DIFEN FLEX®

SODIUM DICLOFENAC PRIDINOL MESYLATE

INJECTABLE SOLUTION

Rx Only
Made in Argentina

Formulation: each ampoule contains: sodium diclofenac 75.000 mg; pridinol mesylate 2.200 mg. Excipients: monobasic sodium phosphate 5.160 mg; benzyl alcohol 250.000 mg; propylene glycol 1140.000 mg; sodium metabisulfite 9.000 mg; sodium chloride 17.500 mg; sodium hydroxide 2.160 mg; hydrochloric acid q.s.; water for injection q.s. 3,000 ml

Therapeutic Action: Analgesic - Anti-inflammatory - Myorelaxant

ATC Code: M01AB55

Indications: inflammatory and/ or painful somatic processes with associated muscle contracture. Articular and extra-articular rheumatic lesions. Fibrosis. Myalgia. Lumbociatalgia, Lower back pain. Torticollis. Trauma. Sprains.

Pharmacological Action: DIFEN FLEX is the combination of non-steroidal, analgesic sodium diclofenac, and pridinol mesylate, a centrally acting muscle relaxant.
Diclofenac
It is chemically the 2-6-aminophenylacetic acid, a non-steroidal anti-inflammatory drug (NSAID) derivatived from the phenylacetic acid with a great anti-inflammatory and analgesic action.
Its pharmacological action results from prostaglandin synthesis inhibition and its release during the inflammatory process. In this regard, diclofenac inhibits the two currently known cyclooxigenase isoenzimes (COX-1 and COX-2). It has been reported that diclofenac at high concentrations inhibits the formation of arachidonic acid metabolites, including leukotrienes and 5-hydroxyeicosatetraenoic acid (5-HETE). In addition, it may inhibit leukocyte migration, including polymorphonuclear leukocytes, towards inflammation site and it inhibits ADP- and collagen-induced platelet aggregation. Diclofenac prevents from lysosomal enzyme release from polymorphonuclear leukocytes and it inhibits superoxide production and leukocyte chemotaxis.
Its analgesic effect is produced by reducing the synthesis of nociceptive pathway mediators, blocking impulse generation at peripheral level.
Furthermore, a central, non-opioid mechanism action at hypothalamic level is postulated. In addition, it has an antipyretic effect related to decreased prostaglandin activity at hypothalamic level, in the thermo-regulatory center, favoring heat loss.
Pridinol
It is a centrally acting muscle relaxant indicated for the treatment of symptomatic spasm and muscle contracture. It exerts a selective inhibitory effect at central nervous system level and, consequently on the spinal segments and their corresponding reflex arcs. Certain antimuscarinic action has been described.

Pharmacokinetics
Diclofenac
Diclofenac maximum plasma concentrations are reached at 20 minutes from intramuscular administration. The area under the curve obtained following intramuscular administration is almost twice than that obtained with oral administration at the same dose.
Two hours later the maximum plasma concentration is reached, the concentration in the synovial fluid is higher than plasma concentration, being this ratio kept up to 12 hours following administration. Elimination mean time in the synovial fluid is 3 to 6 hours. Diclofenac total systemic clearance in plasma amounts to 263 ± 56 ml/ min. Elimination mean time is 1 – 2 hours.
Diclofenac binding to plasma proteins is higher than 99%.
Diclofenac is metabolized by the liver and excreted by biliary and renal route, mainly as metabolites in the form of glucuronates or sulfates. Only 1% of the dose excreted in the urine corresponds to free diclofenac; conjugates represent 5 – 10% of the dose recovered in the urine.
Less than 5% of the dose is eliminated through the bile.
Main metabolite in humans is 4-hydroxy-diclofenac and consists of approximately 40% of the excreted total dose. Other three diclofenac metabolites (3-hydroxy, 5-hydroxy,

4,5-dihydroxy-diclofenac) represent 10-20% of the dose eliminated in the urine.
The elimination of diclofenac and its metabolites is rapid: 40% of the administered dose is eliminated during the first 12 hours following administration.
Diclofenac pharmacokinetics parameters remain constant after repeated administration in healthy subjects. Patients with hepatic dysfunction (chronic hepatitis, cirrhosis without portal descompensation) show no pharmacokinetics changes compared to healthy subjects.

