

DIFEN® PROTECT

DICLOFENAC SODIUM OMEPRAZOLE CAPSULES WITH GASTRO-RESISTANT MICROGRANULES

Rx only Made in Argentina

Formula
Each capsule contains: DICLOFENAC SODIUM 75.00 mg, OMEPRAZOLE (as Omeprazole Pellets) 10.00 mg, 116,500 mg of Omeprazole pellets composed of: Omeprazole 10.00 mg, Sucrose 54,020 mg, Corn starch 8.580 mg, Sodium lauryl sulfate 0.065 µg, Anhydrous disodium phosphate 0.305 mg, Mannitol 3.955 mg, Hydroxypropyl methylcellulose 6000 2.010 mg, Polyethylene glycol 6000 2.010 mg, Talc 6.135 mg, Polysorbate 80 0.885 mg, Titanium Dioxide 2.010 mg. Copolymer of methacrylic acid / polymethacrylate 18.700 mg, Purified water 1.450 mg. Excipients: tricalcium phosphate 20.55 mg microcrystalline cellulose 7.80 mg, starch sodium glycolate 6.50 mg, copovidone 6.50 mg, crospovidone 11.05 mg, talc 4.70 mg, magnesium stearate 1.30 mg, copolymer of methacrylic acid / polymethacrylate 12.37 mg, polysorbate 80 0.30 mg, triethylcitrate 2.38 mg, titanium dioxide 1.55 mg, sodium hydroxide q.s. pH 5.2.

Therapeutic Action: analgesic, antipyretic and non-steroidal anti-inflammatory (NSAIDs). Gastric secretion inhibitor.

Indications: symptomatic treatment of rheumatoid arthritis, osteoarthritis, and other inflammatory processes in patients at risk of gastrointestinal complications induced by NSAIDs.

Pharmacological Action
Diclofenac
DIFEN PROTECT contains diclofenac sodium, non-steroidal anti-inflammatory (NSAID) derived from phenylacetic acid derivative with strong anti-inflammatory and analgesic action. The mechanism of action results in part of the inhibition of the synthesis and release of prostaglandins during the inflammatory process. In this sense, diclofenac inhibits both currently known cyclooxygenases isoenzymes (COX1 and COX2). It has been reported that diclofenac at high concentrations inhibits the formation of arachidonic acid metabolites, including leukotrienes and 5-hydroxyicosatetraenoic acid (5 - HETE). In addition, it can inhibit leukocyte migration, including polymorphonuclear, toward the site of inflammation and inhibits platelet aggregation induced by ADP and collagen. Diclofenac prevents the release of lysosomal enzymes from polymorphonuclear leukocytes and inhibits both the production of superoxide and leukocyte chemotaxis. Its analgesic effect is related to inhibition of the activity of the mediators of the nociceptive via, blocking the generation of impulses at the peripheral level. It is also postulated a central action, of non-opioid mechanism, at hypothalamic level. It also has an antipyretic effect linked to the decrease of prostaglandin activity in the hypothalamic thermoregulatory center, favoring heat loss.

Omeprazole
Omeprazole is a selective inhibitor of the gastric proton pump. Suppresses gastric acid secretion by specific inhibition of the enzymatic system hydrogen- potassium adenosine triphosphatase (H+ K+ ATPase) located in the secretory surface of the parietal cells. That way, it inhibits the final transport of hydrogen ions to gastric lumen. The inhibition includes both the basal and the stimulated secretion, regardless of its source of stimulus. Its activity against Helicobacter pylori occurs through a selective inhibition of urease necessary for its gastric colonization.

