DIFEN® GESIC

FILM-COATED TABLETS

PARACETAMOL
DICLOFENAC POTASSIUM

Made in Argentina
Rx Only

Formulation
Each film-coated tablet contains: paracetamol 400.0 mg, diclofenac potassium 50.0 mg. Excipients: microcrystalline cellulose 42.00 mg; tricalcium phosphate 71.50 mg; povidone VA 64 35.00 mg; sodium starch glycolate 31.50 mg; crospovidone 59.50 mg; talc 9.80 mg; magnesium stearate 4.90 mg; hypromellose E 15 3.30 mg; titanium dioxide 4.70 mg; polyethylene glycol 6000 1.40 mg; povidone K30 0.50 mg; propylene glycol 0.70 mg, saccharin sodium 0.20 mg.

Therapeutic Action: antiinflamatory – painkiller – antipyretic.

Indications: painful and inflammatory symptoms of several parenchymas, especially acute and chronic processes of the musculoskeletal system.

Pharmacological action: DIFEN GESIC action is mediated by the reduction of prostaglandin synthesis through the inhibition of the cyclooxygenase enzyme. A slight central action is also described.

Pharmacokinetics: diclofenac potassium is absorbed almost completely in the gastrointestinal tract, even though due to the effect of the first hepatic step, its bioavailability is 50%. The peak plasma concentration is reached in approximately an hour when taken with an empty stomach, with Cmax at 1.5 μg/mL. Absorption is delayed and peak plasma concentrations are reduced by 40% when taken with a full stomach, although the total absorbed quantity does not change. 65% of diclofenac is eliminated through the urinary tract and 35% through biliary excretion, some conjugated with glucuronide or sulfate and the remaining as free drug.
Paracetamol is rapidly absorbed in the gastrointestinal tract, reaching the peak plasma concentration after 10 to 60 minutes of its administration. At therapeutic doses the percentage of paracetamol linked to plasma proteins is negligible. Elimination half-life oscillates between 1 and 3 hours. Paracetamol is metabolized in the liver and it is excreted in urine conjugated with glucoronides and sulfate.

Posology: one tablet every 12, 8 or 6 hours based on medical criteria. Maximum dose: two tablets that can be administered only as a first dose.

Contraindications
• Hypersensitivity to any of the components.
• History of asthma, urticaria, or other allergic reactions after taking NSAIDs.
• Active peptic ulcer.
• Third trimester of pregnancy.

Warnings
• Gastrointestinal effects: in patients chronically treated with NSAIDs, severe digestive toxicity as bleeding, ulceration or perforation may be observed.
It is more likely that these effects occur more frequently with high doses of these drugs. Physicians must remain alert to symptoms and signs for severe digestive toxicity.

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• Hepatic effects: isolated transaminase elevations may occur and isolated cases of hepatic necrosis and terminal hepatitis have been described.
• Anaphylactoid reactions: the administration of this product must be avoided in patients with asthma who have experienced rhinitis or bronchospasms after taking aspirin. Such patients have suffered lethal reactions.
• Chronic renal impairment: the administration of the product in advanced renal disease must be indicated only under close monitoring of the renal function.

Precautions
• Fluid retention and edemas: have been observed in patients taking diclofenac. Just like other NSAIDs it must be used with caution in patients with history of heart failure, hypertension and other conditions that may boost sodium and water retention.
• Hematological effects: the use of the product may be linked to the arousal of anemia due to gastrointestinal loses or to an incompletely described effect upon erythropoiesis.
• Renal effects: just like other NSAIDs the inhibition of vasodilatory prostaglandins production at renal level may cause falls on the glomerular filter in patients with chronic renal impairment. The suspension of the administration of the drugs is commonly followed by the recovery of the function with pretreatment values.
• Porphyria: the administration of the product in patients with hepatic porphyria must be avoided given to the possibility of a flare-up.
• Aseptic meningitis: it is more common in patients with history of connective tissue disease.
• Asthma: it must not be taken by patients who suffer from asthma and have a history of bronchospasms resulting from the administration of aspirin. It must be used with caution in all patients who suffer from asthma.
• Laboratory tests: in patients treated with NSAIDs the dosage of hepatic transaminase must be requested within the first four weeks of treatment. If high persistent levels or a progressive increase is detected the treatment should be suspended. Periodically, dosage of levels of hemoglobin and the assessment of the arousal of signs or symptoms that are compatible with anemia should be carried out.