Pridinol
When Pridinol is administered intravenously to dogs, only 2% of the dose is found in plasma following injection, less than 9% of the dose is recovered in urine in 2 hours as unchanged pridinol and its glucuronoconjugate. No pridinol is found in urine from 2 to 7 hours after administration.
After oral administration of ^{14}C-pridinol to mice, 94% of the radioactivity leaves the digestive tract in 12 hours. Maximum plasma radioactivity is detected within 1 hour of administration. Between 30 and 40% of the dose is found in bile and tissues, mainly liver and kidneys.
The radioactivity is eliminated by 80% at 24 hours and by 96% in 4 days, of which 56% is urinary excreted.
This behavior indicates that pridinol is rapidly captured by tissues after administration. This is objectively demonstrated analyzing radioactivity after ^{14}C-pridinol administration and it shows that, at 30 minutes, its concentration in tissues is higher than in plasma. Despite pridinol has been used therapeutically for more than 20 years, no pharmacokinetics studies in humans were performed.

Posology and Administration: dose will be individually determined according to medical judgment and patient clinical condition. The recommended mean dose is 1 ampoule up to twice a day, through intramuscular route (e.g.: In the upper external quadrant of the gluteal region), slowly administered.
Keep maximum aseptic measures when medicines for injection are administered and follow usually recommended procedures to avoid intravascular injection. Use an appropriate needle to ensure deep intramuscular administration. Massage gently the application site to facilitate the material distribution once it is injected.
DIFEN FLEX for injection should not be administered for more than 3 days without a new medical consultation.

Contraindications: patients with known hypersensitivity to any formulation compounds. Pregnancy. Lactation. Patients with a history of asthma attack, urticaria or other allergic reactions triggered by acetylsalicylic acid or other NSAIDs.
Gastroduodenal ulcer. Severe hepatic or renal impairment.

Warnings: the probability of adverse effects is higher in elderly patients. Due to possible anticholinergic effects, its administration is not recommended in the following cases: narrow angle glaucoma, urodynamic disorder with micturition residue, mechanical occlusion of gastrointestinal tract, tachyarrhythmia, megacolon and acute pulmonary edema. Special care should be taken when prescribing COX-2 inhibitors, such as diclofenac, to patients with cardiovascular risk, including arterial hypertension, hyperlipidemia, diabetes or smoking, as well as patients with peripheral arterial disease. Regarding the reported association between increased cardiovascular risk (e.g.: coronary events) and exposure to COX-2 inhibitors, including diclofenac, the lowest effective dose during the shortest possible treatment period should be indicated.
Gastrointestinal effects related to NSAID treatment
Close medical vigilance for patients with a history of peptic ulcer and gastrointestinal bleeding is recommended.
Caution is recommended in patients treated with diclofenac, since they may develop peptic ulcer disease, gastrointestinal bleeding and perforations, even in the presence of previous characteristic symptoms of the upper gastrointestinal tract.
Elderly or weak patients seem less capable to tolerate ulcers and bleedings than other individuals and most of the severe gastrointestinal adverse events are produced in this population.
Hepatic effects
Alterations may be present in one or more hepatic tests. These laboratory abnormalities may progress, remain unchanged or be transient.
For hepatic lesion monitoring, glutamic pyruvic transaminase (GPT) follow-up is recommended. Transaminase increases are more frequently observed in arthrous patients than in those with rheumatoid arthritis. In addition to enzyme elevations, more severe hepatic reactions, including

hepatocellular compromise with or without jaundice, have been reported. Based on clinical experience, transaminase should be monitored between the fourth and eighth week after the beginning of diclofenac treatment.
As with other NSAIDs, if abnormal hepatic tests persist or worsen, or other hepatic disease-related clinical signs and symptoms appear (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 product compounds. Reaction typically occurs in asthmatic patients experiencing rhinitis with or without nasal polyps or severe bronchospam after taking aspirin or other NSAID. For such patients, extremely severe reactions have been reported.
Advanced renal disease
In case of advanced renal disease, any NSAID treatment should be initiated only under close renal function monitoring.
Pregnancy
NSAID should not be administered during pregnancy, especially in the last trimester, due to the risk of arterious duct premature closure.

