DIFEN® B12

DICLOFENAC SODIUM 75 mg *INJECTION I.M.*
BETAMETHASONE (as DISODIUM PHOSPHATE) 2 mg
HYDROXOCOBALAMIN (as SULPHATE) 10 mg
Rx only
Made in Argentina

Composition
Each ampoule contains: diclofenac sodium 75,000 mg, betamethasone (as disodium phosphate) 2,000 mg, hydroxocobalamin (as sulfate) 10,000 mg. excipients: benzyl alcohol 120,000 mg, propylene glycol 900,000 mg, sodium metabisulphite 9,000 mg, disodium salt of the acid ethylenediaminetetraacetic 0.300 mg, sodium hydroxide 4,800 mg, water for injection q.s. 3,000 ml.

Therapeutic action: analgesic, anti-inflammatory and anti-neuritic.
ATC code: M01AB55

Indications: painful and intense inflammatory processes, especially with neuritic component. Articular and extraarticular rheumatic conditions. Fibrositis. Myalgia. Back pain. Sciatic pain. Trauma. Sprains.

Pharmacological action: DIFEN B12 contains as one of its active ingredients diclofenac sodium, a nonsteroidal anti-inflammatory drug (NSAIDs) derived from phenylacetic acid with strong anti-inflammatory and analgesic action. Its pharmacological action mechanism is part of the inhibition of the synthesis of prostaglandins and their release during the inflammatory process. In this sense, diclofenac inhibits both isoenzymes of the cyclooxygenases currently known (COX1 and COX2). It has been reported that diclofenac at high concentrations inhibits the formation of metabolites of arachidonic acid, including leukotrienes and acid 5-hidroxieicosaletraenoico (5 - HETE). In addition, it can inhibit the migration of leukocytes, including polymorphonuclear leukocytes, 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 the production of superoxide and leukocyte chemotaxis. Its analgesic effect is related to the decrease of mediators of the nociceptive via, blocking the generation of pulses at the peripheral level. Also a central action of non opioid mechanisms is postulated, at the hypothalamic level. It has also an antipyretic effect linked to the decrease of activity of prostaglandins at hypothalamic level in the thermoregulatory center, favoring their loss. Betamethasone is a steroidal anti-inflammatory drug. Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones: synthetic corticosteroids, such as betamethasone, are used mainly by their powerful anti-inflammatory effect. At high doses, decreases the immune response. Its metabolic and sodium retention effect is smaller than the hydrocortisone. Hydroxocobalamin (vitamin B-12) acts as a Coenzyme in several metabolic functions, including lipid and carbohydrate metabolism and in the synthesis of proteins. It is required in the growth, cell replication, hematopoiesis and in the synthesis of nucleoproteins and myelin, due, in large part, to its effects on the metabolism of methionine, folic acid and malonic acid. At high doses (pharmacological), clinical experimentation has shown a marked effect anti-neuritic.

Pharmacokinetics: Peak plasma concentrations of diclofenac are reached approximately 20 minutes after their intramuscular administration. The area under the curve (AUC) of plasmatic concentration - time obtained following intramuscular injection is almost twice that the obtained with identical doses by oral route. Diclofenac plasma proteins binding is more than 99% and its volume of distribution is 0.12 - 0.17 l/kg
Two hours after reaching peak plasma concentration, the concentration in synovial fluid exceeds the plasma, maintaining this relationship up to 12 hours after administration. In the synovial fluid the elimination half-life is 3 to 6 hours. The total systemic clearance of diclofenac in plasma reaches 263±56 ml/min. The elimination half-life is 1-2 hours. Diclofenac is metabolized by the 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; the conjugates represent a 5-10% of the dose recovered in urine. Less than 5% of the dose was eliminated by bile. The main metabolite in humans is the 4-hidroxidiclofenac, and constitutes approximately 40% of the total dose excreted. Other three metabolites of diclofenac (3-Hydroxy, 5-hydroxy, 4, 5-dihidroxidiclofenac) represent about 10-20% of the dose eliminated in the urine. The elimination of diclofenac and its metabolites is fast: about 40% of the administered dose is eliminated during the first 12 hours after administration. Diclofenac pharmacokinetic parameters remain constant after repeated administration in healthy patients, but in patients with renal failure the drug and/or its metabolites may accumulate (without clinical significance).