Pharmacokinetics
Diclofenac
After oral administration, gastrointestinal absorption of diclofenac is rapid and complete. Peak plasma concentrations are reached approximately 160 minutes after its ingestion. Binding of the diclofenac to plasma proteins is more than 99% and its distribution volume is 0, 12-0, 17 l/kg. Two hours after maximum plasma concentration is reached, the concentration in synovial fluid exceeds the plasmatic one, maintaining this relationship up to 12 hours after administration. In the synovial fluid, the elimination half-time is 3 to 6 hours. The total systemic clearance of diclofenac in plasma reaches to 263 ± 56 ml/min. The elimination half-time is 1-2 hours. Diclofenac is metabolized in liver and excreted via biliary and renal, mainly as metabolites in the form of glucuronates or sulfates. Only 1% of the dose eliminated in the urine corresponds to free diclofenac; conjugates represent a 5-10% of the dose recovered in urine. Less than 5% of this dose is eliminated by bile. The main metabolite in humans is the 4-hydroxydiclofenac, and constitutes approximately 40% of the total dose excreted. Other three metabolites of diclofenac (3-hydroxy; 5-hydroxy-4, 5-dihydroxydiclofenac) represent about 10-20% of the dose eliminated in urine. The elimination of diclofenac and its metabolites is fast: about 40% of the administered dose is removed during the first 12 hours after administration. Pharmacokinetic parameters of diclofenac are kept constant after repeated administration in healthy patients, but in patients with kidney failure the drug and/or its metabolites may have accumulation (although without clinical significance). Patients with disorders of liver function have kinetics and metabolism of the drug similar to healthy subjects.

Omeprazole
Omeprazole is rapidly absorbed after oral administration. Its absolute bioavailability is 30-40% because of its pre-systemic metabolism. These values increase to 100% in patients with hepatic dysfunction due to the decrease in the hepatic first pass. Absorption takes place in the small intestine and is completed at 3-6 hours; the peak concentration is achieved by 0,5-3,5 hours. The average distribution volume of omeprazole is 0.3 l/kg. This value is similar in healthy subjects and in patients with renal failure, being somewhat lower in elderly and patients with liver failure. It binds to plasma proteins by 95% and its bioavailability is not dependent on food intake. Omeprazole is metabolized in the liver through the cytochrome P450 (CYP) enzymatic system. Both the main metabolite (hydroxyomeprazole) and the rest ones haven't shown to have effects on acid secretion. The elimination half-life is 0,5 - 1 hour in patients with normal liver function; in patients with hepatic dysfunction, this value is 3 hours. 70-77% of the dose is eliminated metabolized in urine, while 18-23% is eliminated in the feces. The unaltered drug has been detected in urine. Elimination is not modified in patients with decreased renal function.

Posology and Method of Administration
The dose will be determined by the physician based on the patient's age and severity of the picture. As average orientation dosage is advised 1 capsule of DIFEN PROTECT every 12 hours (with breakfast and dinner). The duration of treatment will be determined according to medical criteria depending on the type and evolution of the condition. Maximum recommended dose: diclofenac 150 mg (2 capsules per day).
Mode of Administration
Swallow the whole capsule with a sufficient amount of liquid.

• Elderly patients: dose adjustment is not necessary. In studies of pharmacovigilance in geriatric patients, receiving proton-pump inhibitor during a long time, and particularly at high doses, an increased frequency of bone fractures has been observed. For this reason we recommend special control in the long-term use of these products.

Drug interactions
Diclofenac
Aspirin
Concomitant administration is discouraged due to the additive effect of nephropathy and gastric irritation of aspirin. Also the possibility of a decrease in the pharmacological effects cannot be ruled out, interaction documented for other NSAIDs, in relation to its displacement of protein binding and increase its metabolism.
Anticoagulants
Although studies have not shown significant interaction with anticoagulants of the warfarin type, caution is advised, because such interaction has been proven with other NSAIDs. Since prostaglandins play an important role in hemostasis and NSAIDs in turn affect platelet function, concomitant oral anticoagulant therapy with all NSAIDs, including diclofenac, requires a strict surveillance of the patients, to assess the need to adjust the dose of anticoagulants.
Digoxin, Methotrexate, Cyclosporine
Diclofenac, as well as other NSAIDs, may affect renal prostaglandins and increase adverse reactions of certain drugs. Administration of diclofenac or the increase of the administered dose may increase the serum concentration of Digoxin and Methotrexate and increase renal adverse effects of Cyclosporine, particularly if renal function is altered. In the case of Digoxin, it may be necessary to control serum levels.
Lithium
Diclofenac may reduce the renal clearance of lithium and elevate its plasma levels, with the consequent increased risk of adverse effects.
Oral hypoglycemic
Diclofenac does not alter the metabolism of glucose in normal subjects nor alter the effects of oral hypoglycemic agent. However, without an established causal relationship, during post marketing stage isolated cases have been reported in which there was both increase and decrease of the effect of insulin and oral hypoglycemic during concomitant treatment