Precautions
General
DIFEN FLEX (diclofenac-pridinol) should not be concomitantly administered with other products containing similar active substances or other NSAIDs.
Before administration, appropriate precautionary measures should be adopted, specially taking into account if the patient has experienced hypersensitive reactions.

Hydrosaline retention and edemas
A wide variety of hydrosaline retention, even with edemas, associated to the use of NSAIDs, including diclofenac, has been observed, so it should be used carefully specially in patients with history of cardiac failure, hypertension, or other conditions favoring edema formation.
Renal effects
Patients with increased risk of adverse effect are those with previous renal function disorder, cardiac failure, hepatic dysfunction, on diuretic treatment and elderly patients.
In patients treated with diclofenac, isolated cases of interstitial nephritis and papillar necrosis have been informed.
A second renal toxicity form, generally associated to NSAIDs, is observed in patients with conditions causing decreased renal flow or blood volume where the renal prostaglandins have a primordial role in maintaining the renal perfusion. In these patients, NSAID administration results in a dose-dependent reduction in prostaglandin synthesis and, secondarily, in renal blood flow, which may precipitate a renal impairment requiring treatment suspension.
Isolated cases of significant renal impairment in patients receiving diclofenac during post-marketing experience have been reported, but no renal impairment in more than 4,000 patients of international clinical trials, during which creatinine serum values were strictly monitored, have been reported.
Since diclofenac metabolites are mainly eliminated by urinary route, close monitoring of diclofenac-treated patients is advisable and eventually dose adjustment is required, especially in those patients with pre-existing significant disorder of renal function.
Porphyria:
The use of diclofenac should be avoided in patients with liver porphyria since, as with other NSAIDs, acute crisis may be triggered, presumably through the induction of porphyric precursor synthetase, delta aminolevulinic acid.

Aseptic meningitis
NSAIDs generally may trigger, rarely, aseptic meningitis with fever and coma especially in diclofenac-treated patients. Although this may occur especially in patients with systemic eritematous lupus and other connective tissue diseases, whenever signs or symptoms of meningitis appear in a patient treated with diclofenac, the possibility of drug-related meningitis should be considered.
Preexisting asthma
Approximately 10% of the asthmatic patients may have asthma sensitive to aspirin (aspirin-sensitive asthma). The use of aspirin in patients with aspirin-sensitive asthma has been associated with bronchospasm episodes, some of them extremely severe. Since cross-reactivity, including bronchospasm, between aspirin and NSAIDs has been reported in such aspirin-sensitive patients, diclofenac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Other precautions
The pharmacological activity of diclofenac in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting some pathologies. Blurred vision, decreased visual acuity, scotomas and chromatic vision alteration occurrences have been reported. If a diclofenac-treated patient develops these disorders, the treatment should be stopped and the patient should be undergone to an ophthalmologic examination.
In NSAID-treated patients, especially during long-term treatment, their hematological parameters should be periodically assessed in order to timely detect potential anemia and other drug-related abnormalities.
Pridinol may affect the ability to drive and/ or to operate machinery.

