DIFEN® PLUS

DICLOFENAC POTASSIUM
BETAMETHASONE

COATED TABLETS
INJECTABLE

Rx only - Made in Argentine

Formulations
DIFEN PLUS — Coated tablets
Each coated tablet contains: Diclofenac potassium 50,000 mg. betamethasone 0,300 mg. Excipients: povidone K-30 8,475 mg, lactose 162,325 mg, corn starch 52,500 mg, calcium carboxymethylcellulose 52,500 mg, sodium croscarmellose 21,000 mg, magnesium stereate 3,500 mg, hydroxypropylmethyl-cellulose E15 3,120 mg, polyethylenglycol 6000 3,000 mg, titanium dioxide 3,600 mg, talc 1,680 mg.
DIFEN PLUS - Injection
Each ampoule contains: Diclofenac potassium 75,00 mg. betamethasone sodium phosphate 2,63 mg. Excipients: Anhydrous disodium phosphate 4,800 mg, benzyl alcohol acid 250,00 mg, propylenglycol 1140,000 mg, methylparaben 2,400 mg, propylparaben 0,450 mg, sodium metabisulfite 9,00 mg, sodium hydroxide q.s. pH 8,3, water for injection q.s. 3,00 ml.

Therapeutic action: Analgesic and anti-inflammatory.

Indications: Symptomatic and short treatment when the patient does not respond to monotherapy of the muscle-skeletical acute inflammatory processes.
The injectable treatment is reserved for cases where the oral treatment is not possible or there is no response whatsoever.

Pharmacological action: Sodium diclofenac is a non-steroidal anti-inflammatory (NSAI) derived from the phenylacetic acid. In pharmacological studies, diclofenac has proved to have an anti-inflammatory, analgesic and antipyretic activity.
As with any other NSAIDS, its method of action is not completely clear; the capacity to inhibit prostaglandin synthesis participates in its pharmacological activity.
Betamethasone is a glucocorticoid suppressing the inflammation by multiple mechanisms: It inhibits the production of several intermediate methods of inflammatory reactions, among them, vasoactive and chemiotactic factors; it lowers the secretion of lipolytic and proteolytic enzymes; it produces less extravasation of leukocytes to the wounded areas and it lowers fibrosis; and finally, it also affects the number and the immune reactions depending on the lymphocytes.

Pharmacokinetics: The coated tablets enable diclofenac release in the high pH of the intestine. Food delays the absorption start, by reducing the plasmatic peak. It joins irreversibly to plasmatic albumin in a percentage higher than 99%. Diclofenac is eliminated by hepatic metabolism and it is then excreted by urine (65%) and bile (35%) such as metabolites conjugated with sulphate or glucuronic. No variation of pharmacokinetics in the geriatric population or in patients with hepatic or renal insufficiency has been detected. After its oral administration, betamethasone is rapidly and completely absorbed, reaching a plasmatic average life of 4 to 6 hours. After the parenteral administration, betamethasone is completely absorbed and, since the disodium phosphate vehicle is water-soluble, the drug action starts completely, reaching the maximum plasmatic peak at the moment of administering intramuscular injection. Its distribution volume is from 75 to 90 liters and it is joined in a 64% to plasmatic proteins. It is metabolized in the liver and eliminated through the urine and bile (as 17 hydroxycorticosteroids).

Dosage and Administration
Coated tablets: A tablet every 8 or 12 hours according to medical criteria. Its administration is recommended after meals.
Injectable: 1-2 ampoules a day intramuscular use only.

Treatment duration depends on patient response and medical criteria. It must be stated that a prolonged corticotherapy lasting more than two weeks entails the risk of causing cortico-suprarenal insufficiency due to inhibition for releasing of ACTH (adreno-corticotripic hormone), which produces an atrophy of suprarenal glands. In case of prolonged treatments, the posology decrease must be progressive so as to avoid the appearance of the above mentioned clinical case.
The use of DIFEN PLUS Injectable is not advised for a period longer than 3 days.

Contraindications: Hypersensitivity to active ingridient. Hypersensitivity to aspirin and other NSAIDs. Active gastroduodenal ulcer, severe renal insufficiency, hepatic insufficiency, uncompensated heart failure, severe arterial hypertension, systemic mycosis, active tuberculosis, gout, hepatitis A, B and non A non B and other viral infections, anticoagulant treatment, pregnancy and breast feeding.