Diuretics
Diclofenac, as well as other NSAIDs, may reduce its prostaglandin dependent natriuretic action and inhibit the increase in plasma renin activity after its administration, and can associate with increased serum levels of potassium, this latter is more accentuated with potassium-sparing diuretics
Other drugs
In small groups of patients, co-administration of azathioprine, gold salts, chloroquine, d-penicillamine, prednisolone, doxycycline, or digoxina did not affect significantly maximum levels or values of the area under the curve (AUC) of diclofenac. In patients under chronic treatment with phenobarbital, adverse reactions by barbiturates have been reported after the start of treatment with diclofenac.
Protein binding
Studies in vitro do not reveal significant interference of diclofenac with various drugs, including salicylic acid, tolbutamide, prednisolone, or warfarin; benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin, and sulfamethoxazole.
Interactions with laboratory tests
Effects on blood coagulation: all the prostaglandin synthetase inhibitor drug can alter the platelet function. The described modifications in some of coagulation tests in association with the use of the active ingredients seem to lack clinical significance, however a careful observation is recommended in order to detect any significant alterations.

Omeprazole
Omeprazole may slow the elimination of other drugs who suffer hepatic oxidative metabolism (for example: diazepam, phenytoin, warfarin) reason for which the possible need to use lower doses of these drugs should be evaluated. The plasma concentrations of omeprazole and clarithromycin are increased during simultaneous administration, but there is no interaction with metronidazole or amoxicillin. Inhibition of gastric acid secretion may interfere with the absorption of drugs in which the pH is an important determinant of its bioavailability (e.g., ampicillin esters, ketoconazole, iron salts, tetracycline). Omeprazole can increase plasma levels of alkaline phosphatase, TGP and TGO, as well as gastrin levels. Carcinogenesis, mutagenesis, alteration of fertility Long-term studies of carcinogenicity in rats given diclofenac sodium to more than 2 mg/kg/day revealed does not significantly increase the incidence of tumors. There was a small increase in the presence of breast fibroadenoma in rats with doses of

0.5 mg/kg/day, but the increase was not significant for this type of tumor. A 2-year study of carcinogenicity in mice using diclofenac at doses above 0.3 mg/kg/day in males and 1 mg/kg/day in females, revealed no oncogenic potential. Diclofenac did not show mutagenic activity in different tests in vitro and in vivo, including chromosomal studies and nuclear abnormalities. Administered to rats males and females at a dose of 4 mg/kg/day did not affect fertility. Pregnancy, teratogenic effects
Reproduction studies carried out in mice given diclofenac (more than 20 mg/kg/day) and in rats and rabbits (more than 10 mg/kg/day for rats and 80 mg for rabbits) have not revealed evidence of teratogenicity, maternal or fetal toxicity. In rats, the toxicity was not associated with dystocia and prolonged gestation, reduced weight or fetal growth and reduced fetal survival. Diclofenac crosses the placental barrier in mice and rats. However, there are no studies in pregnant women. Animal reproduction studies are not always predictive of human response, therefore this medication should not be used during pregnancy, unless the benefit to the mother justifies the potential risk to the fetus. A risk to the fetus is the possibility of premature closure of the ductus arteriosus associated with the use of inhibitors of prostaglandin synthesis, so diclofenac should be avoided in the last stage of pregnancy. Omeprazole studies in animals have not shown so far fetal toxicity and teratogenic effects. Labor and birth Effects of diclofenac on the labor and delivery in pregnant women are not known. On the basis of what happens with other NSAIDs, it is not possible to completely rule out that diclofenac may inhibit uterine contractions and delay the birth. Breastfeeding Due to the potentially serious adverse reactions that may occur in infants, nursing or administration of the product should be discontinued, taking into account the importance of the treatment for the mother. Pediatric use This pharmaceutical form is not suitable for children under 12 years old. Use in geriatrics Elderly patients (older than 65 years) constitute a population at risk for gastrointestinal lesions induced by NSAIDs. Clinical studies have confirmed that the association with omeprazole exert a preventive effect of such injuries in this age group.

