SM PHARMACEUTICALS SDN BHD

ZOBID *(DICLOFENAC SODIUM)* INJECTION 3 ML AND 10 ML

DESCRIPTION:
Colourless, sterile solution.

COMPOSITION:
Diclofenac Sodium 25 mg / ml.

ACTIONS AND MODE OR MECHANISMS OF ACTION:
Diclofenac is a potent non-steroidal anti-inflammatory drug (NSAID) with analgesic property. NSAIDs inhibit the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Although the resultant decrease in prostaglandin synthesis and activity in various tissues may be responsible for many of the therapeutic (and adverse) effects of NSAIDs, other actions may also contribute significantly to the therapeutic effects of these medications.

Anti-rheumatic (non-steroidal anti-inflammatory) -
Act via analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation. These medications do not affect progressive course of rheumatoid arthritis.

In rheumatic diseases, the anti-inflammatory and analgesic properties of Zobid Injection elicit a clinical response characterised by marked relief from signs and symptoms, e.g pain at rest, pain on movement, morning stiffness and swelling of the joints as well as by an improvement in function.

In post-traumatic and post-operative inflammatory conditions, Zobid Injection rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema.

Analgesic -
May block pain impulse generation via a peripheral action that may involve reduction of the activity of prostaglandins, and possibly inhibition of the synthesis or actions of other substances that sensitise pain receptors to mechanical or chemical stimulation.
In clinical trials, Zobid Injection has been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, its onset of effect taking place within 15-30 min.

Antigout agent -
Act via analgesic and anti-inflammatory mechanisms; do not correct hyperuricemia.

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):

Absorption: Diclofenac is rapidly absorbed when given by intramuscular injection. Mean peak plasma concentrations of 2.5 μg/mL (8 μmol/L) are reached approximately 20 min after IM injection of 75mg diclofenac. The plasma concentration is in linear proportion to the size of the dose, over the range 25 – 150 mg.

Distribution: The area under the concentration curve (AUC) is about twice as large after parenteral administration as after oral or rectal doses, because the oral or rectal routes lead to about half of the active substance being metabolised during its first passage through the liver.
99.7% of diclofenac is bound to serum proteins, mainly to albumin (99.4%).
No accumulation occurs if the recommended dosage intervals are observed.
Diclofenac enters the synovial fluid, where peak concentrations are measured 2-4 hrs after the peak plasma values have been reached.

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 mL/min (x ± 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 (glucuronide and sulphate conjugates); <1% is excreted as unchanged substance. The rest of the dose is eliminated in the form of metabolites through the bile in the faeces. The apparent elimination half-life from the synovial fluid is 3-6 hrs. This means that concentrations of active substance in the synovial fluid are already higher than plasma concentrations 4-6 hrs after administration and they remain higher up to 12 hrs after administration.

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 <10 mL/min, the theoretical steady-state plasma levels of metabolites are about 4 times higher than in normal subjects. The metabolites are nevertheless ultimately cleared through the bile.
In patients with impaired hepatic function (chronic hepatitis, non-decompensated cirrhosis), the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

INDICATIONS:
Initial treatment of the following: Acute, severe pain caused by inflammatory and degenerative forms of rheumatism, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthiritis Painful syndromes of the vertebral column. non-articular rheumatism, acute attacks of gout, renal colic and biliary colic. painful post- traumatic and post operative inflammation and swelling.

CONTRAINDICATIONS:
Zobid must not be used in the presence of peptic ulcers or gastrointestinal bleeding, (eg, with asthma attacks, urticaria, acute rhinitis) to acetylsalicylic acid (aspirin) or other NSAIDs. Known hypersensitivity to diclofenac, sodium metabisulphite, benzyl alcohol, propylene glycol, mannitol.

Severe cardiac failure (see section WARNING AND PRECAUTIONS).

SIDE EFFECTS / ADVERSE REACTIONS:
(Including adverse reactions observed using other dosage forms of Zobid).
A review of world-wide clinical studies with diclofenac has reported the incidence of drug-associated adverse effects to be about 12%; about 2% of patients discontinued therapy because of adverse effects. The most frequently reported adverse effects were gastro-intestinal and were reported in 7.6% of patients. CNS-related adverse effects were reported in 0.7% of patients and allergy or local reactions in 0.4%. Adverse effects associated with diclofenac are usually mild and transient and appears to be unrelated to the dose of drug given.