Patients with impaired hepatic function (chronic hepatitis, cirrhosis without portal decompensation) present kinetics and metabolism of the drug similar to healthy subjects.
When injected intramuscularly the hydroxocobalamin is fully absorbed, obtaining the peak plasma levels approximately 1 hour after administration. Once in the systemic circulation, the hydroxocobalamin binds to specific transport proteins, the transcobalamines. Three transcobalamines (Transcobalamines I, II and III) have been determined. Hydroxocobalamin bound to transcobalamin quickly abandons plasma and is distributed with preference in the hepatic parenchyma cells. In the adult, up to 90% of hydroxocobalamin reserves is found in the liver. Bile is the main route of excretion of hydroxocobalamin. Two-thirds of the hydroxocobalamin is excreted in bile and are then reabsorbed by the ileal mucosa, forming in this way an enterohepatic cycle. The rest is eliminated by fecal route and can increase the amount of hydroxocobalamin in them by desquamation of epithelial cells of the digestive tract and the synthesis carried out by bacteria in the colon.
Under normal conditions, hydroxocobalamin urine excretion is very scarce. By progressively increasing the doses administered, the glomerular filtration becomes increasingly important.
After intramuscular administration of betamethasone disodium phosphate, maximum plasma concentrations are achieved in about 60 minutes. In the recommended therapeutic dosage range, binding to plasma proteins, primarily albumin, is 60-70%. The volume of distribution of betamethasone is 1.4 ± 0.3 l/kg. The plasma half-life of betamethasone disodium phosphate administered orally or parenterally is 5 hours, being its biological half-life of 36-54 hours, its renal clearance of 2.9 ± 0.9 ml/min/kg. Betamethasone esters undergo hydrolysis at tissue level at the point of injection. Betamethasone is metabolized in the liver as well as other glucocorticoids and is eliminated mainly biliary, conjugated with glucuronic acid.
Special clinical situations
In hepatic insufficiency and hypothyroidism, the metabolism of glucocorticoids suffers a significant delay, which can accentuate the pharmacological action of betamethasone. Also, both hypoalbuminaemia and hyperbilirubinemia may cause undesired elevated serum concentrations of the active substance not bound to proteins. The elimination half-life of glucocorticoids is prolonged during pregnancy and plasma clearance is less in the newborn than in the infant and adult.

Posology and method of Administration: The dose will be established individually according medical criteria and patient's clinical. Recommended average dosage:
Adults and children over 12 years: 1-2 ampoules per day, intramuscularly, for a period not more than 3 days unless medical indication.
Mode of administration: to minimize the risks of discomfort at the site of injection or local adverse effects, it is recommended to fill carefully the rules of application of injectable, especially: careful asepsis of the site of application. Take care of asepsis during handling. Apply most deeply possible. Inject slowly. Gently massage the area to facilitate the distribution of the liquid.

Contraindications: history of allergy to any of the components of the product. Active gastrointestinal ulcer. Severe hepatic and/or renal failure. Decompensated heart failure. Severe arterial hypertension. Asthmatic patients with a history of precipitation of acute attacks of asthma, rhinitis or urticaria by acetyl salicylic acid or other drugs with inhibitory action on the synthesis of prostaglandins. Active tuberculosis. Systemic mycoses. Viral diseases. Acute glomerulonephritis. Acute psychosis. Osteoporosis. Hepatic porphyria. Pregnancy. Breastfeeding. Children under 12 years old.