Adverse reactions Diclofenac

Contraindications

Patients with known hypersensitivity to any component of the formulation. Pregnancy. Breastfeeding. Children. Patients with a history of asthma crisis, hives, or other allergic reactions associated with the administration of aspirin or other NSAIDs. Active gastroduodenal ulcer, severe hepatic or renal insufficiency.

Warnings

Diclofenac
Gastrointestinal effects associated with treatment with NSAIDs
Peptic ulcer disease, digestive hemorrhages and perforations, even in the absence of prior characteristic symptoms can be generated. Elderly or weakened patients seem to tolerate less the ulcers or bleeding that other individuals and most extremely serious gastrointestinal adverse events occur in this population group. Clinical studies have shown that the association with omeprazole significantly reduces the appearance of these gastrointestinal complications.
Hepatic effects
Alterations may appear in one or more liver tests. These laboratory abnormalities may progress, remain unchanged or be transitional.
For monitoring of liver injury, glutamic pyruvic transaminase (GPT) follow-up is recommended. Elevations of transaminases were observed more frequently in arthritic patients than in those with rheumatoid arthritis. In addition to enzyme elevations, reported in clinical trials to pharmacovigilance systems, rare cases of more severe hepatic reactions, including hepatocellular involvement with or without jaundice have been reported.

Based on clinical experience, transaminases in the fourth to eighth week after chronic treatment with diclofenac should be evaluated.
As with other NSAIDs, if abnormal liver tests persist or worsen, appeared clinical signs and/or symptoms related to liver disease (e.g., nausea, vomiting, fatigue, pruritus, jaundice, rash, eosinophilia) treatment should be discontinued.
Anaphylactoid reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without previous exposure to components of the product.
Its administration is not recommended in patients with allergy to aspirin or other NSAIDs. The typical allergy occurs in asthmatic patients who experience rhinitis with or without nasal polyps or who manifest severe bronchospasm after taking aspirin or other NSAIDs. Extremely serious reactions have been reported in such patients.
Advanced Renal Disease
In cases of advanced renal disease, all treatment with NSAIDs should only be started under strict control of renal function.
Pregnancy
The administration of NSAIDs in this condition should be avoided because of risk of premature closure of the ductus arteriosus, mainly in the last quarter.

Omeprazole

The use of medication by reducing gastric acid secretion, may favor the bacterial overdevelopment in the gastrointestinal tract.
Before and during treatment with the product, the diagnostic procedures necessary to rule out the presence of a gastric neoplasm must be performed.
Precautions
Diclofenac
General
It should not be given concomitantly with other products containing the same active substance or other NSAIDs.
Taking into account if the patient has presented hypersensitivity reactions, caution measures should be taken prior to its administration.
Hydroxaline retention and edema
Different degrees of retention of salt even with edema has been observed in association with the use of NSAIDs, including diclofenac, so caution is recommended, especially in patients with a history of cardiac decompensation, hypertension, or other pathology that predisposes to salt retention.
Renal effects
Patients with highest risk of presenting adverse effects are those with previous disorders of kidney function, heart failure, hepatic dysfunction, diuretic therapy and elderly in general.
In patients treated with diclofenac rarely isolated cases of interstitial nephritis and papillary necrosis have been reported.
A secondary form of renal compromise, associated with the use of NSAIDs is observed in patients with clinical disorders with reduced renal plasma flow, where renal prostaglandins have a support role in the maintenance of renal perfusion. In those patients, the administration of a NSAID causes a dose-dependent fall in prostaglandin synthesis and secondarily in a reduced plasmatic-renal flow, which may precipitate renal failure, whose recovery may require the discontinuation of the treatment. Isolated cases of significant renal failure have been reported in patients receiving diclofenac during the postmarketing stage, but it was not observed in more than 4000 patients in international clinical trials, during which serum creatinine values were rigorously monitored. There were only 11 patients (0.3%) in whom serum creatinine and urea values were greater than 2mg/dl and 40mg/dl, respectively, while receiving diclofenac. Because diclofenac metabolites are eliminated primarily by urinary tract, it is advisable to strictly monitor and eventually stop the drug should the patient undergo treatment with this drug, especially those who have a significant impairment of renal function.