Drug interactions
Diclofenac
Aspirin: concomitant administration is not recommended because of aspirin additive effect of nephropathy and gastric irritation. In addition, it may cause decreased pharmacological effect, documented interaction for other NSAIDs, in relation to its displacement of protein binding and increased metabolism.
- Anticoagulants: Although the studies have not shown significant interaction between diclofenac and oral anticoagulants, like warfarin, their concomitant administration should be performed with caution due to the interactions described for other NSAIDs. Since prostaglandinas play an important role in the hemostasia and NSAIDs in turn alter the platelet function, the concomitant administration of oral anticoagulant treatment and any NSAIDs, including diclofenac, requires a carefully follow up of the patient to assess the need for anticoagulant dose adjustment.
Digoxine, methrotexate and cyclosporine: diclofenac, like other NSAIDs, may affect renal prostaglandins and increase adverse reactions of certain drugs. Diclofenac administration or the increase of the administered dose may increase digoxine and methrotexate serum concentrations and the cyclosporine renal adverse effects, particularly if renal function is impaired. In the case of digoxine, serum level monitoring may be required.
Lithium: diclofenac may decrease renal lithium clearance and increase its plasma levels, thus increasing the risk of adverse effects.
Oral hypoglucemiants: no alteration of glucose metabolism or of oral hypoglucemiant effects on healthy subjects is produced by diclofenac. However, without established causal relationship, during post-marketing experience, isolated cases of both increase and decrease of insulin and oral hypoglucemiant effects during concomitant treatment have been reported.
Diuretics: diclofenac, like others NSAIDs, may reduce its prostaglandin-dependant natriuretic action and inhibit the increase of rennin plasma activity following its administration, which may be associated to increased potassium serum level, most notably with potassium-sparing diuretics.
Other drugs: in small groups of patients, no concomitant administration of azathioprine, gold salts, chloroquine, d-penicillamine, prednisolone, doxycycline or digitoxin affects significantly the maximum levels or the area under the curve values of diclofenac. Adverse reactions produced by barbiturates after the initiation of diclofenac treatment have been reported.
Protein binding: no in vitro studies reveal significant interference of diclofenac with diverse drugs, including salicylic acid, tolbutamide, prednisolone, warfarin, benzylpenicillin, ampicillin, oxacillin, chlortetracycline, doxycycline, cephalothin, erythromycin and sulfamethoxazole.

Pridinol
Amantadine, quinidine, tricyclic antidepressant and neuroleptic drugs: possible anticholinergic effects may be evident or enhanced by concomitant administration.
Alcohol, psychotropic substances: may produce additive effects.
Laboratory test interactions
Effects on blood coagulation: any prostaglandin-synthetase inhibitor drug may interfere to some degree with platelet function. Modifications described in some of the coagulation tests in relation with the use of the active substances appear to be of no clinical significance; however a careful observation to detect potential significant abnormalities is recommended.
Carcinogenesis, mutagenesis and impairment of fertility
Carcinigenesis long-term studies conducted in rats administered with more than 2 mg/kg/day sodium diclofenac have shown no significant increased tumor incidence. A slight increase in the presence of breast fibroadenoma in rats at 0.5 mg/kg/day dose was observed but the increase was not significant for this type of tumor. A 2-year carcinogenicity study conducted in mice administered with diclofenac at doses higher than 0.3 mg/kg/day for male and 1 mg/kg/day for female, revealed no oncogenic potential.
Diclofenac showed no mutagenic activity in several in vitro and in vivo tests, including chromosomal and nuclear abnormality studies; administered to male and female rats at 4 mg/kg/day dose did not affect fertility.

