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THE WEINBERG GROUP INC.

VIA COURIER

June 27, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petitions

Dear Sir or Madam:

Enclosed please find four (4) copies of a submission containing a Citizen Petition (Attachment 1) and a Suitability Petition (Attachment 2), along with supporting documentation (Attachments 3 and 4).

Should there be any questions regarding the enclosed petitions, please do not hesitate to contact me via telephone (202.833.8077) or facsimile (202.833.7057).

Very truly yours,

Nicholas M. Fleischer, R.Ph., Ph.D.
Vice President, Clinical Pharmacology & Biopharmaceutics
THE WEINBERG GROUP INC.

NMF/kh

Enclosures

cc Gary Buehler, Director, Office of Generic Drugs (w/encls.)

2003P-0298

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SUITABILITY PETITION

The undersigned submits this petition in accordance with 21 CFR §10.20, §10.30, §314.93, and §314.122 to request the Commissioner of the Food and Drug Administration to declare that the drug product, Diclofenac Potassium Capsules 25 mg, is suitable for submission as an abbreviated new drug application (ANDA).

A. Action requested

The petition is submitted for a change in dosage form of the drug product from "Tablets" to "Capsules." The reference listed drug product upon which this petition is based is Cataflam® (diclofenac potassium) Tablets 25 mg, approved under NDA 20-142 on November 24, 1993. A copy of the approved labeling for Cataflam® Tablets 25 mg is provided in Attachment 3. Although Cataflam® Tablets 25 mg were the subject of approved NDA 20-142, the Agency's publication entitled *Approved Drug Products with Therapeutic Equivalence Evaluations*, known as the Orange Book, lists Cataflam® Tablets 25 mg in the Discontinued Section. Thus, in accordance with 21 CFR §314.122, this petition is accompanied by a separate petition that seeks a determination whether the listed drug was withdrawn from sale for safety or effectiveness reasons (see Attachment 1).

The proposed drug product, Diclofenac Potassium Capsules 25 mg, will contain the same active ingredient as the reference listed drug; the route of administration and the recommendations for use will also be the same as those of the listed drug product. A copy of the proposed labeling for Diclofenac Potassium Capsules 25 mg is provided in Attachment 4. The proposed product would differ only in dosage form from Cataflam® Tablets 25 mg. It is therefore requested that the Commissioner of the Food and Drug

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Administration declare that Diclofenac Potassium Capsules 25 mg are suitable for submission as an abbreviated new drug application (ANDA) that refers to the approved, though not marketed, Cataflam® Tablets 25 mg.

B. Statement of grounds

Background

The proposed product, Diclofenac Potassium Capsules 25 mg, is an encapsulated formulation of diclofenac potassium. The product's active moiety, diclofenac potassium, is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac, as the sodium or potassium salt, is employed in the treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; products that contain diclofenac potassium in particular are indicated for the management of acute pain and primary dysmenorrhea when prompt onset of pain relief is desired. Diclofenac Potassium Capsules 25 mg are designed to provide an encapsulated dosage form for patients unable to swallow tablets and to provide a lower dose of drug.

Diclofenac, a drug with an extensive history of use, is used in over 24 countries throughout the world for a variety of painful and inflammatory conditions. It is currently available within the U.S. in a variety of formulations, including an immediate-release potassium-salt tablet formulation (as Cataflam®, NDA 20-142, and its generics), a delayed-release sodium-salt tablet formulation (as Voltaren® and its generics), an extended-release sodium-salt tablet formulation (as Voltaren®-XR and its generics), an ophthalmic sodium-salt solution formulation (as Voltaren®), a topical sodium-salt gel formulation (as Solaraze®), and a combination oral tablet formulation of the sodium salt and misoprostol (as Arthrotec®). Diclofenac was originally launched abroad in 1973, and the U.S. FDA approved the first diclofenac formulation in 1988 (Voltaren®; NDA 19-201).

Reliance on a listed drug that is no longer marketed

The regulations allow for submission of an ANDA or a suitability petition that refers to or relies on a listed drug that has been voluntarily withdrawn from sale in the U.S. As described in 21 CFR §314.122, such a submission must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons. Thus, this petition is accompanied by a separate petition to that effect (see Attachment 1).

When a petition relies on a listed drug that has been withdrawn from sale, FDA may grant approval of the petition unless the Agency determines that the listed drug was withdrawn from the market for reasons of safety or effectiveness. As of the date of this petition, the petitioner has not determined why Cataflam® (diclofenac potassium) Tablets 25 mg have been listed as discontinued in the Orange Book. It has been verified that the approval of NDA 20-142, under which the product was approved, has not been withdrawn or

suspended because Cataflam® (diclofenac potassium) Tablets 50 mg, the other product covered by NDA 20-142, continues to be marketed in the U.S. It has therefore been requested (in the petition in Attachment 1) that the FDA provide a determination whether Cataflam® (diclofenac potassium) Tablets 25 mg have been withdrawn from sale for reasons of safety or effectiveness.

The proposed drug product is expected to demonstrate bioequivalence to the listed drug.

C. Environmental impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR §25.31.

D. Economic impact

Pursuant to 21 CFR §10.30(b), a statement of the effect of requested action on various economic indicators will be submitted only if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

Nicholas M. Fleischer, R.Ph., Ph.D.
Vice President, Clinical Pharmacology & Biopharmaceutics
THE WEINBERG GROUP INC.

