ANALPAN

DESCRIPTION:

ANALPAN INJECTION 75mg / 3ml: A clear, colourless to almost colourless liquid in ampoule for I/M injection.
ANALPAN INJECTION 25mg / ml : A clear, colourless to almost colourless liquid in vial for I/M injection.

COMPOSITION:

Each ml contains 25mg/ml Diclofenac Sodium.

PHARMACODYNAMICS:

Diclofenac Sodium is structurally similar to both the phenyl-alkanoic acid series (e.g. Ibuprofen, Alclofenac) and the anthranilic acid series (e.g. Flufenamic acid, Mefenamic Acid). As with other NSAIDS, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. Analpan injection contains the sodium salt of diclofenac, a non-steroidal substance with pronounced antirheumatic, anti- inflammatory, analgesic and antipyretic effects.

PHARMACOKINETICS:

Distribution: Mean peak plasma concentration of 2.5µg/ml (8µmol/L) are reached approximately 20 min after IM injection of 75mg diclofenac. Plasma concentrations are in linear proportion to the size of the dose. The plasma concentrations observed in children after administration of equivalent doses (mg/kg body weight) are similar to those reached in adults. Pharmacokinetics behavior does not change after repeated administration. No accumulation occurs if the recommended dosage intervals are observed. 99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%). Diclofenac enters the synovial fluid, where peak concentrations are measured 2-4 hours after peak plasma levels have been reached. The apparent elimination half-life from the synovial fluid is 3-6 hours. This means that concentrations of active substance in the synovial fluid are already higher than plasma concentrations 4-6 hours after administration and they remain higher for up to 12 hours.

Metabolism: Biotransformation takes place by glucuronidation partly of the intact molecule, but mainly after single and multiple hydroxylation.

Elimination: The active substance is eliminated from the plasma with a systemic clearance of 263±56 ml/min (±SD). The terminal half-life is 1-2 hrs. Approximately 60% of the dose administered is excreted via the kidneys in the form of metabolites, <1% is excreted as unchanged substance. The rest of the dose is eliminated in the form of metabolites through the bile in the faeces. Kinetics in Special Clinical Situations: No relevant age dependent differences in absorption, metabolism and excretion have been observed.

In patients with impaired renal function, no accumulation of the unchanged active substance can be inferred from the single dose kinetics under the usual dosage schedule. At a creatinine clearance of <10ml/min, the theoretical steady-state plasma levels of metabolites are about 4 times higher than in normal subjects. The metabolite is nevertheless ultimately cleared through the bile. In patients with impaired hepatic function (chronic hepatitis), non-decompensated liver cirrhosis, the kinetics and metabolism of diclofenac are the same in patients without liver disease.

INDICATIONS:

1. Inflammatory & degenerative forms of rheumatism
2. Rheumatoid arthritis
3. Ankylosing spondylitis
4. Osteoarthritis, spondylarthritis
5. Non-articular rheumatism
6. Painful inflammatory conditions of non-rheumatic origin

RECOMMENDED DOSAGE:

Adult: Depending on the severity of the condition, commence therapy with a dosage of 75 to 150 mg daily, given in 2 or 3 divided doses, for I/M injection; 75 mg (3mL) per dose. For maintenance in long term therapy 75 or 100 mg daily in 2 or 3 times divided doses is usually sufficient. Analpan injection is not suitable for children and adolescents because of their dosage strength.

Note: After assessing the risk/ benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. The higher dose is more often required in patients with rheumatoid arthritis than in patients with osteoarthritis. Diclofenac Sodium Injection should not be given for more than 2 days. If necessary, treatment can be continued with tablets or suppositories. Diclofenac Injection also should not be administered by intravenous injection.

Special populations: Established cardiovascular disease or significant cardiovascular risk factors

The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heartdisease, peripheral arterial disease) or uncontrolled hypertension. If diclofenac treatment is needed, patients with established cardiovascular disease, uncontrolled hypertension or significant cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should be treated only after careful consideration and at doses ≤100 mg daily when initial treatment with diclofenac injection continues with diclofenac tablets or suppositories for more than 4 weeks. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, diclofenac should always be prescribed at the lowest effective daily dose and for the shortest duration possible.

CONTRAINDICATIONS:

1. Known allergy to diclofenac sodium, sodium metabisulphite or any of the excipients.
2. Cross sensitivity has been demonstrated between diclofenac, aspirin and naproxen. Diclofenac should not be given to aspirin sensitive patients. Sensitivity phenomena include asthma, rhinitis and urticaria.
3. Active gastrointestinal bleeding (eg. peptic ulcer perforation) recurrent dyspepsia or other gastrointestinal pathology.
4. Severe hepatic impairment
5. Pregnancy - see "Use in Pregnancy"

The use of high dose diclofenac (150mg/day) for more than 4 weeks is contraindicated in patients with established cardiovascular disease (congestive heart failure, established ischemic heart disease, peripheral arterial disease) or uncontrolled hypertension.