Warnings: DIFEN PLUS, due to having diclofenac, as with any non-steroidal anti-inflammatory drug, may cause a digestive hemorrhage or perforation with or without previous symptoms or pathology at any time of the treatment. This is more probable in old people. Diclofenac can rarely cause severe allergic reactions of anaphylactic or anaphylactoid type.
Betamethasone can cover some infection signs. No immunization procedure must be carried out in patients treated with DIFEN PLUS, due to the possible alteration of an immune response. It must also be administered with great care in patients suspected of suffering from infection by Strongyloides because it may predispose to spread of the affection, putting life at risk. Patients with latent tuberculosis or reactivity to tuberculin must be controlled carefully since a reactivation of the disease is possible. During prolonged patients, these patients must receive chemoprophylaxis. Prolonged corticotherapy longer than two weeks entails the risk of causing cortico-suprarenal insufficiency due to inhibition for releasing of ACTH (adrenocorticotropic hormone), which produces an atrophy of suprarenal glands. Suprarenal insufficiency may appear, in these cases, in stressful situations (surgery, severe traumatism, and severe infections) or as a consequence of the abrupt suspension of the steroid treatment. It is recommended, in these situations, the administration of a quick action Corticoid so as to prevent the case of suprarenal insufficiency. In cases where the suspension of prolonged treatments with corticosteroids is decided, we advise to perform it gradually.

Precautions: DIFEN PLUS, since it contains diclofenac, must be used carefully in patients with disorders of renal failure, heart or hepatic failure, and in patients who underwent major surgery or who suffered from depletion of intravascular volume. Diclofenac may cause acute episodes in patients with hepatic porphyria and may also cause acute exacerbations in patients with bronchial asthma.
Strict medical vigilance in patients with medical history of duodenal ulcer, ulcerative collitis or Crohn disease must be observed. Patients with hemostasis disorders or who receive oral anticoagulants must be also strictly controlled.

DIFEN PLUS, due to its content in betamethasone, must be administered cautiously in patients with diverticulitis, recent intestinal anastomosis, medical history of peptic ulcer, ulcerative colitis, abscesses or other pyogenic infections, arterial hypertension, osteoporosis and myasthenia gravis. It must also be used cautiously in patients with ocular herpes simplex, in patients with emotional instability or psychotic tendencies and in hypothyroid patients. During the prolonged treatment with DIFEN PLUS, hematological, renal and hepatic controls must be performed. In old patients, the minor dose of DIFEN PLUS showing its efficacy must be used.

Drug interactions: Simultaneous administration of DIFEN PLUS with other systemic non-steroidal anti-inflammatory drugs may favor the appearance of adverse effects. A strict control of coagulation in patients taking oral anticoagulants is recommended.
DIFEN PLUS may inhibit the pharmacological action of diuretics. Potassium retainer action of potassium saving diuretics may be also increased. Caution must be taken when this product is administered 24 hs before of after a treatment with metrotexate since it may increase its plasmatic level and toxicity. The simultaneous administration of DIFEN PLUS and lithium salts may increase the plasmatic levels of the last one, without producing overdose signs. Since DIFEN PLUS contains a steroid (betamethasone) in its formula, the following situations are listed:

Not advised associations: erythromycin i.v., astemizole, bepridil, halofantrine, pentamidine,

terfenadine, sultopride, vincamine, upon the risk of appearance of "torsade de pointes" (hypokaelemia, bradycardia and a prolonged QT interval increase the risk of developing this arrhythmia).
Associations needing use cautions: Antiarrhythmics predisposing the development of "torsade de pointes", such as: amiodarone, bretylium, disopyramide, quinidine, sotalol. Digital due to a risk increase of toxic effects upon kalemia decrease.
Agents producing hypokalemia as amphotericin B via i.v., thiazide, loops diuretics and laxatives.
Acetylsalicylic acid: Corticoids increase the elimination of salicylate. Therefore, there is a risk of overdose of salicylate alter suspending a Corticoid treatment. Adaptation of the salicylate dose after suspending a corticoid treatment is then recommended.
Oral anticoagulants and heparin via parenteral: in these cases, we recommend reinforcing the patient follow-up since corticoids increase the risk of hemorrhages. This effect appears when high doses of corticoids are administered in periods higher than 10 days.
Insulin, metformin, hypoglycemic sulphamides: In these cases, we recommend reinforcing the self-monitoring of glucemia by the patient and, eventually, adapting the posology of anti-diabetic agents during the Corticoid treatment and after its suspension.
Isoniazide: Plasmatic levels of isoniazide are lowered when it is associated to Corticoids. In these cases, clinical and microbiological supervision is recommended.
Phenobarbital, phenytoin, primidone, carbamazepine, rifabutin, rifamycin: All these are enzyme inducers agents which decrease Corticoids efficiency and thus, adapting eventually the product posology during and after the treatment with these drugs is recommended.
Gastrointestinal topical agents (magnesium, aluminum and calcium oxide and hydroxide): They produce a decrease of Corticoid absorption. In case of associating them in the treatment, the administration of them in different timeframes is recommended (with a difference higher than 2 hs, if possible).