NMF/kh

cc Gary Buehler, Director, Office of Generic Drugs

Attachment 3

CATAFLAM®
diclofenac potassium
Immediate-Release Tablets

VOLTAREN®
diclofenac sodium
Delayed-Release [enteric-coated] Tablets

Prescribing Information

DESCRIPTION

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

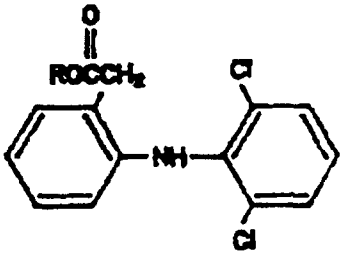


Figure 1
R = K: **Cataflam®**, diclofenac potassium
R = Na: **Voltaren®**, diclofenac sodium

Diclofenac, as the potassium or sodium salt, is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. Molecular weights of the potassium and sodium salts are 334.25 and 318.14 , respectively. It is freely soluble in methanol, soluble in ethanol and practically insoluble in chloroform and in dilute acid. Diclofenac potassium is soluble in water while diclofenac sodium is sparingly 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 25 mg and 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.

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).

CLINICAL PHARMACOLOGY

Pharmacodynamics

Diclofenac, the anion in Cataflam and Voltaren, 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 and Voltaren Delayed-Release Tablets, both 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. Conversely, Voltaren Delayed-Release [enteric-coated] Tablets are in a pharmaceutic formulation that resists dissolution in the low pH of gastric fluid but allows a rapid release of drug in the higher pH-environment in the duodenum. The primary pharmacokinetic difference between the two products is in the pattern of drug release and absorption, as illustrated in Figure 2:

FIGURE 2 TO BE ADDED

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

Absorption

Cataflam Immediate-Release Tablets: Diclofenac is rapidly and completely absorbed from the gastrointestinal tract, with measurable plasma levels being observed, in some fasting volunteers, 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. Only 50% of the absorbed dose of diclofenac from Cataflam is systemically available, due to first-pass metabolism. Peak plasma concentrations after oral administration of 25-mg and 50-mg Cataflam tablets were dose-proportional.

The extent of absorption of diclofenac from Cataflam tablets is comparable to that from a buffered-solution of diclofenac potassium. After repeated oral administration of Cataflam, 50 mg t.i.d., no accumulation of diclofenac in plasma occurred.

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%.

Voltaren Delayed-Release Tablets: Diclofenac is completely absorbed from the gastrointestinal tract after fasting oral administration of Voltaren. Of this, only 50% of the absorbed dose of diclofenac from Voltaren is systemically available, due to first-pass metabolism. 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 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.

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, respec-

tively. More than 99% of diclofenac is reversibly bound to human plasma albumin.

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).

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.

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 gynecological, oral, and orthopedic surgery), osteoarthritis of the knee, and primary dysmenorrhea. The

effectiveness of Cataflam in studies of pain of 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-gynecological 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 28 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 on 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.

Voltaren Delayed-Release Tablets in Ankylosing Spondylitis: Voltaren was evaluated for the management of the signs and symptoms of ankylosing spondylitis in a total of 132 patients in one active controlled clinical trial against indo-

methacin (N = 130). Both Voltaren and indomethacin patients were started on 25 mg t.i.d. and were permitted to increase the dose 25 mg per day each week to a maximum dose of 125 mg/day. Voltaren 75-125 mg/day was found to be comparable to indomethacin 75-125 mg/day.

G.I. Blood Loss/Endoscopy Data: G.I. blood loss and endoscopy studies were performed with Voltaren Delayed-Release [enteric-coated] Tablets that, unlike Immediate-Release Tablets, do not dissolve in the stomach where the endoscopic lesions are primarily seen; Cataflam Immediate-Release Tablets have not been similarly studied. A repeat-dose endoscopy study in patients with rheumatoid arthritis or osteoarthritis treated with Voltaren Delayed-Release Tablets 75 mg b.i.d. (N = 101), or naproxen (immediate-release tablets) 500 mg b.i.d. (N = 103) for three months, resulted in a significantly smaller number of patients with an increase in endoscopy score from baseline and a significantly lower mean endoscopy score after treatment in the Voltaren-treated patients. Two repeat-dose endoscopic studies, in normal volunteers, showed that daily doses of Voltaren Delayed-Release Tablets 75 or 100 mg (N = 6 and 14, respectively) for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those observed following daily 500-mg doses of naproxen (immediate-release tablets). In healthy subjects, the daily administration of 150 mg of Voltaren (N = 8) for 3 weeks resulted in a mean fecal blood loss of less than that observed with 3.0 g of aspirin daily (N = 8). In four repeat-dose studies, mean fecal blood loss with 150 mg of Voltaren was also less than that observed with 750 mg of naproxen (N = 8 and 6) or 150 mg of indomethacin (N = 8 and 6). *The clinical significance of these findings is unknown since there is no evidence available to indicate that Voltaren is less likely than other drugs of its class to cause serious gastrointestinal lesions when used in chronic therapy.*

INDIVIDUALIZATION OF DOSAGE

Diclofenac, like other NSAIDs, shows interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60 kg (132 lbs.), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of Cataflam or Voltaren should be reduced. Experience with other NSAIDs has shown that starting therapy with maximal doses in patients at increased risk due to renal or hepatic disease, low body weight (< 60 kg), advanced

age, a known ulcer diathesis, or known sensitivity to NSAID effects, is likely to increase frequency of adverse reactions and is not recommended (see PRECAUTIONS).