WARNING & PRECAUTIONS:

History of gastrointestinal haemorrhage or ulcer: Diclofenac should be used with caution in these patients. Patients with history of dyspepsia or other gastrointestinal disorder such as Crohn's disease and ulcerative colitis or with pre-existing dyshaemopoiesis or disorders of blood coagulation, as well as those with severe hepatic or renal disease, should be kept under close surveillance. In elderly patients who are generally more prone to side effects, particular caution should be exercised. If peptic ulcer or gastrointestinal bleeding occurs during treatment with diclofenac, administration of the drug must cease immediately.

Haematological effects: A slight reduction in haemoglobin has been observed in some patients during long-term therapy with diclofenac. On rare occasions, blood dyscrasias have been reported. It is advisable to perform blood counts, at intervals, in patients receiving long-term therapy. Like other NSAIDs, **Analpan** may temporarily inhibit platelet aggregation. Patients with defects of hemostasis should be carefully monitored. Discontinue diclofenac sodium immediately if rash occurs.

CardiovascularThrombotic Events: Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular event, principally myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk of an adverse cardiovascular event in patient taking NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration. There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension: NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired antihypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure: Fluid retention and oedema have been observed in some patients taking NSAIDs, there caution is advised in patients with fluid retention or heart failure.

Severe Skin Reactions: NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Pre-existing asthma: In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria. Special caution is recommended when diclofenac sodium is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.

Hepatic effects: Close medical surveillance is required when prescribing diclofenac sodium to patients with impaired hepatic function, as their condition may be exacerbated. As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac sodium, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac sodium should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms. Caution is called for when using diclofenac sodium in patients with hepatic porphyria, since it may trigger an attack.

Renal effects: As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with substantial extracellular volume depletion from any cause, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure when using diclofenac sodium in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Geriatrics: To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly, the treatment should be initiated and maintained at the lowest effective dose. Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low-dose acetylsalicylic acid (ASA)/aspirin or other medicinal products likely to increase gastrointestinal risk. Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reuptake inhibitors. Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated.

Cardiovascular effects: Treatment with NSAIDs, including diclofenac, particularly at high dose and in long term, may be associated with a small increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used for the shortest duration possible. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially when initial treatment with diclofenac injection continues with diclofenac tablets or suppositories for more than 4 weeks. Patients should be advised to remain alert for the signs and symptoms of serious arteriothrombotic events (e.g. chest pain, shortness of breath, weakness, slurring of speech), which can occur without warnings. Patients should be instructed to see a physician immediately in case of such an event.

WARNING FOR SODIUM METABISULPHITE: This preparation contains sodium metabisulphite, a sulphite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.

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WARNINGS: RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctor should warn patient about signs and symptoms of serious gastrointestinal toxicity. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

INTERACTION WITH OTHER MEDICATIONS:

Lithium & Digoxin: Diclofenac sodium may increase plasma concentrations of lithium and digoxin.
Anticoagulants: Clinical investigation do not appear to indicate that Diclofenac Sodium affects the activity of anticoagulants (eg: warfarin) but there have been isolated reports of an increased risk of haemorrhage with the combined use of these agents. Close monitoring is therefore recommended.
Antidiabetic: Clinical studies have shown that Diclofenac Sodium can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of hypoglycaemic and hyperglycaemic effects, which have required adjustments to the dosage of hypoglycaemic agents.
Ciclosporin: Cyclosporin nephrotoxicity may be increased by the effect of non-steroidal anti-inflammatory drugs on renal prostaglandins.
Methotrexate: Caution should be exercised if NSAIDs and methotrexate are administered within 24 hours of each other since NSAIDs may increase methotrexate plasma levels resulting in increased toxicity.
Quinolone Antibacterials: There have been isolated reports of convulsions, which may have been due to concomitant use of quinolones and NSAIDS.
CYP2C9 inhibitors: Caution is recommended when prescribing diclofenac with potent CYP2C9 inhibitors (e.g. sulfinpyrazone & voriconazole) as coadministration of these drugs could result in a significant increase in peak plasma concentrations & exposure to diclofenac due to inhibition of diclofenac metabolism.
Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity. Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently.
Drugs known to cause hyperkalemia: Concomitant use of diclofenac with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.
Others NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects. Concurrent treatment with aspirin lowers the plasma concentration, peak plasma levels and AUC values of diclofenac. The use of both drugs concurrently is not recommended.
SSRIs: Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.
Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

USE IN PREGNANCY & LACTATION:

Use in Pregnancy: NSAIDS inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation, and delay labour and birth. The use of diclofenac during the third trimester of pregnancy is contraindicated. Safety of diclofenac sodium in the first and second trimesters of pregnancy has not been established. Therefore Analpan should not be used in pregnant women or those likely to become pregnant unless the expected benefits are likely to outweigh any possible risk.
Use in Lactation: Diclofenac passes into breast milk in small amounts. As with other drugs that are excreted in milk, Analpan is not recommended for use in nursing women.

