DIFEN® FLEX

SODIUM DICLOFENAC
PRIDINOL MESYLATE

COATED TABLETS
IM INJECTION

Rx only
Made in Argentina

Formulation:
Coated tablets. Each coated tablet contains: sodium diclofenac 50.00 mg, pridinol mesylate 4.00 mg. Excipients: lactose monohydrate 95.00 mg, microcrystalline cellulose 34.00 mg, sodium croscarmellose 9.00 mg, magnesium stearate 1.80 mg, coloidal silicon dioxide 2.00 mg, hydroxypropylmethylcellulose E15 7.33 mg, yellow iron oxide 95.20 ug, red iron oxide 18.10 ug, titanium bioxide 0.57 mg; polyethylenglycol 6000 1.33 mg; Talc 4.77 mg.
For injection. Each ampoule with solvent contains: sodium diclofenac 75.0 mg. Excipients: mannitol 18.00 mg, propylenglycol 800.00 mg; benzyl alcohol 120.00 mg, Sodium metabisulfite 9.00 mg, sodium hydroxide q.s. pH 8,6; water for injection q.s. 3.00 ml.
Each vial with lyophilized contains: pridinol mesylate 2.20 mg. Excipients: mannitol 67.80 mg.

Therapeutical action: analgesic. antiinflammatory. Muscle relaxant.

Indications: DIFEN® FLEX is indicated in painful inflammatory processes with muscular contracture. Articular and extra-articular reumatic processes. Myalgias. Lumbar pains. Ciatalgias. Torticollis. Traumas. Sprains.

Pharmacological action: diclofenac is a non-steroid anti-inflammatory drug acting through the inhibition of prostaglandin synthesis.
Pridinol is a central-action muscular relaxant which is effective in the muscular spasm.

Pharmakokinetics: diclofenac is well absorbed from the gastrointestinal tract, however, due to the metabolic first pass effect, only the 50% of the absorbed dose is systemically available. The peak plasma levels are reached at 2 hours with a range of 1 to 4 hours. The area under the curve is proportional to the dose in the 25 - 150 mg range. The peak plasma level for a 50 mg-dose is 1,5 ug/ml approximately. After the repeated oral administration of the product in two daily doses diclofenac is not accumulated in plasma. When it is administered together with the meals, the absorption is delayed in 1 to 4.5 hours and the peak plasma levels are reduced by 40%. However, the diclofenac absorption degree is not significantly affected. It is reversibly bound to the plasma albumin in a percentage superior to 99%. As with other NSAID, diclofenac difuses towards the articular space when the plasma levels are higher than the levels in the synovial liquid. Diclofenac is eliminated by urinary excretion (65%) and biliary excretion (35%) as conjugated metabolites (glucuronide and sulfate). The plasma half-life is 1 to 2 hours. Diclofenac is also detected in human milk.
Pridinol is absorbed in the gastrointestinal tract reaching the peak plasma concentration one hour alter its administration. 30-40% of the dose is concentrated in bile and in other tissues, especially liver and kidney. The urinary elimination is produced as non-conjugated drug in 9% and a similar percent as its glucuronide conjugate.

Posology - Dosage and Administration: *DIFEN® FLEX - Coated tablets:* One tablet twice a day, preferably after meals. It may be adjusted according to physician's criterion.
DIFEN® FLEX for injection: An intramuscular vial twice a day. Introduce the ampoule content

in the vial and shake softly.
Use before one hour of being preparated.

Contraindications: history of allergy to any of the product components. Active gastrointestinal ulcer. Severe liver and/ or renal failure. Patients with history of asthma, rhinitis or urticaria triggered by acetylsalicylic acid or other non-steroid anti-inflammatory drugs. Pregnancy and nursing.

Warnings:
Gastrointestinal effects: serious gastrointestinal toxicity such as bleeding, ulceration, and perforation with or without alarm symptoms may occur at any moment of the therapy. The physician should inform the patient about serious toxicity signs and symptoms and what to do in these cases.
Liver effects: alterations of the liver function tests may occur during diclofenac treatment. These alterations may progress, remain stable, or be transitory with the continuous treatment. TGP periodical monitoring is recommended for the follow-up.
Severe liver reactions, including liver necrosis, jaundice, and fulminating hepatitis, have been exceptionally described.
Anaphylactoid reactions: patients with history of hypersensibility to aspirin may have rhinitis or potentially fatal bronchospasm episodes after taking the medicine.
Renal failure: diclofenac treatment may precipitate acute renal failure in patients with previous renal disease.
Pregnancy: in the last trimester of pregnancy, as with other NSAID, diclofenac may cause arterious duct premature closure.