Analgesia/Primary Dysmenorrhea: Because of earlier absorption of diclofenac from Cataflam Immediate-Release Tablets, it is the formulation indicated for management of pain and primary dysmenorrhea when prompt onset of pain relief is desired. The results of clinical trials suggest an initial Cataflam dose of 50 mg for pain or for primary dysmenorrhea, followed by doses of 50 mg every 8 hours, as needed. With experience, some patients with recurrent pain, such as dysmenorrhea, may find that an initial dose of 100 mg of Cataflam, followed by 50 mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg.

Osteoarthritis/Rheumatoid Arthritis/Ankylosing Spondylitis: The usual starting dose of Voltaren Delayed-Release or Cataflam Immediate-Release Tablets, for patients with osteoarthritis, is 100 to 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. In two variable-dose clinical trials in osteoarthritis, of 266 patients started on 100 mg/day, 176 chose to increase the dose to 150 mg/day. Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

The usual starting dose of Voltaren Delayed-Release or Cataflam Immediate-Release Tablets for most patients with rheumatoid arthritis is 150 mg/day, using a b.i.d. or t.i.d. dosing regimen. Patients requiring more relief of pain and inflammation may increase the dose to 200 mg/day. In clinical trials, patients receiving 200 mg/day were less likely to drop from the trial due to lack of efficacy than patients receiving 150 mg/day. Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis because of increased risk of adverse events.

The recommended dose of Voltaren Delayed-Release or Cataflam Immediate-Release Tablets for patients with ankylosing spondylitis is 100 to 125 mg/day, using a q.i.d. dosing regimen (see DOSAGE AND ADMINISTRATION regarding the 125 mg/day dosage regimen). In a variable-dose clinical trial, of 132 patients started on 75 mg/day, 122 chose to increase the dose to 125 mg/day. Dosages above 125 mg/day have not been studied in patients with ankylosing spondylitis.

INDICATIONS AND USAGE

Cataflam Immediate-Release or Voltaren Delayed-Release Tablets are indicated for the acute and chronic treatment of signs and symptoms of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Only Cataflam is indicated for the management of pain and primary dysmenorrhea, when prompt pain relief is desired, because it is formulated to provide earlier plasma concentrations of diclofenac (see

CLINICAL PHARMACOLOGY, Pharmacokinetics and Clinical Studies).

CONTRAINDICATIONS

Diclofenac in either formulation, Cataflam or Voltaren, is contraindicated in patients with hypersensitivity to diclofenac. Diclofenac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac have been reported in such patients.

WARNINGS

Gastrointestinal Effects

Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated chronically with diclofenac even in the absence of previous G.I. tract symptoms. It is recommended that patients be maintained on the lowest dose of diclofenac 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 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 NSAIDs, elevations of one or more liver tests may occur during diclofenac therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations, (i.e., less than 3 times the ULN [=the Upper Limit of the Normal range]), or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT 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 ALT and/or AST 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 higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

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.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label), that 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 diclofenac. Based on this experience, if diclofenac is used chronically, the first transaminase measurement should be made no later than 8 weeks after the start of diclofenac 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.), diclofenac 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 patients should take if these signs and symptoms appear.

PRECAUTIONS

General

Allergic Reactions: As with other NSAIDs, allergic reactions including anaphylaxis, have been reported with diclofenac. 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 marketing experience with diclofenac. Anaphylaxis has rarely been reported from foreign sources; in U.S. clinical trials with diclofenac 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 diclofenac. Therefore, as with other NSAIDs, diclofenac 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, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. In oral diclofenac studies in animals, some evidence of renal toxicity was noted. Isolated incidents of papillary necrosis were observed in a few animals at high doses (20-120 mg/kg) in several baboon subacute studies. In patients treated with diclofenac, rare cases of interstitial nephritis and papillary necrosis have been reported (see ADVERSE REACTIONS).

A second form of renal toxicity, generally associated with NSAIDs, 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 an NSAID 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 diuret-

ics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving diclofenac have been reported from marketing experience, but were not observed in over 4000 patients in clinical trials during which serum creatinine and BUN values were followed serially. There were only 11 patients (0.3%) whose serum creatinine and concurrent serum BUN values were greater than 2.0 mg/dL and 40 mg/dL, respectively, while on diclofenac (mean rise in the 11 patients: creatinine 2.3 mg/dL and BUN 28.4 mg/dL).

Since diclofenac 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, demonstrated in rats, for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Information for Patients

Diclofenac, 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 and, more rarely, liver toxicity (see WARNINGS, Hepatic Effects) which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the management of pain but they also may be commonly employed for conditions that 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*). If diclofenac is used chronically, patients should also be instructed to report any signs and symptoms that might be due to hepatotoxicity of diclofenac; these symptoms may become evident between visits when periodic liver laboratory tests are performed (see WARNINGS, Hepatic Effects).

Drug Interactions

Aspirin: Concomitant administration of diclofenac and aspirin is not recommended because diclofenac 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 diclofenac 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 diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics of these drugs. They should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

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

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that 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: Diclofenac 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 diclofenac.

Protein Binding

In vitro, diclofenac 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 diclofenac in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: 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, however, and are unlikely to be clinically important. Diclofenac 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 diclofenac sodium up to 2 mg/kg/day (12 mg/m²/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-treated (0.5 mg/kg/day or 3 mg/m²/day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A two-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m²/day) in males and 1 mg/kg/day (3 mg/m²/day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in *in vitro* point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems; and was nonmutagenic in several mammalian *in vitro and in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24 mg/m²/day) did not affect fertility.

Teratogenic Effects

There are no adequate and well-controlled studies in pregnant women. Diclofenac should be used during pregnancy only if the benefits to the mother justify the potential risk to the fetus.