Pregnancy and teratogenic effect: reproductive studies conducted in mice administered with diclofenac (higher than 20 mg/kg/day) and rats and rabbits (higher than 10 mg/kg/day for rats and 80 mg/kg/day for rabbits) have shown no evidences of teratogenicity, maternal or fetal toxicity. In rats, toxicity was not associated to dystocia, prolonged gestation, reduced fetal weight or growth or reduced fetal survival.
It was shown that diclofenac crosses placental barrier in mice and rats. However, there are no adequate studies conducted in pregnant women.
Animal reproduction studies are not always predictive of human response; therefore, the use of this drug during pregnancy should be avoided, unless the benefit for the mother justifies the potential risk for the fetus. A fetus risk is the possibility of arterious duct premature closure associated to the use of prostaglandin synthesis inhibitors, therefore diclofenac should be avoided during the last trimester of pregnancy.
Labor and delivery: diclofenac effects on labor and delivery in pregnant women are unknown. Based on other NSAID profiles, it cannot be ruled out that diclofenac may inhibit uterine contractions and delay parturition.
Lactation: because of the potentially serious adverse reactions that diclofenac may occur in nursing infants, nursing or drug administration should be discontinued, taking into account the importance of the treatment to the mother.
Pediatric use: this pharmaceutical form is not indicated for children.
Geriatric use: more than 6,000 patients have been treated with diclofenac in clinical trials, 31% of whom were elderly patients older than 65 years.
Globally there were no differences in efficacy, adverse events or kinetics profiles of the elderly compared to young adults. However, like with other NSAIDs, it is likely that elderly patients have less tolerance to adverse reactions than young adults.

Adverse Reactions: at therapeutic doses, the product is generally well tolerated. The following adverse reactions have been described:
Diclofenac
Occasional: Incidence 1 – 10%
General: abdominal pain, cephalea, hydrosaline retention, abdominal distention.
Gastrointestinal: diarrhea, dyspepsia, nausea, constipation, flatulence, abnormal hepatic tests. In <3% peptic ulcer with or without perforation and/ or bleeding.
Nervous System: vertigo.
Skin: rash, pruritus.
Senses: tinnitus.
Rare: Incidence <1%
General: general discomfort, lip and tongue edema, photosensitivity, anaphylactoid reactions, isolated cases of anaphylaxis and laryngeal edema.
Cardiovascular: hypertension, congestive cardiac failure.
Gastrointestinal: vomiting, jaundice, melena, stomatitis, mucosal dryness, hepatitis, pancreatitis. In isolated cases: esophageal lesion, hepatic necrosis, cirrhosis, hepatorenal syndrome, colitis.
Hematological: decreased hemoglobin, leucopenia, thrombocytopenia, purpura. In isolated cases: eosinophilia, anemia, neutropenia, agranulocytosis, pancytopenia.
Nervous system: insomnia/ somnolence, depression, anxiety, diplopia, irritation. In isolated cases: aseptic meningitis and seizures.
Respiratory: epistaxis, asthma, laryngeal edema.
Skin and appendages: alopecia, urticaria, dermatitis, angioedema. In isolated cases: Stevens-Johnson's syndrome, erythema multiforme, bullous dermatitis.
Senses: blurred vision, scotoma, hearing impairment, dysgeusia.
Urogenital: proteinuria. In isolated cases: nephrotic syndrome, oliguria, papillary necrosis, acute renal failure, interstitial nephritis.

Pridinol
Although rarely at recommended doses, it is possible that certain sensitive patients present, generally mild and anticholinergic-type side effects, such as: decreased sweating, skin redness, accommodation disorders, increased intraocular pressure, mucosa dryness, tachycardia, micturition disorder, psychomotor excitation and/or hallucinations (notably with overdosage), somnolence.
Related to intramuscular administration: drug intramuscular administration may cause application site disturbances, which may be related to the drug, the administration technique and /or patient individual factors. As a consequence of intramuscular administration the following may occur: burning or pain feeling, redness, induration, abscesses and exceptionally, severe conditions such as aseptic tissue necrosis (Nicolau's Syndrome), necrotizing fasciitis and extensive muscle necrosis caused by group A β-hemolytic streptococcus.

Overdosage: no case of untreated overdosage of the combination diclofenac – pridinol has been reported up to the present.
In the event of an overdosage, go to the nearest Hospital or contact the Toxicology Center:
Hospital A. Posadas: (011) 4654-6648/4658-7777.
Hospital de Pediatría Ricardo Gutiérrez: (011) 4962-6666/2247.
Optionally other Toxicology Centers.

How-supplied: Package containing 6 ampoules.

Last revision date: december 2013

Storage Condition
- Keep at room temperature below 30ºC.
- Keep out of the reach of children.