Warnings: administration of corticosteroids may favour the development of infections, hydrosaline retention, exacerbation of acid peptic gastroB12denal disorders.
Gastrointestinal effects associated with treatment with NSAIDs or corticosteroids: a close medical monitoring of patients with a history of peptic ulcer and gastrointestinal hemorrhage is advised. It is recommend caution in patients treated chronically with diclofenac, for the possibility of generating peptic ulcer disease and gastrointestinal bleeding and perforations, even in the absence of the characteristic previous symptoms of the upper digestive tract. The elderly or debilitated patients, appear to tolerate less ulcers or bleeding that other individuals and most extremely serious gastrointestinal adverse events occur in this age group population.
Hepatic effects: alterations in one or more liver tests may occur. These laboratory abnormalities may progress, remain unchanged or be transitional. For the monitoring of liver injury, the follow up of glutamic pyruvic transaminase levels (GPT) is recommended. Elevations of transaminases were observed more frequently in arthritic patients than in those with rheumatoid arthritis. In addition to enzyme elevations, reported to pharmacovigilance systems in clinical trials, rare cases of more severe hepatic reactions, including hepatocellular involvement with or without jaundice have been reported. Based on clinical experience, the transaminases in the fourth to eighth week after having started a continued treatment with diclofenac should be controlled. As with other NSAIDs, if abnormal liver tests persist or worsen, if clinical signs and/or symptoms related to liver disease appear (e.g., nausea, vomiting, fatigue, pruritus, jaundice, rash, eosinophilia), treatment should be cautiously discontinued.

Anaphylactoid reactions: as is the case with other NSAIDs anaphylactoid reactions can occur in patients without prior exposure to components of the product. Product administration is not recommended to patients with allergy to aspirin or who experience rhinitis with or without nasal polyps or who manifest severe bronchospasm after taking aspirin or other NSAIDs. Extremely serious reactions in such patients have been reported.
Advanced renal disease: in cases of advanced renal disease, any treatment with NSAIDs should only start under strict control of renal function.
Pregnancy: particularly in the late stage of pregnancy, it is recommended to prevent the administration of NSAIDs, because of risk of premature closure of the ductus arteriosus.

Precautions: DIFEN B12 should not be used concomitantly with other products that contain similar active principles or other NSAIDs. Prior to its administration precaution measures should be taken, considering whether the patient has presented hypersensitivity reactions.
Hydrosaline retention and edema: it has been observed different degree of hydrosaline retention even with oedema in association with the use of anti-inflammatories, so caution is advised, especially in patients with a history of cardiac decompensation, hypertension, or other pathology that predisposes to hydrosaline retention.
Renal effects: patients with increased risk of suffering adverse effects are those with previous impaired renal function, heart failure, liver dysfunction, those under diuretic treatment and the elderly in general. In patients treated with diclofenac isolated cases of interstitial nephritis and papillary necrosis were rarely reported. A secondary form of renal impairment associated with NSAID use is seen in patients with disorders such as: reduction in renal plasma flow or blood volume, where renal prostaglandins play a role of support in the maintenance of renal perfusion. In those patients, an NSAID administration results in a dose-dependent decrease in the synthesis of prostaglandins and secondarily a reduction of renal plasma flow, which can precipitate kidney failure, whose recovery may require discontinuation of the treatment. Isolated cases of significant renal failure in patients receiving diclofenac have been reported, but not observed in more than 4000 patients in international clinical trials, during which the serum creatinine values were rigorously monitored. There were only 11 patients (0.3%) with serum creatinine and urea values were greater than 2 mg/dl and 40 mg/dl, respectively, while given diclofenac. Because diclofenac metabolites are primarily eliminated by urinary tract, it is advisable to strictly monitor and eventually adjust the dose to patients under treatment with this association, especially for those who have significant impairment of renal function.
Porphyria: the use of diclofenac should be avoided in patients with porphyria hepatica, considering that, as with other NSAIDs, there is the possibility of triggering crisis of this pathology, presumably through induction of the of the porphyrin precursor synthetase, delta aminolevulinic acid.
Aseptic meningitis: like with other NSAIDs aseptic meningitis with fever and coma has been observed very rarely in patients treated with diclofenac. Although it is likely that this happens in patients with systemic lupus erythematosus or other connective tissue diseases, whenever signs or symptoms of meningitis in a patient treated with diclofenac is present it should be consider that this is related to the administration of the drug.
Preexisting asthma: approximately 10% of patients with asthma may suffer asthma crisis triggered by aspirin (aspirin-sensitive asthma). The use of aspirin in patients with aspirin-sensitive asthma, has been associated with episodes of bronchospasm, some even of extreme gravity. Since cross reactions with other NSAIDs, including bronchospasm, have been reported in aspirin-sensitive patients diclofenac should not be given to patients with this sensitivity to aspirin and should be used with caution in all patients with pre-existing asthma.
Other precautions: the pharmacological activity of diclofenac can reduce both fever and inflammation and therefore reduce their usefulness as diagnostic signs of certain diseases. Blurred and diminished vision, scotomas or altered vision of the colors have been reported. If a patient developes these changes while receiving diclofenac, the drug should be discontinued and perform ophthalmological examinations to the patient. In patients treated with NSAIDs, especially during prolonged treatments, it is advisable to periodically evaluate haematological parameters in order to timely detect the possibility of anemia or other alterations associated with its use. Corticosteroids should be used with caution in patients with: ulcerative colitis (risk of perforation), recent intestinal anastomosis, renal failure, high blood pressure, osteoporosis, myasthenia gravis, diabetes. In some patients especially in the elderly slight drowsiness may appear, so it should be paid attention in tasks that require special care