Porphyria
The use of diclofenac should be avoided in patients with hepatic porphyria, given that, as with other NSAIDs, there is the possibility of triggering an acute crisis presumably through induction of the acid delta aminolevulinic synthetase enzyme.
Aseptic meningitis
As with other NSAIDs, aseptic meningitis has been observed very rarely with fever and coma in patients treated with diclofenac. Although it is most likely that this happens in patients with systemic lupus erythematosus or other connective tissue diseases, when severe signs or symptoms of meningitis in a patient treated with diclofenac occur, it should be considered the possibility that this is related to the administration of the drug.
Pre-existing asthma
Since cross reactions with other NSAIDs, including bronchospasm, have been observed in sensitive aspirin patients, diclofenac should not be given to patients with this sensitivity to aspirin and should be used with caution in the patients with pre-existing asthma.
Other precautions
The pharmacological activity of diclofenac may decrease both fever and inflammation and therefore reduce its usefulness as a sign of suspicion of certain pathologies.
Blurred and decreased vision, scotomas and/or alteration of the vision of colors have been reported. If a patient develops these changes while receiving diclofenac, the drug should be discontinued and submitted to the patient to ophthalmological examinations.
In patients treated with NSAIDs, especially during prolonged treatments, it is advisable to periodically evaluate hematological parameters in order to timely detect the possibility of anemia or other alterations associated with its use.

Omeprazole

• Patients with renal function disorders: adjustment of dose in these patients is not necessary.
• Patients with liver function disorders: in these cases there is an increase of the plasma half-life of omeprazole, and a dosage adjustment may be required.

with the administration of diclofenac: Occasional (incidence 1-10%) General: abdominal pain, headache, hydropsaline retention, bloating, Gastrointestinal: diarrhea, dyspepsia, nausea, constipation, flatulence, alteration of liver tests. In less than 3% peptic ulcer with or without perforation and/or bleeding Nervous system: dizziness. Skin: rash, pruritus. Senses: tinnitus. Rare (incidence < 1%) General: general discomfort, swelling of the lips and tongue, photosensitivity, anaphylactoid reactions, rare cases of anaphylaxis. Cardiovascular: hypertension, congestive heart failure. Gastrointestinal: vomiting, jaundice, melena, stomatitis, dryness of mucous membranes, diarrhea, hepatitis, pancreatitis. Isolated: esophageal lesions, liver necrosis, cirrhosis, hepatorenal syndrome, colitis. Hematologic: decrease in hemoglobin, leucopenia, thrombocytopenia, purpura. Isolated: Eosinophilia, anemia, agranulocytosis. Nervous system: insomnia/drowsiness, depression, anxiety, diplopia, irritability. Isolated: aseptic meningitis and seizures. Respiratory: epistaxis, asthma, laryngeal edema. Skin and faneras: alopecia, urticaria, dermatitis, angioedema. Isolated: Stevens-Johnson Syndrome, erythema multiforme, blistering dermatitis. Senses: blurred vision, scotoma, loss of hearing, dysgeusia. Urogenital: proteinuria. Isolated: nephrotic syndrome, oliguria, papillary necrosis, acute renal failure, interstitial nephritis.