Pregnancy Category B: Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day, or 60 mg/m²/day) and in rats and rabbits given

diclofenac sodium (up to 10 mg/kg/day, or 60 mg/m²/day for rats, and 80 mg/m²/day for rabbits), 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. Diclofenac has been shown to cross the placental barrier in mice and rats.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contraction.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of diclofenac in children have not been established.

Geriatric Use

Of the more than 6000 patients treated with diclofenac in U.S. trials, 31% were older than 65 years of age. No overall difference was observed between efficacy, adverse event or pharmacokinetic profiles of older and younger patients. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

In a 6-month, double-blind trial comparing Cataflam Immediate-Release Tablets (N = 196) vs. Voltaren Delayed-Release Tablets (N = 197) vs. ibuprofen (N = 197), adverse reactions were similar in nature and frequency. In 718 patients treated for shorter periods, i.e., 2 weeks or less, with *Cataflam Immediate-Release Tablets*, adverse reactions were reported one-half to one-tenth as frequently as by patients treated for longer periods.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks with *Voltaren Delayed-Release Tab-*

lets. 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 0.6% (95%-confidence interval: 0.2% to 1.0%) of approximately 1800 patients during their first 3 months of diclofenac treatment and 1.6% (95%-confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.

Gastrointestinal symptoms were followed in frequency by central nervous system side effects such as headache (7%) and dizziness (5%).

Meaningful (exceeding 3 times the Upper Limit of Normal) elevations of ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of Voltaren treatment. Unlike aspirin-related elevations, which 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 ULN) were seen in 1% of patients treated for 2-6 months (see WARNINGS, Hepatic Effects).

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

Incidence Greater Than 1% - Causal Relationship Probable:
(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 tests 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:
The following reactions have been reported in patients taking diclofenac under circumstances that do not permit a clear attribution of the reaction to diclofenac. These reactions are being included as alerting information for physicians. Adverse reactions reported only in *worldwide marketing experience* or 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, hepati-

tis, *hepatic necrosis,* 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, *aseptic meningitis*

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 worldwide marketing experience or 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 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old male who suffered loss of consciousness, increased intracranial pressure, aspiration pneumonitis, and died 2 days after overdose. The next highest doses of diclofenac were 4.0 g and 3.75 g. The 24-year-old female who took 4.0 g and the 28- and 42-year-old females, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal LD_{50} values 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 diclofenac (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 of diclofenac.

DOSAGE AND ADMINISTRATION

Diclofenac may be administered as 25-mg and 50-mg Cataflam Immediate-Release Tablets or as 25-mg, 50-mg and 75-mg Voltaren Delayed-Release Tablets. Regardless of the indication, the dosage of diclofenac should be individualized to the lowest effective dose of Cataflam or Voltaren to minimize adverse effects (see INDIVIDUALIZATION OF DOSAGE).

Analgesia and Primary Dysmenorrhea: The recommended starting dose of Cataflam Immediate-Release Tablet is 50 mg t.i.d. With experience, physicians may find that in some patients an initial dose of 100 mg of Cataflam, followed by 50 mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg.

Osteoarthritis: The recommended dosage is 100 to 150 mg/day in divided doses, 50 mg b.i.d. or t.i.d. (Voltaren or Cataflam) or 75 mg b.i.d. (Voltaren only). Dosages above 150 mg/day have not been studied in patients with osteoarthritis.

Rheumatoid Arthritis: The recommended dosage is 150-200 mg/day in divided doses, 50 mg t.i.d. or q.i.d. (Voltaren or Cataflam) or 75 mg b.i.d. (Voltaren only). Dosages above 225 mg/day are not recommended in patients with rheumatoid arthritis.

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

Cataflam Tablets 25 mg - light pink, round, biconvex (imprinted Cataflam on one side and 25 on the other side)

Bottles of 100 . . . . . NDC 0028-0150-01

Unit Dose (blister pack)

Box of 100 (strips of 10)

. . . . . NDC 0028-0150-61

Cataflam Tablets 50 mg - light brown, round, biconvex (imprinted Cataflam on one side and 50 on the other side)

Bottles of 100 . . . . . NDC 0028-0151-01

Unit Dose (blister pack)

Box of 100 (strips of 10)

. . . . . NDC 0028-0151-61

Do not store above 86°F (30°C).

Dispense in tight container (USP).

Voltaren Delayed-Release Tablets 25 mg - yellow, biconvex, triangular-shaped (imprinted VOLTAREN 25)

Bottles of 60 . . . . . NDC 0028-0258-60

Bottles of 100 . . . . . NDC 0028-0258-01

Unit Dose (blister pack)

Box of 100 (strips of 10)

. . . . . NDC 0028-0258-61

Voltaren Delayed-Release Tablets 50 mg - light brown, biconvex, triangular-shaped (imprinted VOLTAREN 50)

Bottles of 60 . . . . . NDC 0028-0262-60

Bottles of 100 . . . . . NDC 0028-0262-01

Bottles of 1000 . . . . . NDC 0028-0262-10

Unit Dose (blister pack)

Box of 100 (strips of 10)

. . . . . NDC 0028-0262-61

Voltaren Delayed-Release Tablets 75 mg - light pink, biconvex, triangular-shaped (imprinted VOLTAREN 75)

Bottles of 60 . . . . . NDC 0028-0264-60

Bottles of 100 . . . . . NDC 0028-0264-01

Bottles of 1000 . . . . . NDC 0028-0264-10

Unit Dose (blister pack)

Box of 100 (strips of 10)

. . . . . NDC 0028-0264-61

Do not store above 86°F (30°C). Protect from moisture.