Drug interactions
Diclofenac
- Oral anticoagulants and heparin: diclofenac could increase its effect.
Methotrexate: may increase the hematologic toxicity of methotrexate. Diuretics: it can decrease the activity of diuretics.
- Sulfonylureas: can increase the effect of hypoglycemic sulfonylureas.
- Digoxin and/or lithium: can increase the plasma concentration of Digoxin and/or lithium.
- Cyclosporine: can increase the nephrotoxicity of Cyclosporine.
- Acetyl salicylic acid: concomitant use with acetylsalicylic acid reciprocally reduces the bioavailability.
Hydroxocobalamin (vitamin B12)
- Alcohol (excessive intake for more than 2 weeks), amino salicylates.

- Colchicine (especially in association with aminoglycosides): can reduce absorption of vitamin B12 from the gastrointestinal tract.
- Antibiotics: may interfere with the method of microbiological assay for vitamin B12 determinations in serum and erythrocytes, giving rise to falsely low results.
- Folic acid: in high and continuous doses, can reduce concentrations of vitamin B12 in blood.
Betamethasone
- Aspirin: reduction of the salicylemia.
Heparin and oral anticoagulants: decrease anticoagulant effects.
Oral contraceptives: increases the toxicity of the corticosteroid.
Tricyclic antidepressants: risk of psychopathy.
Hormones (estrogen/androgen): edema, weight gain.
Immunosuppressant: risk of developing opportunistic infections (e.g.: Tuberculosis).
Oral antidiabetics and insulin: hyperglycemia by reduced tolerance to carbohydrates.
Antihypertensive: decrease of the effect antihypertensive salt retention. Attenuated virus vaccines: risk of severe generalized illness. Interferon-alfa: risk of inhibition of its action.
Enzyme inducers (e.g.: rifampin, anticonvulsants such as carbamazepine, phenobarbital, phenytoin, primidone): decrease of the activity of corticoids.
Drugs that induce "torsades de pointes" (antiarrhythmic amiodarone like, bretylium, disopyramide, quinidine, sotalol and non antiarrhythmic such as astemizole, terfenadine, vincamine, pentamidine): the possible hypokalemia caused by corticosteroids can trigger the syndrome.
Digitalis: the possible hypokalemia promotes the toxic effects of digitalis.
Other hypokalemic (certain diuretics, certain stimulant laxatives): additive effects.
Carcinogenesis, mutagenesis, alteration of fertility: long term studies of carcinogenicity in rats that received diclofenac sodium to more than 2 mg/kg/day have revealed that the incidence of tumors is not increased significantly. 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 rats using diclofenac at doses above 0.3 mg/kg/day in males and 1 mg/kg/day in females does not reveal any oncogenic potential.
Diclofenac did not show mutagenic activity in different tests in vitro and in vivo, including chromosome studies and nuclear abnormalities; administered to rats males and females at a dose of 4 mg/kg/day not affected fertility.
Pregnancy, teratogenic effects: reproduction studies that have been published in mice receiving diclofenac (more than 20 mg/kg/day) and rats and rabbits (more than 10 mg/kg/day for rats and 80 mg for rabbits) have not revealed evidence of teratogenicity, fetal or maternal toxicity. In rats, the toxicity was not associated with dystocia and prolonged gestation, weight or reduced fetal growth and reduced fetal survival. Diclofenac showed cross 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 product 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, by that diclofenac should be avoided in the last stage of pregnancy.
Labor and delivery: there are no known effects of diclofenac on the labor and delivery in pregnant women. On the basis of what is happening with other NSAIDs, it is not possible to completely rule out that diclofenac may inhibit uterine contractions and delay birth.
Breastfeeding: because of the potential adverse reactions product may result in infants, should discontinue nursing or the drug, taking into account the importance of the treatment for the mother.
Pediatric Use: This dosage form is not suitable for children.
Use in geriatrics: There were no differences observed together among efficacy, adverse events or kinetic profiles of elderly people compared to young adults. As with other NSAIDs, it is likely that the elderly have lower tolerance to adverse reactions than the young.