Gastrointestinal Tract: Occasional: Epigastric pain, other gastrointestinal symptoms, e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence and anorexia.
Rare: Gastrointestinal bleeding, haematemesis, melaena, peptic ulcer with or without bleeding or perforation, bloody diarrhea. Isolated cases: Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), apthous stomatitis, glossitis, oesophageal lesions, constipation.

Central (and Peripheral) Nervous System: Occasional: Headache, dizziness or vertigo.
Rare: Tiredness. Isolated cases: Sensory disturbances including paraesthesia, memory disturbances, disorientation, disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, taste disturbances.

Skin: Occasional: Skin eruptions, rash or eruptions. Rare: Urticaria. Isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura (including allergic purpura).

Kidney: Isolated cases: Acute renal failure, haematuria, proteinuria, interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver: Occasional: Elevated serum aminotransferase values (SGOT, SGPT). Rare:Hepatitis with or without jaundice. Isolated cases: Fulminant hepatitis.

Blood: Isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, hemolytic anaemia, aplastic anaemia.

Hypersensitivity Reactions: Rare: Asthma, systemic anaphylactic/anaphylactoid reactions (including hypotension).
Other Organ Systems: Rare: Oedema symptoms at the site of injection, e.g. local pain and induration; in isolated cases abscesses and local necrosis. Isolated cases: Impotence (association with Zobid questionable), palpitation, chest pain, hypertension.

Cardiac disorders
Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain.

*The frequency reflects data from long-term treatment with a high dose (150mg/day).

Description of selected adverse drug reactions
Arteriothrombotic events
Meta –analysis and pharmacoepidemiological data point towards an increased risk of arteriothrombotic events (for example myocardial infarction) associated with the use of diclofenac, particularly at a high dose (150mg daily) and during long-term treatment (see section WARNINGS AND PRECAUTIONS.

Cardiac disorders:
Kounis syndrome : Frequency "not known"

PRECAUTIONS / WARNINGS:

Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy: Serious gastrointestinal toxicity, e.g. bleeding, ulceration and perforation can occur at any time with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper gastrointestinal problems, e.g. dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated 3-6 months, and in about 2-4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to he associated with peptic ulcer disease, e.g. alcoholism, smoking, etc, no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

Measures, e.g. the use of physical therapy and mild analgesics like paracetamol (when inflammation is not a major factor) should be instituted prior to initiation of the therapy with NSAIDs. These drugs should only be used after proper appraisal of potential risks to patients. This drug should not be co-administered with other NSAIDs. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should offset the potential increased risk of GI toxicity.

Owing to the importance of prostaglandins in maintaining renal blood flow, particular caution is called for in patients with impaired cardiac or renal function, as well as in elderly

patients, patients taking diuretics and patients with extracellular volume depletion of any aetiology, e.g. before or after major surgery. Monitoring of renal function is recommended as a precautionary measure if Zobid Injection is administered in such cases. There is normally a return to the pre-treatment state after discontinuation of Zobid Injection.

Like other NSAIDs, Zobid Injection increases the activity of one or more liver enzymes. It is therefore advisable as a precautionary measure to monitor hepatic function during prolonged treatment with Zobid Injection.

Zobid Injection should be discontinued if hepatic disorders persist or worsen, and if clinical signs or symptoms indicative of liver disease or other manifestations of hepatic dysfunction (e.g., eosinophilia, skin rash) occur. Hepatitis can occur without prodromal symptoms. Caution should be exercised when using Zobid Injection in patients with hepatic porphyria, because the substance may trigger an attack.

Blood counts are recommended during prolonged treatment with Zobid Injection as is the case with other NSAIDs.

Like other NSAIDs, Zobid Injection may trigger allergic reactions, including anaphylactic / anaphylactoid reactions even if the patient is receiving the preparation for the first time. Severe cutaneous reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Patients who suffer from asthma, hayfever, nasal polyps or chronic airways' infection and patients with hypersensitivity to analgesic and rheumatism drugs of all types are threatened with asthma attacks when using Diclofenac Sodium (so-called analgesic intolerance, analgesic-induced asthma). Discontinue diclofenac sodium immediately if rash occurs.