Dispense in tight container (USP).

Samples, when available, are identified by the word *SAMPLE* appearing on each Cataflam or Voltaren tablet.

GEIGY

Distributed by:

Geigy Pharmaceuticals

Division of CIBA-GEIGY Corporation

Ardsley, New York 10502

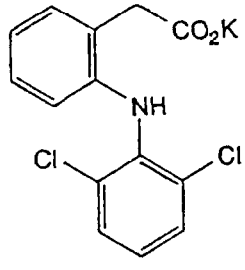
Attachment

4

Diclofenac potassium capsules
25 mg

DESCRIPTION

Diclofenac potassium is a benzeneacetic acid derivative, designated chemically as 2-[(2,6- dichlorophenyl) amino] benzeneacetic acid monopotassium salt. The structural formula is shown below:



$C_{14}H_{10}Cl_2NKO_2$ M.W. = 334.25

Diclofenac potassium is a faintly yellowish white to light beige, virtually odorless, slightly hygroscopic crystalline powder. It is freely soluble in methanol, soluble in ethanol and water, and practically insoluble in chloroform and in dilute acid. The n-octanol/water partition coefficient is 13.4 at pH 7.4 and 1545 at pH 5.2. It has a single dissociation constant (pKa) of 4.0 ± 0.2 at 25°C in water.

Diclofenac potassium capsules 25 mg are orally administered and contain 25 mg of diclofenac potassium. The inactive ingredients and the capsule shell ingredients will be furnished when the ANDA is submitted, since this is proprietary information. The inactive ingredients and the capsule shell ingredients are GRAS ingredients at the appropriate levels. The ink imprinting on the gelatin capsules contains black edible ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Diclofenac 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

Diclofenac potassium capsules 25 mg are formulated to release diclofenac in the stomach. Additional data will be provided upon completion of pharmacokinetic studies that will support the ANDA.

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.

In some fasting volunteers, measurable plasma levels are observed within 10 minutes of dosing. 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 diclofenac potassium capsules 25 mg are 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, no accumulation of diclofenac in plasma occurred.

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

Geriatric Population: A 4-week study, comparing plasma level profiles of an enteric-coated formulation of diclofenac sodium (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). An 8-day study, comparing the kinetics of an extended-release tablet formulation of diclofenac sodium (100 mg 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

Diclofenac Potassium Immediate-Release Tablets in Analgesia/Primary Dysmenorrhea: The analgesic efficacy of diclofenac potassium immediate-release tablets 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 diclofenac potassium immediate-release tablets 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.

Diclofenac potassium immediate-release tablets were 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 that of 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), diclofenac potassium immediate-release tablets 50 mg t.i.d. were comparable in efficacy to ibuprofen 800 mg t.i.d and to a delayed-release (enteric-coated) tablet formulation of diclofenac sodium (50 mg t.i.d.).

Special Studies (*The clinical significance of the findings outlined below is unknown.*)

G.I. Blood Loss/Endoscopy Data: G.I. blood loss and endoscopy studies were performed with diclofenac sodium delayed-release (enteric-coated) tablets that, unlike immediate-release tablets, do not dissolve in the stomach where the endoscopic lesions are primarily seen; diclofenac potassium immediate-release tablets have not been similarly studied. A repeat-dose endoscopy study, in patients with rheumatoid arthritis or osteoarthritis treated with diclofenac sodium delayed-release (enteric-coated) tablets 75 mg b.i.d. (N=101), or naproxen (immediate-release tablets) 500 mg b.i.d. (N=103) for 3 months, resulted in a significantly smaller number of patients with an increase in endoscopy score from baseline and a significantly lower mean endoscopy score after treatment in the patients treated with diclofenac sodium delayed-release (enteric-coated) tablets. Two repeat-dose endoscopic studies in normal volunteers showed that daily doses of diclofenac sodium delayed-release (enteric-coated) tablets 75 or 100 mg (N=6 and N=14, respectively) for 1 week caused fewer gastric lesions, and those that did occur had lower scores than those observed following daily 500-mg doses of naproxen (immediate-release tablets). In healthy subjects, the daily administration of 150 mg of diclofenac sodium (N=8) for 3 weeks resulted in a mean fecal blood loss less than that observed with 3.0 g of aspirin daily (N=8). In four repeat-dose studies, mean fecal blood loss with 150 mg of diclofenac sodium was also less than that observed with 750 mg of naproxen (N=8 and N=6) or 150 mg of indomethacin (N=8 and N=6).

INDIVIDUALIZATION OF DOSAGE

Diclofenac, like other NSAIDs, shows interindividual differences in both pharmacokinetics and clinical response (pharmacodynamics). Consequently, the recommended strategy for initiating therapy is to use a starting dose likely to be effective for the majority of patients and to adjust dosage thereafter based on observation of diclofenac's beneficial and adverse effects.

In patients weighing less than 60 kg (132 lb), or where the severity of the disease, concomitant medication, or other diseases warrant, the maximum recommended total daily dose of diclofenac potassium should be reduced. Experience with other NSAIDs has shown that starting therapy with maximum doses in patients at increased risk due to renal or hepatic disease, low body weight (<60 kg), advanced age, a known ulcer diathesis, or known sensitivity to NSAID effects is likely to increase frequency of adverse reactions and is not recommended (see PRECAUTIONS).