Drug interactions: diclofenac is displaced from its bonding sites by aspirin, which reduces its plasma concentrations. Concomitant administration of NSAIDs and warfarin may enhance anticoagulant effects of the latter. NSAIDs may increase digoxin, methotrexate, cyclosporine, and lithium toxicity to reduce their renal excretion. An isolated alteration of the response of diabetic patients to insulin and antidiabetics administered orally during concomitant treatment with diclofenac has been described. Some studies have shown an increase in the half-life of chloramphenicol when administered concomitantly with paracetamol. In patients who are administered enzyme-inducing drugs like carbamazepine, phenytoin, barbiturates and rifampicin, paracetamol toxicity may be boosted.

Pregnancy: the administration of NSAIDs during the last stages of pregnancy must be avoided due to a possible risk of premature closing of the ductus arteriosus of the fetus. While studies in animals have not shown teratogenic effects with diclofenac and paracetamol, their administration during pregnancy must be done only after a thorough evaluation of the benefit/risk ratio.
Nursing: given to the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug in those mothers receiving NSAIDs.
Pediatric use: the safety of the product in pediatric patients has not been established.

Adverse reactions: all those of its therapeutic class. Abdominal pain, diarrhea, nauseas, constipation, flatulence, transaminase increase, peptic ulcer, erosive gastritis, headaches, dizziness, tinnitus, rashes and pruritus have been observed with a frequency higher than 1%. With a frequency lower than 1% cases of allergic reactions, including anaphylactic and anaphylactoid, photosensitivity, hypertension, heart failure, jaundice, hepatic necrosis, hepatorenal syndrome, pancreatitis, anemia, leucopenia, thrombocytopenia, eosinophilia, purpura, uremia, insomnia, depression, anxiety, diplopia, aseptic meningitis, seizures, epistaxis, asthma, larynx edema, Stevens-Johnson syndrome, alopecia, rash, polymorph erythema, changes in taste, escotomas, hypoacusis, nephrotic syndrome, interstitial nephritis, papillary necrosis and acute renal impairment, have been described.

Overdose: intoxications with NSAIDs may cause central effects (slight lethargy, somnolence) and gastrointestinal symptoms (abdominal pain, nausea and vomits). However, more severe symptoms like digestive bleeding, acute renal impairment, seizures and coma may be observed. Ingestion of 10 to 15 g of paracetamol in adults may cause severe hepatocellular necrosis and less frequent renal tubular necrosis. Symptoms start within the first 24 hours with nauseas, vomits, depression of the senses and sweating. Hepatic damage is usually revealed through abdominal pain within 48-72 hours possibly followed by encephalopathy, coma or death. Progressive increase of prothrombin time is an indicator of evolution towards liver failure. Patients with history of alcoholism or those receiving enzyme-inducing drugs are especially sensitive to the development of hepatic failure.
In case of overdose the patient must be hospitalized so as to immediately perform a gastric lavage, administer activated coal and start treatment with acetylcysteine orally or intravenously. The antidote is more effective when administered within the first 8 hours.
The initial parenteral dose recommended of acetylcysteine is of 150 mg/kg in 200 mL of dextrose solution at 5% for 15 minutes. Followed by 50 mg/kg in 500 mL of the same solution for 4 hours and finally 100 mg/kg in 1 liter of solution in the next 16 hours. The initial dose administered orally is 140 mg/kg as a solution at 5% followed by 70 mg/kg/4 hours until completing 17 doses.
Methromine can be used as an alternative in doses of 2.5 g administered orally every 4 hours.
Forcing urine output is a theoretically beneficial measure for the elimination of diclofenac when the use of dialysis and hemoperfusion is unknown.
In case of overdose, go to the nearest Hospital or contact any of the following Poison Control Centers:
Ricardo Gutiérrez Pediatric Hospital: (011) 4961-666/2247.
A. Posadas Hospital: (011) 4654-6648/4658-7777.
Other Poison Centers.

How supplied: packs containing 15 and 30 coated tablets.
Date of the last revision: June 2010.

Conservation
- Keep in a fresh and dry environment, especially at a temperature between 15 and 30°C.
- Keep out of the reach of children.

Technical Direction: Dr. Luis M. Radici – Pharmacist.
MEDICINAL PRODUCT AUTHORIZED BY THE MINISTRY OF HEALTH.
Certificate N° 35.279
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