Effects on the ability to drive or operate machineries:

Patients experiencing dizziness or other disturbances of the central nervous system during treatment with Zobid Injection should not drive or operate machinery.

Neonates

No data are available on the use of the drug in neonates.

Children

Diclofenac sodium has been shown to be both effective and well tolerated on long-term treatment of rheumatoid arthritis. Diclofenic is not recommended for other indications in children.

The elderly

Caution is indicated in elderly patients on fundamental medical grounds in particular. It is advisable for those who are either frail or of low body weight to be given the lowest effective dose.

In acute toxicity tests in rats, the LD50 was shown to be 226-240 mg/.kg while chronic toxicity studies demonstrated a dose-dependent gastrointestinal haemorrhage, ulceration and, sometimes, perforation. No toxic changes other than these gastrointestinal lesions were observed.

Carcinogenicity

No oncogenic potential was demonstrated with diclofenac sodium in a 2-year carcinogenicity study in male mice given up to 0.3mg/kg of body weight (0.9 mg/ m^2 meter of body surface area) per day or in female mice given up to 1 mg/kg (3 mg/m^2) per day.

Tumorigenicity

No tumorigenicity was demonstrated in studies in rats receiving up to 2 mg/kg per day (approximately the recommended human dose). Although there was a slight increase in benign mammary fibroadenomas in female rats given 0.5 mg/kg (3 mg/ m^2) per day, the increase was not significant.

Mutagenicity

No mutagenic activity was demonstrated in *in vitro* tests using mammalian cells or bacterial (with or without microsomal activation) or in *in vivo* tests, including dominant lethal and male germinal epithelial chromosomal studies in mice and nucleus anomaly and chromosomal aberration studies in Chinese hamsters.

Pregnancy / Reproduction

No impairment of fertility was demonstrated in reproduction studies in rats receiving up to 4 mg/kg (24 mg/m^2) per day.

Diclofenac sodium should not be prescribed during pregnancy unless there is some compelling reason to do so. This applies particularly to the last 3 months of pregnancy (owing to the possibility of suppression of the uterine activity and/or premature closure of the ductus arteriosus).

Breast-feeding

Diclofenac is distributed into breast milk. In one study, long-term use of 150 mg per day produced concentrations of 100 nanograms per gram in the breast milk. An infant of 4 to 5 kg consuming one litre per day would thereof ingest approximately 0.03 mg / kg per day.

Nursing mothers

Because of the potential for serious adverse reactions in nursing infants from diclofenac, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Cardiovascular effects
Treatment with NSAIDs including diclofenec,particulary at high dose and long term, may associated with increased risk of serious cardiovascular thrombotic events(including myocardial infarction and stroke).
Treatment with diclofenec is generally not recommended in patients with established cardiovascular disease(congestive heart failure, established ischemic heart disease,peripheral arterial disease) or uncontrolled hypertension.If needed, patients with established cardiovascular disease,uncontrolled hypertension, or significant risk factors for cardiovascular disease(e.g. hypertension,hyperlipidaemia,diabetes mellitus and smoking)should be treated with diclofenac only after careful consideration and only at doses ≤100mg daily when treatment continues for more than 4 weeks.
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 treatment continues for more than 4 weeks.
Patients should remain alert for the signs and symptoms of serious arteriothrombotic events (.e.g. chest pain, shortness of breat, weekness, slurring speech), which can occur without warnings. Patients should instructed to see a physician immediately in case of such an event.

WARNING: SODIUM METABISULPHITE.
This product contains Sodium Metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersentitive to bisulphites.

As this preparation contains Benzyl Alcohol, its use should be avoided in children under 2 years of age. Not to be used in neonates.

Gastrointestinal effects

NSAIDs, including diclofenac, may be associated with increased risk of

gastrointestinal anastomotic leak. Close medical surveillance and caution

are recommended when using diclofenac after gastrointestinal surgery.