Analgesia/Primary Dysmenorrhea: Because of earlier absorption of diclofenac from diclofenac potassium capsules, it is the formulation indicated for management of pain and primary dysmenorrhea when prompt onset of pain relief is desired. The results of clinical trials suggest an initial diclofenac potassium dose of 50 mg for pain or for primary dysmenorrhea, followed by doses of 50 mg every 8 hours, as needed. With experience, some patients with recurring pain, such as dysmenorrhea, may find that an initial dose of 100 mg of diclofenac potassium, followed by 50-mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg.

Osteoarthritis/Rheumatoid Arthritis: The usual starting dose of diclofenac potassium capsules for patients with osteoarthritis is 100 to 150 mg/day, using a b.i.d. or t.i.d. dosing regimen.

For most patients with rheumatoid arthritis, the usual starting dose of diclofenac potassium capsules is 150 mg/day, using a b.i.d. or t.i.d. dosing regimen.

INDICATIONS AND USAGE

Diclofenac potassium capsules are indicated for the acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis. In addition, diclofenac potassium capsules are indicated for the treatment of ankylosing spondylitis. Only diclofenac potassium capsules are indicated for the management of pain and primary dysmenorrhea, when prompt pain relief is desired, because they are formulated to provide earlier plasma concentrations of diclofenac (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Clinical Studies).

CONTRAINDICATIONS

Diclofenac potassium capsules are contraindicated in patients with known hypersensitivity to diclofenac-containing products. Diclofenac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to diclofenac have been reported in such patients (see WARNINGS – Anaphylactoid Reactions, and PRECAUTIONS – Preexisting Asthma). Diclofenac potassium capsules contain gelatin and should not be given to patients with known hypersensitivity to bovine protein.

WARNINGS

Gastrointestinal Effects

Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diclofenac. Physicians and patients should therefore remain alert for ulceration and bleeding in patients treated with diclofenac even in the absence of previous G.I. tract symptoms. It is recommended that when multiple doses are required, patients be maintained on the lowest dose of diclofenac 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 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

Elevations of one or more liver tests may occur during diclofenac therapy. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Borderline elevations (i.e., less than 3 times the ULN [Upper Limit of the Normal range]) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients. Of the hepatic enzymes, ALT (SGPT) is the one recommended for the monitoring of liver injury.

In clinical trials, meaningful elevations (i.e., more than 3 times the ULN) of AST (SGOT) (ALT was not measured in all studies) occurred in about 2% of approximately 5700 patients at some time during diclofenac sodium treatment. In a large, open, controlled trial, meaningful elevations of ALT and/or AST 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 higher incidence of borderline (less than 3 times the ULN), moderate (3-8 times the ULN), and marked (>8 times the ULN) elevations of ALT or AST was observed in patients receiving diclofenac when compared to other NSAIDs. Transaminase elevations were seen more frequently in patients with osteoarthritis than in those with rheumatoid arthritis (see ADVERSE REACTIONS).

In addition to enzyme elevations seen in clinical trials, postmarketing surveillance has found rare cases of severe hepatic reactions, including liver necrosis, jaundice, and fulminant fatal hepatitis with and without jaundice. Some of these rare reported cases underwent liver transplantation.

Physicians should measure transaminases periodically in patients receiving long-term therapy with diclofenac, because severe hepatotoxicity may develop without a prodrome of distinguishing symptoms. The optimum times for making the first and subsequent transaminase measurements are not known. In the largest U.S. trial (open-label) that 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 diclofenac. Postmarketing experience has shown severe hepatic reactions can occur at any time during treatment with diclofenac. Cases of drug-induced hepatotoxicity have been reported in the first month, and in some cases, the first two months of therapy. Based on these experiences, transaminases should be monitored within 4 to 8 weeks after initiating treatment with diclofenac (see PRECAUTIONS – Laboratory Tests). 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.), diclofenac should be discontinued immediately.

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 patients should take if these signs and symptoms appear.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without prior exposure to diclofenac. Diclofenac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after aspirin or other

nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see CONTRAINDICATIONS, and PRECAUTIONS – Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

In cases with advanced kidney disease, treatment with diclofenac, as with other NSAIDs, should only be initiated with close monitoring of the patient's kidney functions (see PRECAUTIONS – Renal Effects).

Pregnancy

In late pregnancy, diclofenac should, as with other NSAIDs, be avoided because it will cause premature closure of the ductus arteriosus (see PRECAUTIONS – Pregnancy, Teratogenic Effects, Pregnancy Category B, and Labor and Delivery).

PRECAUTIONS

General

Diclofenac potassium capsules should not be used concomitantly with other diclofenac-containing products since they also circulate in plasma as the diclofenac anion.

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

Hematologic Effects: Anemia is sometimes seen in patients receiving diclofenac or other NSAIDs. This may be due to fluid retention, G.I. blood loss, or an incompletely described effect upon erythropoiesis.

Renal Effects: As a class, NSAIDs have been associated with renal papillary necrosis and other abnormal renal pathology in long-term administration to animals. In oral diclofenac studies in animals, some evidence of renal toxicity was noted. Isolated incidents of papillary necrosis were observed in a few animals at high doses (20-120 mg/kg) in several baboon subacute studies. In patients treated with diclofenac, rare cases of interstitial nephritis and papillary necrosis have been reported (see ADVERSE REACTIONS).

A second form of renal toxicity, generally associated with NSAIDs, 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 an NSAID 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 reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Cases of significant renal failure in patients receiving diclofenac have been reported from marketing experience, but were not observed in over 4000 patients in clinical trials during which serum creatinine and BUN values were followed serially. There were only 11 patients (0.3%) whose serum creatinine and concurrent serum BUN values were greater than 2.0 mg/dL and 40 mg/dL, respectively, while on diclofenac (mean rise in the 11 patients: creatinine 2.3 mg/dL and BUN 28.4 mg/dL).