Associations to take into account
Antihypertensives: corticoids produce a decrease its therapeutic effects. Interferon alpha: Corticoids may inhibit its therapeutic action.
Vaccines to attenuated live germs: There is a risk of developing eventually life-threatening generalized diseases. The risk will be higher in previously immunosuppressed patients due to an underlying disease. Use mainly vaccines to inactive germs.
Pregnancy and breast-feeding: DIFEN PLUS must not be prescribed during pregnancy, except when being imperative, and in particular, in the last trimester of gestation, since diclofenac may inhibit uterine contractions and cause an early closing of the arterious conduit. Corticoids are eliminated partially in breast milk.

Adverse reactions: DIFEN PLUS may cause different adverse reactions in the following systems:
- Gastrointestinal tract: Epigastric pain, nausea, vomiting, diarrhea, abdominal distension, digestive hemorrhage, gastric or duodenal ulcer with or without hemorrhage or perforation.
- Central Nervous System: convulsions, increase of endocranial pressure, dizziness, cephaleas and sleepiness.
- Liver: Occasionally, increase of transaminases and, rarely, hepatitis with or without jaundice.
- Skin: Occasionally, erythema and skin rush. Rarely urticaria. Isolated cases of Stevens Johnson, multiform erythema and toxic epidermolysis. Delay in wound healing-up, skin fragility, petechias and ecchymosis, facial erythema. Some adverse reactions depend on its parenteral administration: Hyperpigmentation or hypopigmentation, cutaneous and subcutaneous atrophy, sterile abscesses.
- Kidney: Isolated cases of acute renal insufficiency, haematuria and proteinuria.
- Hematological system: Isolated cases of leukopenia, hemolytic anaemia and agranulocytosis.
- Cardiovascular system: Arterial hypertension, congestive heart failure and palpitations.
- Hydroelectrolytic dicorders: Sodium retention, edema, potassium loss and hypokalemic alkalosis.
- Musculoskeletal system: Muscle weakness, steroid myopathy, loss of muscular mass, osteoporosis, vertebral fractures due to compression, aseptic necrosis of femoral and/or humeral head and pathological fractures of long bones.
-Endocrine system: Menstrual disorders, cushingoid condition, growth suppression in children, suprarenal insufficiency, in particular in stressful situations such as traumatisms, surgery, systemic diseases. Decrease of tolerance to carbohydrates and increase of insulin and oral hypoglycemic substances requirements in diabetic patients.

- Organs of the senses: posterior subcapsular cataracts, increase of intraocular pressure, glaucoma, exophtalmos and tinnitus.
- Metabolism: Negative nitrogen balance due to protein catabolism.

Overdose: In case of overdose, the gastric emptying inducing emesis must be carried out (this measure is contraindicated in patients with conscious deterioration) or through gastric lavage. In a second step, activated carbon to decrease the absorption and interrupt the diclofenac enterohepatic circuit must be administered. Administration of antacids or other alkaline substances of urine reinforces the excretion of non-steroidal anti-inflammatory drugs such as diflunisal or sulindac. Hemodialysis, necessary in some cases for the treatment of secondary renal insufficiency to intoxication due to NSAIDs, may accelerate the elimination of diclofenac. The hemodynamic condition of the patient must be monitored and, upon the appearance of hypotension, plasmatic expanders must be indicated. Upon the presence of convulsions, diazepam and other benzodiazepines are indicated intravenously. Probable appearance of hemorrhage or gastrointestinal ulceration must be considered and supplement of K vitamin for treating hypoprothrombinemia is indicated.

If an overdose occurs, go to the closest hospital or communicate with the Toxicological Centers. Ricardo Gutiérrez Pediatric Hospital: (011) 962-6666/2247. A. Posadas Hospital: (011) 654-6648/658-7777.
Optionally, other Intoxication Centers.

How supplied
Coated tablets: Packages with 15 coated tablets.
Injectable: Packages with 5 ampoules.

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Storage
Coated tablets: Protect from humidity, temperature under 30°C.
Injectable: Preserve in a cool and dry place, temperature under 30°C
Keep all drugs away from children.

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