DRUG INTERACTIONS:

Acetaminophen
(Prolonged concurrent use of acetaminophen with an NSAID may increase the risk of adverse renal effects; it is recommended that patients be under close medical supervision while receiving such combined therapy)

Alcohol or Corticosteroids, glucocorticoid or Corticotropin (chronic therapeutic use) or Potassium supplements
(Concurrent use with an NSAID may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage; however, concurrent use with a glucocorticoid or corticotropin in the treatment of arthritis may provide additional therapeutic benefit and permit reduction of glucocorticoid or corticotropin dosage)

Anticoagulants, coumarin-or indandione-derivative or Heparin or Thrombolytic agents
(Inhibition of platelet aggregation by NSAIDs, and the possibility of NSAID-induced gastrointestinal ulceration or bleeding, may be hazardous to patients receiving anticoagulant or thrombolytic therapy; although with usual doses, diclofenac, may be less likely than other NSAIDs to significantly alter platelet aggregability).

Antidiabetic agents, oral or Insulin
(NSAIDs may increase the effect of these medications because prostaglandins are involved in regulatory mechanisms of glucose metabolism and possibly because of displacement of the oral antidiabetics from serum proteins; dosage adjustments of the antidiabetic agent may be necessary)
(Diclofenac has also been reported to decrease the effects of these medications, leading to hyperglycemia)

Antihypertensives or Diuretics, especially Triamterene
(Increased monitoring of the response to an antihypertensive agent may be advisable when any NSAID is used concurrently because flurbiprofen, indomethacin, ibuprofen, naproxen, oxaprozin, and piroxicam have been shown to reduce or reverse the effects of antihypertensives, possibly by inhibiting renal prostaglandin synthesis and/or causing sodium and fluid retention)
(Concurrent use of an NSAID and a diuretic may increase the risk of renal failure secondary to a decrease in renal blood flow caused by inhibition of renal prostaglandin synthesis)
(Concurrent use of a potassium-sparing diuretic with diclofenac may increase the risk of hyperkalemia)

Aspirin or NSAIDs, two or more concurrently
(Concurrent use of two or more NSAIDs, including aspirin, is not recommended; concurrent therapy may increase the risk of gastrointestinal toxicity, including ulceration or hemorrhage, without providing additional symptomatic relief) (concurrent use of aspirin with other NSAIDs may also increase the risk of bleeding at sites other than the gastrointestinal tract because of additive inhibition of platelet aggregation)

(Concurrent administration of two or more NSAIDs may alter the pharmacokinetic profile of at least one of the medications, which may alter the therapeutic effect and/or increase the risk of adverse effect; specifically, aspirin decreases the bioavailability of diclofenac [by 50 %])

Bone marrow depressants
(leukopenic and/or thrombocytopenic effects of these medications may be increased with concurrent or recent therapy if an NSAID cause the same effects; dosage adjustment of the bone marrow depressant, if necessary, should be based on blood counts)

Cefamandole or Cefoperazone or Cefotetan or Plicamycin or Valproic acid
(These medications may cause hypoprothrombinemia; in addition, plicamycin or valproic acid may inhibit platelet aggregation; concurrent use with an NSAID may increase the risk of bleeding because of additive interference with platelet function and/or the potential occurrence of NSAID-induced, gastrointestinal ulceration or hemorrhage)

Colchicine
(Concurrent use with an NSAID may increase the risk of gastrointestinal ulceration or hemorrhage)
(Inhibition of platelet by NSAIDs, added to colchicine's effects on blood clotting mechanisms [colchicines may cause thrombocytopenia with chronic use and clotting defects, including disseminated intravascular coagulation, with overdose], may increase the risk of bleeding at sites other than the gastrointestinal tract)

Cyclosporine or Gold compound or Nephrotoxic medications,other
(Inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporine and/or the risk of cyclosporine-induced nephrotoxicity; patients should be carefully monitored during concurrent use)
(The risk of adverse renal effects may also be increased when an NSAID is used concurrently with other nephrotoxic medications, possibly including gold compounds [although NSAIDs and gold compounds are commonly used concurrently in the treatment of arthritis])

Digitalis glycosides
(diclofenac has been shown to increase serum digoxin concentrations, leading to an increased risk of digital toxicity, increased monitoring and dosage adjustments of the digitalis glycoside may be necessary during and following concurrent NSAID therapy)

Lithium
(diclofenac has been reported to increase the steady-concentration of lithium, possibly by decreasing its renal clearance; increased monitoring of lithium concentration is recommended during and following concurrent use)