Since diclofenac 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, demonstrated in rats, for causing such attacks by diclofenac, as well as some other NSAIDs, is through stimulation of the porphyrin precursor delta-aminolevulinic acid (ALA).

Aseptic Meningitis: As with other NSAIDs, aseptic meningitis with fever and coma has been observed on rare occasions in patients on diclofenac therapy. Although it is probably more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in patients who do not have an underlying chronic disease. If signs or symptoms of meningitis develop in a patient on diclofenac, the possibility of its being related to diclofenac should be considered.

Preexisting Asthma: About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, diclofenac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with preexisting asthma.

Other Precautions: The pharmacologic activity of diclofenac may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting underlying conditions.

In order to avoid exacerbation of manifestations of adrenal insufficiency, patients who have been on prolonged corticosteroid treatment should have their therapy tapered slowly rather than discontinued abruptly when diclofenac is added to the treatment program.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving diclofenac, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Information for Patients

Diclofenac, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, and more rarely, liver toxicity (see WARNINGS, Hepatic Effects), which may result in hospitalization and even fatal outcomes.

NSAIDs are often essential agents in the management of arthritis and have a major role in the management of pain, but they also may be commonly employed for conditions that 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.

Because serious G.I. tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients, if treated chronically, for the signs and symptoms of ulceration and bleeding and should inform them of the importance of follow-up (see WARNINGS, Gastrointestinal Effects, Risk of G.I. Ulcerations, Bleeding, and Perforation with NSAID Therapy). If diclofenac is used chronically, patients should also be instructed to report any signs and symptoms that might be due to hepatotoxicity of diclofenac; these symptoms may become evident between visits when periodic liver laboratory tests are performed (see WARNINGS, Hepatic Effects, and PRECAUTIONS – Laboratory Tests).

Laboratory Tests

Hepatic Effects: Transaminases and other hepatic enzymes should be monitored in patients treated chronically with NSAIDs. For patients on diclofenac therapy, it is recommended that a determination be made within 4 weeks of initiating therapy and at intervals thereafter. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and abnormal liver tests are detected, persist, or worsen, diclofenac should be discontinued immediately.

Hematologic Effects: Patients on long-term treatment with NSAIDs, including diclofenac, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

Drug Interactions

Aspirin: Concomitant administration of diclofenac and aspirin is not recommended because diclofenac 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 diclofenac 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 diclofenac, and warfarin requires close monitoring of patients to be certain that no change in their anticoagulant dosage is required.

Digoxin, Methotrexate, Cyclosporine: Diclofenac, like other NSAIDs, may affect renal prostaglandins and increase the toxicity of certain drugs. Ingestion of diclofenac may increase serum concentrations of digoxin and methotrexate and increase cyclosporine's nephrotoxicity. Patients who begin taking diclofenac or who increase their diclofenac dose or any other NSAID while taking digoxin, methotrexate, or cyclosporine may develop toxicity characteristics for these drugs. They should be observed closely, particularly if renal function is impaired. In the case of digoxin, serum levels should be monitored.

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

Oral Hypoglycemics: Diclofenac does not alter glucose metabolism in normal subjects nor does it alter the effects of oral hypoglycemic agents. There are rare reports, however, from marketing experiences, of changes in effects of insulin or oral hypoglycemic agents in the presence of diclofenac that 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: Diclofenac 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 diclofenac. Phenobarbital toxicity has been reported to have occurred in a patient on chronic phenobarbital treatment following the initiation of diclofenac therapy.

Protein Binding

In vitro, diclofenac 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 diclofenac in human serum.

Drug/Laboratory Test Interactions

Effect on Blood Coagulation: 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, however, and are unlikely to be clinically important. Diclofenac 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 diclofenac sodium up to 2 mg/kg/day (or 12 mg/m^2/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-treated (0.5 mg/kg/day or 3 mg/m^2/day) female rats (high-dose females had excessive mortality), but the increase was not significant for this common rat tumor. A 2-year carcinogenicity study conducted in mice employing diclofenac sodium at doses up to 0.3 mg/kg/day (0.9 mg/m^2/day) in males and 1 mg/kg/day (3 mg/m^2/day) in females did not reveal any oncogenic potential. Diclofenac sodium did not show mutagenic activity in in vitro point mutation assays in mammalian (mouse lymphoma) and microbial (yeast, Ames) test systems and was nonmutagenic in several mammalian in vitro and in vivo tests, including dominant lethal and male germinal epithelial chromosomal studies in mice, and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. Diclofenac sodium administered to male and female rats at 4 mg/kg/day (24-mg/m^2/day) did not affect fertility.

Pregnancy, *Teratogenic Effects, Pregnancy Category B*

Reproduction studies have been performed in mice given diclofenac sodium (up to 20 mg/kg/day or 60 mg/m^2/day) and in rats and rabbits given diclofenac sodium (up to 10 mg/kg/day or 60 mg/m^2/day for rats, and 80 mg/m^2/day for rabbits), 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. Diclofenac has been shown to cross the placental barrier in mice and rats. There are, however, no adequate and well-

controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should not be used during pregnancy unless the benefits to the mother justify the potential risk to the fetus. Because of the risk to the fetus resulting in premature closure of the ductus arteriosus, diclofenac should be avoided in late pregnancy.

Labor and Delivery

The effects of diclofenac on labor and delivery in pregnant women are unknown. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), use of diclofenac during late pregnancy should be avoided and, as with other nonsteroidal anti-inflammatory drugs, it is possible that diclofenac may inhibit uterine contractions and delay parturition.