SIDE EFFECTS:

Eye disorders: *In isolated cases:* Visual disturbance, vision blurred, diplopia.
Ear disorders: *More than 1%:* Vertigo.
In isolated cases: Tinnitus, hearing impaired. **Respiratory, thoracic and mediastinal disorders:** *More than 1%:* Asthma (including dyspnoea).
In isolated cases: Pneumonitis.
Infections and infestations: *In isolated cases:* Injection site abscess.
Vascular disorders: *In isolated cases:* Hypertension, vasculitis.
Gastrointestinal Tract: *Up to 20%:* Epigastric pain, other gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia.
Less than 2%: Gastrointestinal bleeding, haematemesis, malaena, gastritis, gastric or intestinal ulcer with or without bleeding or perforation, bloody diarrhoea.
In isolated cases: Lower gut disorders such as non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's proctocolitis; aphthous stomatitis, glossitis, oesophageal lesions, constipation, diaphragm-like intestinal strictures, pancreatitis.
Central (and peripheral) Nervous System: *More than 1%:* Headache, dizziness, or vertigo. *Less than 1%:* Drowsiness.
In isolated cases: Disturbances of sensation, including paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing; tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, taste alteration disorders, myoclonic encephalopathy (described in two patients), aseptic meningitis, cerebrovascular accident.
Cardiovascular System: *In isolated cases:* Exacerbation of angina pectoris or congestive heart failure may occur but it is rare, as result of impaired renal function induced by diclofenac. Symptoms induce chest pain, shortness of breath, tightness in chest and wheezing, myocardial infarction, palpitation, hypertension.
Skin: *More than 1%:* Rashes or skin eruptions.
Less than 1%: Urticaria.
In isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reaction, purpura, including allergic purpura.
Urogenital System: *Less than 1%:* Oedema.
In isolated cases: acute renal failure, urinary abnormalities such as haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.
Liver: *Up to 2%:* elevation of serum aminotransferase enzymes (ALT, AST)
Less than 1%: Hepatitis with or without jaundice.
In isolated cases: Fluminant hepatitis, hepatic necrosis and hepatic failure.
Blood: *In isolated cases:* Thrombocytopenia, leukopenia, anaemia (haemolytic anaemia, aplastic anaemia), agranulocytosis, positive Coombs' test.
Hypersensitivity: *Less than 1%:* Hypersensitivity reactions such as bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension.
In isolated cases: Vasculitis, pneumonitis, angioedema.
Cardiac disorders: Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain
*The frequency reflects data from long-term treatment with high dose (150mg/day)
Description of selected adverse drug reactions Arteriothrombotic events: Meta-analysis and pharmacoepidemiological data point towards a small increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150 mg daily) and during long-term treatment.

INCOMPATIBILITIES:

Analpan injection should not be mixed with other injections.

SYMPTOMS AND TREATMENT OF OVERDOSE:

Overdosage: There have been no recorded cases of overdosage with Diclofenac. In the event of acute poisoning, the following symptoms and signs might be encountered.
Nervous System: Headache, motor restless, muscular twitching, hyperexcitability, ataxia, dizziness. *Convulsions:* especially in small children. *Gastrointestinal:* Epigastric pain, nausea, vomiting, haemorrhage, diarrhoea, acute ulceration of stomach or intestine. *Liver:* Disorder of hepatic function. *Kidneys:* Oliguria. *Laboratory:* Raised SGOT/SGPT, Hyperbilirubinaemia.
Treatment: There is no specific antidote. General measures should be taken to reduce the amount of Diclofenac absorbed (e.g. induction of vomiting, gastric lavage, or the use of activated charcoal) and to increase the rate of eliminations (e.g. dialysis, especially indicated in the presence of renal failure). Convulsion may be controlled by the use of diazepam or phenobarbitone. Surveillance should also include monitoring of the blood picture, serum electrolytes, liver and kidney function, and examination of stools (for occult blood).

STORAGE CONDITIONS:

Store below 30°C. Protect from light. Keep out of reach of children. Jauhkan daripada kanak-kanak

PACK SIZE:

Injections - Ampoules : 3ml x 10 ampoules and 3ml x 100 ampoules.
- Vials : 10ml x 1 vial, 10ml x 25 vials, 10ml x 100 vials
Not all presentations may be available locally.

SHELF LIFE:

Shelf life is 3 years

MANUFACTURER:

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