The extent of diclofenac absorption is not significantly affected when Cataflam is taken with food. However, the rate of absorption is reduced by food, as indicated by a delay in T_{max} and decrease in C_{max} values by approximately 30%. After repeated oral administration of Cataflam 50 mg t.i.d. no accumulation of diclofenac in plasma occurred.

Voltaren Delayed-Release Tablets: Peak plasma levels are achieved in 2 hours in fasting normal volunteers, with a range from 1 to 4 hours. The 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 2.0 µg/mL for 25-mg, 50-mg, and 75-mg doses, respectively. It should be noted that the administration of several individual Voltaren tablets may not yield equivalent results in peak concentration as the administration of one tablet of a higher strength. This is probably due to the staggered gastric emptying of tablets into the duodenum. After repeated oral administration of Voltaren 50 mg b.i.d., diclofenac did not accumulate in plasma.

When Voltaren is taken with food, 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, and a reduction in peak

plasma levels of approximately 40%. The extent of absorption of diclofenac, however, is not significantly affected by food intake.

Voltaren-XR Extended-Release Tablets: The extent of diclofenac absorption from the extended-release tablet is not significantly affected when the drug is taken with food, however, food significantly altered the absorption pattern as indicated by a delay of 1 to 2 hours in T_{max} and a two-fold increase in C_{max} values. The plasma profile of the extended-release tablet, under fasting conditions, was characterized by multiple peaks and high intersubject variability in blood profiles. In contrast, the plasma profile for the extended-release tablets under fed conditions showed a more consistent absorption pattern with a single peak usually occurring between 5 and 6 hours after the meal.

Distribution

Plasma concentrations of diclofenac decline from peak levels in a biexponential fashion, with the terminal phase having a half-life of approximately 2 hours. Clearance and volume of distribution are about 350 mL/min and 550 mL/kg, respectively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

As with other NSAIDs, diclofenac diffuses into and out of the synovial fluid. Diffusion into the joint occurs when plasma levels are higher than those in the synovial fluid, after which the process reverses and synovial fluid levels are higher than plasma levels. It is not known whether diffusion into the joint plays a role in the effectiveness of diclofenac.

Metabolism and Elimination

Diclofenac 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 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. Conjugates of the principal metabolite 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 together account for 10%-20% of the dose excreted in the urine and for small amounts excreted in the bile. The elimination half-life values for these metabolites are shorter than those for the parent drug. Urinary excretion of an additional metabolite (half-life 80 hours) accounts for only 1.4% of the oral dose. The degree of accumulation of diclofenac metabolites is unknown. Some of the metabolites may have activity.

Special Populations

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

Geriatric Population: An 8-day study, comparing the kinetics of diclofenac (100 mg Voltaren-XR q.d.) in osteoarthritis patients older than 65 years versus younger than 65 years showed no significant differences between the two groups with respect to peak plasma levels, time to peak levels, or AUC.

Patients with Renal and/or Hepatic Impairment: To date, no differences in the pharmacokinetics of diclofenac have been detected in studies of patients with renal (50 mg intravenously) or hepatic impairment (100-mg oral solution). 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.

Clinical Studies

Cataflam Immediate-Release Tablets in Analgesia/Primary Dysmenorrhea: The analgesic efficacy of Cataflam was demonstrated in trials of patients with postoperative pain (following gynecologic, oral, and orthopedic surgery), osteoarthritis of the knee, and primary dysmenorrhea. The effectiveness of Cataflam in studies of pain or primary dysmenorrhea showed that onset of analgesia began, in some patients, as soon as 30 minutes, and relief of pain lasted as long as 8 hours, following single 50-mg or 100-mg doses. Duration of pain relief was judged by the time at which approximately half of the patients needed remedication. The onset and duration of pain relief for either the 50-mg or 100-mg dose was essentially the same, whether patients had moderate or severe pain at baseline.

Cataflam was studied in single-dose and multiple-dose pain trials. The pain models in single-dose studies were post-dental extraction and post-gynecologic surgery: the efficacy of the 50-mg dose (N=258) and the 100-mg dose (N=255) was comparable to aspirin 650 mg in onset of pain relief, but generally provided a longer duration of analgesia than aspirin. The pain models for multiple-dose trials were post-orthopedic surgery pain as well as pain associated with primary dysmenorrhea: the efficacy of the 50-mg dose (N=101) and the 100-mg dose (N=442), followed by 50 mg every 8 hours, was comparable to naproxen sodium 550 mg followed by 275 mg every 8 hours. In one study of chronic pain, in patients with osteoarthritis (N=196), Cataflam 50 mg t.i.d. was comparable in efficacy to ibuprofen 800 mg t.i.d. and Voltaren Delayed-Release Tablets 50 mg t.i.d.

Voltaren Delayed-Release Tablets in Osteoarthritis: Voltaren was evaluated for the management of the signs and symptoms of osteoarthritis of the hip or knee in a total of 633 patients treated for up to 3 months in placebo- and active-controlled clinical trials against aspirin (N=449), and naproxen (N=92). Voltaren was given both in variable (100-150 mg/day) and fixed (150 mg/day) dosing schedules in either b.i.d. or t.i.d. dosing regimens. In these trials, Voltaren was found to be comparable to 2400 to 3600 mg/day of aspirin or 500 mg/day of naproxen. Voltaren was effective when administered as either b.i.d. or t.i.d. dosing regimens.

Voltaren Delayed-Release Tablets in Rheumatoid Arthritis: Voltaren was evaluated for managing the signs and symptoms of rheumatoid arthritis in a total of 468 patients treated for up to 3 months in placebo- and active-controlled clinical trials against aspirin (N=290), and ibuprofen (N=74). Voltaren was given in a fixed (150 or 200 mg/day) dosing schedule as either b.i.d. or t.i.d. dosing regimens. Voltaren was found to be comparable to 3600 to 4800 mg/day of aspirin, and 2400 mg/day of ibuprofen. Voltaren was used b.i.d. or t.i.d., administering 150 mg/day in most trials, but 50 mg q.i.d. (200 mg/day) was also studied.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.