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants from diclofenac, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of diclofenac in pediatric patients have not been established.

Geriatric Use

Of the more than 6000 patients treated with diclofenac in U.S. trials, 31% were older than 65 years of age. No overall difference was observed between efficacy, adverse event, or pharmacokinetic profiles of older and younger patients. As with any NSAID, the elderly are likely to tolerate adverse reactions less well than younger patients.

ADVERSE REACTIONS

Adverse reaction information is derived from blinded, controlled, and open-label clinical trials, as well as worldwide marketing experience. In the description below, rates of more common events represent clinical study results; rarer events are derived principally from marketing experience and publications, and accurate rate estimates are generally not possible.

In a 6-month, double-blind trial comparing diclofenac potassium immediate-release tablets (N=196) versus diclofenac sodium delayed-release tablets (N=197) versus ibuprofen (N=197), adverse reactions were similar in nature and frequency. In 718 patients treated for shorter periods, i.e., 2 weeks or less, with diclofenac potassium immediate-release tablets, adverse reactions were reported one-half to one-tenth as frequently as by patients treated for longer periods.

The incidence of common adverse reactions (greater than 1%) is based upon controlled clinical trials in 1543 patients treated up to 13 weeks with diclofenac sodium delayed-release tablets. 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 0.6% (95% confidence interval: 0.2% to 1%) of approximately 1800 patients during their first 3 months of diclofenac treatment and in 1.6% (95% confidence interval: 0.8% to 2.4%) of approximately 800 patients followed for 1 year.

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 ALT (SGPT) or AST (SGOT) occurred at an overall rate of approximately 2% during the first 2 months of diclofenac sodium treatment. Unlike aspirin-related elevations, which 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 ULN) were seen in 1% of patients treated for 2-6 months (see WARNINGS, Hepatic Effects).

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

Incidence Greater Than 1% - Causal Relationship Probable:
(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 worldwide marketing experience or 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, *esophageal lesions*, aphthous stomatitis, dry mouth and mucous membranes, bloody diarrhea, hepatitis, *hepatic necrosis, cirrhosis, hepatorenal syndrome*, appetite change, pancreatitis with or without concomitant hepatitis, *colitis*.

Hemic and Lymphatic: Hemoglobin decrease, leukopenia, thrombocytopenia, *eosinophilia, hemolytic anemia, aplastic anemia, agranulocytosis*, purpura, *allergic purpura.*
Metabolic and Nutritional Disorders: Azotemia.
Nervous System: Insomnia, drowsiness, depression, diplopia, anxiety, irritability, *aseptic meningitis, convulsions.*
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 and irreversible hearing loss, scotoma.
Urogenital: *Nephrotic syndrome*, proteinuria, *oliguria, interstitial nephritis, papillary necrosis, acute renal failure.*

Incidence Less Than 1% - Causal Relationship Unknown:
(The following reactions have been reported in patients taking diclofenac under circumstances that do not permit a clear attribution of the reaction to diclofenac. These reactions are included as alerting information to physicians. Adverse reactions reported only in worldwide marketing experience or 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, *hypotension.*
Digestive: *Intestinal perforation.*
Hemic and Lymphatic: *Bruising.*
Metabolic and Nutritional Disorders: Hypoglycemia, *weight loss.*
Nervous System: Paresthesia, memory disturbance, nightmares, tremor, tic, *abnormal coordination, 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 of overdosage with diclofenac cover 66 cases. In approximately one-half of these reports of overdosage, concomitant medications were also taken. The highest dose of diclofenac was 5.0 g in a 17-year-old male who suffered loss of consciousness, increased intracranial pressure, aspiration pneumonitis, and died 2 days after overdose. The next highest doses of diclofenac were 4.0 g and 3.75 g. The 24-year-old female who took 4.0 g and the 28- and 42-year-old females, each of whom took 3.75 g, did not develop any clinically significant signs or symptoms. However, there was a report of a 17-year-old female who experienced vomiting and drowsiness after an overdose of 2.37 g of diclofenac.

Animal LD_{50} values show a wide range of susceptibilities to acute overdosage, with primates 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 diclofenac (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 of diclofenac.

DOSAGE AND ADMINISTRATION

Diclofenac potassium capsules may be administered as 25 mg capsules. Diclofenac potassium capsules are the formulation indicated for management of acute pain and primary dysmenorrhea when prompt onset of pain relief is desired because of earlier absorption of diclofenac.

The dosage of diclofenac should be individualized to the lowest effective dose to minimize adverse effects (see INDIVIDUALIZATION OF DOSAGE).

Osteoarthritis: The recommended dosage is 100 to 150 mg/day: two diclofenac potassium capsules (50 mg) two or three times a day.

Rheumatoid Arthritis: The recommended dosage is 100 to 200 mg/day: two diclofenac potassium capsules (50 mg) two or three times a day.

Analgesia and Primary Dysmenorrhea: The recommended starting dose of diclofenac potassium is two of 25 mg capsules three times a day. With experience, physicians may find that in some patients an initial dose of 100 mg, followed by 50-mg doses, will provide better relief. After the first day, when the maximum recommended dose may be 200 mg, the total daily dose should generally not exceed 150 mg.

HOW SUPPLIED

Diclofenac potassium capsules are supplied as 25 mg capsules with appropriate identifying markings in black ink. The capsules are packaged either in plastic bottles (100 capsules/bottle) or blister packs (4 capsules/pack).

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Protect from moisture. Dispense in tight container (USP).