Adverse reactions: therapeutic doses product is usually well tolerated. The following adverse reactions have been described.
Occasional: Incidence 1-10%
- General : abdominal pain, headache, hydrosaline retention, abdominal distension. Gastrointestinal: diarrhea, dyspepsia, nausea, constipation, flatulence, alteration of liver tests. In < 3% with or without perforation d/or bleeding peptic ulcer.
- *Hydroelectrolytic:* hypokalemia, sodium retention with occasional high blood pressure and even congestive heart failure.
- *Endocrine metabolic:* menstrual irregularities.
- *Nervous system:* vertigo.
- *Skin:* rash, pruritus.
- *Senses:* tinnitus.
Rare: Incidence < 1%
- *General:* general discomfort, swelling of lips and tongue, photosensitivity, anaphylactoid reactions, rare cases of anaphylaxis and laryngeal edema. Cardiovascular: hypertension, congestive heart failure.
Gastrointestinal: vomiting, jaundice, melena, stomatitis, dryness of mucous membranes, hepatitis, pancreatitis.
Isolated: esophageal injury, liver necrosis, cirrhosis, hepatorenal syndrome/colitis.
Hematologic: decrease of hemoglobin, leucopenia, thrombocytopenia, purpura. Isolated eosinophilia, anemia, neutropenia, agranulocytosis, pancytopenia.
Endocrine metabolic: decrease in tolerance to glucose, presentation of a latent diabetes.
Isolated: Cushing Syndrome, ACTH hyposecretion, adrenal cortical atrophy, arrest of growth in children.
Nervous system: insomnia/drowsiness, depression, anxiety, diplopia, irritability. Isolated: aseptic meningitis and seizures.
Respiratory: epistaxis, asthma, laryngeal edema.
Skin and appendages: alopecia, urticaria, dermatitis, angioedema.
Isolated: Stevens-Johnson Syndrome, erythema multiforme, bullous dermatitis. Senses: blurred vision, scotoma, loss of hearing, dysgeusia. Urogenital: proteinuria. Isolated: nephrotic syndrome, oliguria, papillary necrosis, acute renal failure, interstitial nephritis.
Musculoskeletal: isolated, muscular atrophy preceded by muscle weakness, osteoporosis, bone fractures, aseptic necrosis of femoral head.
Local undesirable effects have been described at the site of application, such as pain post-injection, induration and -exceptionally- abscess and necrosis (the latter especially in elderly diabetic subjects). Given the characteristics of brevity that generally present the treatments, the possibility of occurrence of these adverse effects is scarce.

Overdosing: in the event of an overdose, go to the nearest Hospital or contact the toxicological centers: Hospital A. Posadas: (011) 4654-6648/4658-7777. Pediatric Hospital Ricardo Gutierrez: (011) 4962-6666/2247. Optionally other toxicological centers.

Presentation: boxes with 3 and 5 ampoules.
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Storge Conditions
- Store between 15 and 30° C.
- Keep away from the reach of children.

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