Technical Direction: Dr. Luis M. Radici – Pharmacist.
MEDICINE AUTHORIZED BY MINISTRY OF HEALTH.
Certificate No. 47.789
Laboratorios CASASCO S.A.I.C.
Av. Boyacá 237 - Autonomous City of Buenos Aires

PATIENT INFORMATION
- CONSULT YOUR PHYSICIAN -

What is DIFEN FLEX?
DIFEN FLEX is a medicine consisting of two active substances, sodium diclofenac and pridinol. Diclofenac belongs to a medicine group named non-steroidal anti-inflammatory drugs (NSAID) and pridinol is a muscle relaxant.

What is DIFEN FLEX used for?
DIFEN FLEX is prescribed for the treatment of intense pain in joints and/or muscles, when there is muscle spasm (contracture) associated to the pain. This is very frequent in painful conditions of the spinal column, but it may occur in other body regions.

Before using DIFEN FLEX
Do not use DIFEN FLEX if
- You are allergic to diclofenac, pridinol or any of the compounds of this medicine;
- ou are allergic or have had allergic reactions to acetylsalicylic acid or other similar analgesics. Reactions may include asthma (difficulty in breathing), urticaria or acute rhinitis (nasal mucosa swelling);
- You have active intestinal inflammatory disease (ulcerous colitis, Crohn's disease);
- You have moderate or severe kidney disease;
- You have a severe liver disease;
- You suffer from blood coagulation disorders or you receive treatment for this condition;
- You have had stomach or duodenal bleeding or you have had perforation of the gastrointestinal tract while taking a non-steroidal anti-inflammatory medicine;
- You have now or you have had more than once: stomach or duodenal ulcer or hemorrhage;
- You have serious cardiac failure;
- You are in the third trimester of pregnancy

Take special care with DIFEN FLEX
- If you have had a stomach or intestinal disease, if you have had stomachache or burning after taking anti-inflammatory medicines in the past;
- If you have any of the following diseases: asthma, heart, liver or kidney disease, hypertension, bleeding disorders or other blood disorder including hepatic porphyria;
- If you are taking diuretic medicine (increasing urine volume);
- you have or have had stomach or duodenal ulcer, hemorrhage or perforation, which may produce intense or persistent abdominal pain and/or black stools or even without previous alert symptoms;
- Risk is greater with high doses and prolonged treatment in patients with a history of peptic ulcer and in the elderly. In these cases your physician will consider the possibility to add stomach

protector medicine.

Tell your physician
- If you simultaneously take medicines that alter blood coagulation or increase the risk of ulcers, such as oral anticoagulants or antiplatelet drugs, e.g.: acetylsalicylic acid. You also have to tell your doctor about the use of other medicines, such as corticoids, that could increase the risk of said hemorrhages. Also if you take medicines to treat depression, anxiety or any other psychopharmaceutical drugs;
- If you have Crohn's disease or ulcerous colitis since **DIFEN FLEX**-like medicines may worsen these pathologies.
You should use the lowest dose which relieves/controls pain; you should not use **DIFEN FLEX** longer than necessary to control symptoms.
Pregnancy and lactation: in case of pregnancy or lactation **DIFEN FLEX** for injection is not recommended.
Since administration of **DIFEN FLEX** –type medicines is associated to the increased risk of suffering congenital anomalies / abortion its administration is not recommended during the first and second trimester of pregnancy unless its administration is considered strictly necessary. In these cases doses and duration will be limited to the lowest possible ones.
During the third trimester, administration of **DIFEN FLEX** is contraindicated.
For patients of childbearing age, **DIFEN FLEX** –type medicines have been associated to impaired fertility.

Driving and using machinery
You should not drive or operate machinery during **DIFEN FLEX** treatment.