Omeprazole

Occasional (incidence 1-10%) General: headache, asthenia, low back pain. Gastrointestinal: diarrhea/constipation, nausea, vomiting, abdominal pain, bloating, acid regurgitation. Respiratory: upper airways infection, cough. Neurological: dizziness. Dermatological: skin rash. Rare (incidence < 1%) General: reactions allergic (even isolated cases of anaphylaxis), fever, fatigue, pain and general discomfort, burning. Cardiovascular: chest pain of angor, bradycardia/tachycardia, palpitations, high blood pressure, peripheral edema. Gastrointestinal: anorexia, irritable bowel, change in color of the stool, esophageal candidiasis, lingual mucous atrophy, dry mouth. Isolated cases of benign gastric polyps reversible with the suppression of the treatment. Isolated reports of gastroduodenal carcinoma in patients with Zollinger-Ellison syndrome under prolonged treatment, likely related with the disease and not with the drug. Hepatic: mild, isolated; marked increase in transaminase, gamma glutamyl transpeptidase, alkaline phosphatase and bilirubin (jaundice). Isolated: manifest liver disease with variable commitment (necrosis and failure - sometimes of extreme gravity-; Cholestasis, encephalopathy) has been described Pancreatic: pancreatitis, some extremely serious. Metabolic: hyponatremia, hypoglycemia, weight gain. Skeletal muscle: pain, weakness or muscle cramps, arthralgia. Neurological: drowsiness/insomnia, vertigo, paresthesia, hemi-facial dyesthesia. Psychiatric: mental confusion of reversible character, depression, apathy, disruption of sleep, agitation, nervousness, anxiety, hallucinations (in patients with serious illnesses). Respiratory: epistaxis, pharyngeal pain. Dermatological: isolated cases of generalized reactions, some serious (Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, erythema multiforme); purpura and/or petechia, dermatitis, urticaria, angioedema, pruritus, alopecia, xeroderma/hyperhidrosis. Sensory: tinnitus, alteration of taste Genitourinary: interstitial nephritis, urinary infection, polakiuria, micropiuria, hematuria, glucosuria, elevated creatininemia; testicular pain, gynecomastia. Hematologic: rare cases of pancytopenia, agranulocytosis (some extremely serious), thrombocytopenia, anemia, leukocytosis.

Overdosing

Diclofenac overdose can result in an increase in the incidence or severity of any of the known adverse reactions. Reports of overdose with omeprazole in humans have been received. The doses ranged up to 2400 mg (120 times the dose usually recommended in clinical practice). The manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, facial flushing, headaches, dry mouth and other adverse reactions similar to those observed in the normal clinical experience (see Adverse Reactions). Symptoms were transient and no serious evolutions were reported when only omeprazole was taken. Specific antidote for overdose with omeprazole is not known. Omeprazole is widely binded to proteins and therefore does not dialyze easily.

Initial indicative treatment in overdosing

After careful clinical evaluation of the patient, of the evaluation of the elapsed time since ingestion or administration, of the amount of toxic ingested and discarding the contraindication of certain procedures, the professional will decide performing or not general rescue treatment: provocative vomiting or gastric lavage, activated carbon, saline laxative (45 to 60 min after coal), hemodialysis. In the event of an overdose, go to the nearest Hospital or contact the Toxicological Centers: Hospital A. Posadas: (011) 4654-6648/4658 - 7777. Pediatrics Hospital Ricardo Gutierrez: (011) 4962-6666/2247. Optionally other Toxicological Centers. **Presentation:** boxes with 10 and 30 capsules. Last revision date: February 2014

Storage conditions

-Keep in a cool and dry place, temperature up to 30° C.
-Keep away from the reach of children.

Technical Direction: Dr. Alejandro D. Santarelli - Pharmacist.
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The following adverse reactions have been described in possible causal relationship