Methotrexate
(NSAIDs may decrease protein binding and/or renal elimination of methotrexate, resulting in increased and prolonged methotrexate plasma concentrations and increased risk of toxicity, especially during high dose methotrexate infusion therapy; fatalities have been reported; it is recommended that NSAID therapy be withheld for varying periods of time, depending on the elimination half-life of the individual NSAID [12 to 24 hours for agents with a short elimination

half-life to up to 10 or 12 days for agents with a very long elimination half-life] prior to administration of a high-dose methotrexate infusion: also, NSAID therapy should not be resumed following the infusion until the methotrexate plasma concentration has decreased to a level, usually at least 12 hours)
(Severe, sometimes fatal, methotrexate toxicity has also been reported when NSAIDs were used concurrently with low to moderate doses of methotrexate, including doses commonly used in the treatment of rheumatoid arthritis or psoriasis; caution in concurrent use is recommended, with dosage of methotrexate being adjusted as determined by monitoring the plasma methotrexate concentration and/or adequacy of the patient's renal function)

Photosensitizing medications, other
(Concurrent use with photosensitising NSAIDs may cause additive photosensitising effects)

Platelet aggregation inhibitors, other
(Concurrent use with an NSAID may increase the risk of bleeding because of additive inhibition of platelet aggregation, as well as the potential for NSAID induced gastrointestinal ulceration or hemorrhage)
(Concurrent use of sulfinpyrazone with NSAIDs may also increase the risk of gastrointestinal ulceration or hemorrhage)

Probenecid
(Probenecid may decrease excretion and increase serum concentrations of NSAIDs possibly enhancing effectiveness and/or increasing the potential for toxicity; a decrease in dosage of the NSAID may be necessary if adverse effects occur)

RECOMMENDED DOSAGE, DOSAGE SCHEDULE AND ROUTE OF ADMINISTRATION:

Adults:The usual dosage is 75 mg (3 ml) and 1 ampoule daily, administered by deep intragluteal injection into the upper outer quadrant. In severe cases, (e.g., colic) the dosage may be raised exceptionally to 2 injections (150 mg) and ampoules daily, allowing an interval of several hours to elapse between injections (a different site of injection should be used e.g. the other buttock). Alternatively, 1 injection (75 mg) and ampoule can be combined with other dosage forms of diclofenac up to a maximum daily dosage of 150 mg.

The injections and ampoules should be given for 2 days only, after which treatment should be continued with diclofenac coated tablets or suppositories, if necessary.

Children: Zobid injections and ampoules are not suitable for children.

As a general recommendation, the dose should be individually adjusted. Adverse affects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms (see section WARNINGS AND PRECAUTIONS).

Established cardiovascular disease or significant cardiovascular risk factors

Treatment with diclofenec is generally not recommended in patients with established cardiovascular disease,peripheral arterial disease)or uncontrolled hypertension.If needed patients with established cardiovascular disease,uncontrolled hypertension or significant risk factor for cardiovascular disease(e.g. hypertension,hyperlipidaemia,diabetes mellitus and smoking) should be treated with diclofenec only after careful consideration and only at doses ≤100mg daily if treated for more than 4 weeks(see section WARNING AND PRECAUTIONS).

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):
Management of acute poisoning with NSAIDs consists essentially of supportive and symptomatic measures. Overdosage of diclofenac produces no typical clinical picture. Supportive and symptomatic treatments are indicated for complications, e.g. hypotension, renal failure, convulsions, gastrointestinal irritation and respiratory depression.
It is unlikely that specific measures, e.g., forced diuresis, dialysis or haemoperfusion are helpful in eliminating nonsteroidal antirheumatic agents owing to their high protein-binding rate and extensive metabolism.

PACKING / PACK SIZES:
For 3 ml: 3 ml in transparent ampoules, 10 ampoules in a carton.
For 10 ml: 10 ml in transparent vials, 10 vials in a carton.

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:
Store below 30°C. Protect from light and freezing.
Pharmaceutical Incompatibilities:As a rule, Zobid injection for IM use should not be mixed with other injection solutions..

SHELF LIFE: 3 Years

Manufacturer and Product Registration Holder:
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