Medicine appropriate use
Follow these instructions unless otherwise stated by your physician. In case of doubt consult your physician or pharmacist.
The usual dose is 1 ampoule (75 mg sodium diclofenac and 2.2 mg pridinol) once a day. Route administration is intramuscular; by deep intragluteal route, in the upper external quadrant of the gluteal region.
Exceptionally, two daily injections may be administered separated by an interval of several hours. Once acute crisis is controlled, treatment may be continued with oral medication. If an ampoule is combined with any of the oral formulations of diclofenac, diclofenac dosage should not exceed 150 mg/ day.

Use in children
The use of **DIFEN FLEX** is not recommended in children.

Use in elderly patients
Elderly patients may be more sensitive to **DIFEN FLEX** effects. Therefore, is especially important that elderly patients tell immediately their doctor about any adverse effect they experience.

Administration
Medicine will be injected by deep intragluteal route in the right upper quadrant of the gluteal region.

Adverse effects
Like all medicines, **DIFEN FLEX** may cause adverse effects.
These include stomachache, nausea, vomiting, diarrhea, abdominal cramps, difficult digestion, (dyspepsia), flatulence, loss of appetite, headache, dizziness, vertigo, skin eruptions.
Less frequent adverse effects (less than 1% of the treated patients) are:
Gastrointestinal tract: most frequent adverse effects occurring with medicines like **DIFEN FLEX** are the gastrointestinal ones: peptic ulcer, gastrointestinal hemorrhage, perforation (fatal in some cases), especially in elderly patients. Nausea, vomiting, diarrhea, flatulence, constipation, stomach burning, abdominal pain, blood in faeces, canker sore, worsening of ulcerous colitis and Crohn's disease have been also observed. Gastritis has been less frequently observed.
Cardiovascular: edema (fluid retention), arterial hypertension and cardiac failure related to treatments with **DIFEN FLEX** –type medicines.
Respiratory: shortness of breath (asthma, laryngeal edema).
Central nervous system: somnolence, disorientation, insomnia, irritation, seizures, depression, anxiety, nightmares, tremor, aseptic meningitis.
Sense organs: vision disturbances (blurred or double vision), hearing problems, ear wheezing,

taste alterations.
Skin: urticaria, severe skin reactions, hair loss, increased skin sensitivity to natural light, blood effusion on the skin, decreased sweating, skin redness.
Kidneys: renal function impairments which produce face, foot and leg swelling, sudden decrease of urine volume, bloody urine, urinary difficulties, medicines like **DIFEN FLEX** may be rarely associated to hepatic disorders which produce yellowish of skin and eyes, sometimes with elevated fever or swelling and sensitivity of upper abdomen. In this case, discontinue treatment and IMMEDIATELY contact your physician.
Blood: symptoms of severe abnormalities of blood cells.
Hypersensitivity: allergic reactions such as chest wheezing, shorten of breath and fainting.
Others: extremity tangling, persistent sore throat and high fever.
If any of the following reactions occurs discontinue treatment and IMMEDIATELY contact your physician:
- Acute pain during intramuscular injection.
- Gastric discomfort, stomach burning, or upper abdomen pain.
- Blood vomiting, black faeces or blood in urine.
- Skin problems such as eruption or itching.
- Chest wheezing, shortness of breath.
- Yellowish of skin and eyes.
- Persistent sore throat or high fever.
- Face, foot or leg swelling.
- Acute headache.
- Thoracic pain when coughing.

If you receive doses of DIFEN FLEX higher than the required ones
Due to the **DIFEN FLEX** administration route, it is unlikely that overdosage conditions are produced.
In the event of overdosage, immediately contact your physician or pharmacist.
In the event of an overdosage, go to the nearest Hospital or contact the Toxicology Center:
Hospital A. Posadas: (011) 4654-6648/4658-7777.
Hospital de Pediatría Ricardo Gutiérrez: (011) 4962-6666/2247.
Optionally other Toxicology Centers.
"This medicine has been prescribed only for your current medical condition. Do not recommend it to other persons".

How-supplied: packages containing 6 ampoules.

Storage Condition
- Keep at room temperature below 30ºC.
- Keep out of the reach of children.

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