Precautions
Hydrosaline retention and edemas: it should be used carefully in patients with history of cardiac failure, hypertension, or other conditions favoring the hydric retention.
Hematological effects: in some cases, anemia, probably due to hydric retention, gastrointestinal losses, or erithropoiesis effects have been observed. In patients with long-term treatment with diclofenac it is recommended that the hematocrit and hemoglobin bemeasured periodically.
Renal effects: in patients treated with NSAIDs, isolated cases of papillar necrosis and interstitial nephritis have been described. A second form of renal toxicity, generally associated to NSAIDs, is observed in patients with conditions causing decreased blood volume or renal flow where the prostaglandins have a primordial role in maintaining the renal perfusion. In these patients the administration of these drugs may cause acute renal failure. Treatment suspension, in all cases, causes the generally complete recovery of the renal function to pre-treatment levels
Since diclofenac metabolites are mainly eliminated through the kidney, the patients with renal failure should be controlled closer than those with normal renal function.
Porphyria: the use of this product should be avoided in patients with liver porphyria.
Aseptic meningitis: NSAIDs generally may trigger, rarely, aseptic meningitis with fever and coma especially in patients with history of eritematous lupus and other connective tissue diseases.
Previous asthma: Diclofenac should not be administered to patients with history of bronchospasm triggered by aspirin. It should be taken into account that up to a 10% of the asthmatic patients may have asthma sensitive to aspirin.
Other precautions: blurred vision, decreased visual acuity, chromatic vision alteration and scotomas occurrences. In case these symptoms occur, the treatment should be stopped and the patient should undergo an ophthalmologic examination.

Drug interactions
- *Aspirin:* the concomitant administration of aspirin and diclofenac causes displacement of the latter of its binding sites producing low plasma concentrations and decreased peak plasma levels.
- *Anticoagulants:* although the studies have not shown interaction between diclofenac and oral

anticoagulants, like warfarin, their concomitant administration should be performed with caution due to the interactions described for other non-steroid anti-inflammatory drugs. Diclofenac therapy alters the platelet function and the prostaglandin role in the hemostasia, so the concomitant administration of these drugs and aspirin requires a carefully followed up of the patient.
- *Digoxine, methrotexate, cyclosporine:* diclofenac treatment may increase the digoxine and methrotexate plasma concentrations and the cyclosporine nephrotoxicity.
- *Lithium:* in patients administered with diclofenac and lithium, the lithium plasma concentrations may be increased. Therefore, in these cases the development of lithium toxicity should be controlled.
- *Oral hypoglucemiants:* changes in the effect of insulin or oral hypoglucemiants have been reported in the concomitant treatment with diclofenac. Hypoglucemiant and hyperglucemiant effects have been detected.
- *Diuretics:* diclofenac may decrease the diuretics activity. The concomitant administration of diclofenac and potassium sparing duretics may increase the plasma levels of this last ion.
- *Drug-drug interactions and laboratory tests:* diclofenac increases the platelet aggregation time but it does not affect the bleeding time, thrombin time, plasma fibrinogen or the levels of V, VII and XII factor. Statistically significant changes have been observed in the prothrombin time and thromboplastin partial time in healthy volunteers. These changes probably have not clinical significance.

Carcinogenesis, mutagenesis and impairment of fertility: in several animal studies this kind of effects has not been described.

Pregnancy and nursing: DIFEN® FLEX should not be administered during pregnancy, especially in the last trimester, due to the risk of arterious duct premature closure. It should not be administer either during nursing due to the potential risk of adverse events in the infant.

Pediatric use: the product safety and efficacy have not been established.

Adverse Reactions

The following adverse events have been described with diclofenac:

Gastrointestinal Tract: diarrhea, nauseas, constipation, meteorism, abnormalities in the liver function tests, peptic ulcer with or without hemorrhage or perforation, erosive gastritis. Liver necrosis, jaundice, hepatorenal syndrome.

Central Nervous System: somnolence, depression, anxiety, irritability, aseptic meningitis, seizures.

Skin: rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome.

Sense organs: tinnitus, blurred vision, scotomas, taste disorders.

Cardiovascular: hypertension, congestive cardiac failure.

Hematological effects: anemia, leukopenia, thrombocitopenia.

Kidney effects: olyguria, interstitial nephritis, papillar necrosis, acute renal failure.

Respiratory System: epistaxis, asthma, laryngeal edema.

The following side effects have been reported with pridinol:

Cardiovascular: hypertension.

Nervous System: dizziness and falls, muscular hypotonia, myastenia, visual accommodation disorders, hallucinations, acathisia.

Skin: urticaria and pruritus.

Overdosage: acute overdosage symptoms include headache, psychomotor agitation, muscular spasm, seizures, epigastric pain, nauseas, vomits, hematemesis, diarrhea, gastroduodenal ulcer, liver function disorders and olyguria.

Optionally other Toxicology Centers.

Inicial orientative treatment of overdosage: In case of an overdosage, it is recommended the immediate gastric emptying by lavages or vomit induction.

To cause forced diuresis may be beneficial since drugs are excreted in urine. Dialysis or hemoperfusion efficacy has not been stated in the product elimination. The use of activated charcoal may help to reduce the drug absorption.

How-supplied:
DIFEN® FLEX - coated tablets: Containers having 15 and 30 coated tablets.
DIFEN® FLEX -IM injection: Containers having 6 ampoules with solvent and 6 vials with lyophilized
DIFEN® FLEX -IM injection: Containers having 3 ampoules with solvent and 3 vials with lyophilized.

Storage
- Keep in a cool and dry place, preferably between 15º and 30°C.
- Keep out of the reach of children.

Technical Direction: Dr. Luis M. Radici - Pharmacist.
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