Summary of Product Characteristics

Dicloran® Tablet

Dicloran® SR 100 Tablet

Dicloran® Injection

Dicloran®
(Diclofenac Sodium)

1. NAME OF THE PRODUCT
Dicloran® (Diclofenac Sodium) 50mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dicloran® 50mg Tablets
Each enteric coated tablet contains:
Diclofenac Sodium BP..... 50mg

3. PHARMACEUTICAL FORM
Tablet

Appearance: White to off-white, round biconvex enteric coated tablets.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis for back pain. Relief of acute or chronic pain states in which there is an inflammatory component. Symptomatic treatment of primary dysmenorrhoea.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Usual Adult dose: 25 to 50mg taken three times daily. Initially this dose may be increased to 150mg daily and may be reduced to 75 to 100mg daily in milder cases or for long-term and maintenance therapy. **Dicloran®** is not recommended for use in children as safety and efficacy have not been established. The dose in children is 2mg per kilogram body mass per day in three divided doses. The tablets should be swallowed whole, with or after a meal.
Method of administration:
For oral use only.

4.3. CONTRAINDICATIONS:
- Hypersensitivity to the active substance or any of the excipients.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of gastrointestinal bleeding or perforation, relating to previous NSAID therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

- Last trimester of pregnancy.
- Severe hepatic, renal or cardiac failure.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac Sodium is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Acute allergic reactions have been reported. Because of the possibility of cross sensitivity due to structural relationship which exist among non-steroidal anti-inflammatory medicines, acute allergic reactions may be more likely to occur in patients who have exhibited allergic reactions to these compounds. Allergic reactions which include angio-oedema, bronchospasm, urticarial, and anaphylactic reactions, have occurred. In view of the products inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients. Plasma concentrations are significantly decreased by the concomitant administration of therapeutic doses of aspirin. When given together with preparations containing lithium or digoxin, diclofenac sodium may raise their plasma concentrations. Concomitant administration of glucocorticoids or other non-steroidal anti-inflammatory agents may aggravate gastro-intestinal side-effects. Concurrent administration with two or more non-steroidal anti-inflammatory agents may promote the occurrence of side-effects. Should be used with caution in patients with asthama or bronchoconstriction. Use carefully in elderly patients. Decreased platelet aggregation with increased bleeding time may occur. May increase the half-life of probenecid. Use with care together with other protein-bound medicines e.g. Tolbutamine, coumarin and hydantoin.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects.

Anti-hypertensive: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased risk of nephrotoxicity.

Mifepristone: NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin.

Quinolone Antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and Quinolones may have an increased risk of developing convulsions.
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding.
Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.
Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with Zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy: Congenital abnormalities have been reported in association with NSAID administration in man, however, these are low in frequency and do not appear to follow any discernible pattern. In view of the known effects of appear to follow any discernible pattern. In view of the known effects of NSAIDs on the foetal cardiovascular system (risk of closure of the ductus arteriousus), use in the last trimester of pregnancy is contraindicated. The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child. NSAIDs should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential benefit to the patient outweighs the potential risk to the foetus.
Breast-feeding: In limited studies so far available, NSAIDs can appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breast-feeding.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8. UNDESIRABLE EFFECTS:

Gastrointestinal experiences including abdominal pain, constipation, diarrhoea, dyspepsia, flatulence gross bleeding/perforation, heartburn, nausea, GI-ulcers (Gastric/duodenal) and vomiting. Abnormal renal function, anaemia, dizziness, oedema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes and tinnitus.

4.9. OVERDOSE:

Symptoms: Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma,

drowsiness, dizziness, tinnitus, fainting and occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures: Patients should be treated symptomatically as required. Within one hour of ingestion of potentially life-threatening overdose. Good urine output should be ensured. Renal and liver function should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances.

ATC code: M01A B05.

Mechanism of action: Diclofenac Sodium, the active substance of **Dicloran®**, is a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain and fever. Diclofenac Sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

5.2. PHARMACOKINETICS:

Absorption and Distribution: Diclofenac sodium is completely absorbed from the intestinal tract but undergoes first pass metabolism and peak plasma concentrations occur in about 2 to 4 hours; at therapeutic concentrations it is more than 99% bound to plasma proteins.

Metabolism and elimination: Diclofenac Sodium is almost entirely metabolized in the liver and the terminal plasma half-life is about 1-2 hours, with metabolic excretion mainly via the kidneys and also in the bile.

5.3. PRECLINICAL SAFETY DATA:

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with Diclofenac Sodium revealed no specific hazard for humans at the intended therapeutic doses. In standard preclinical animal studies, there was no evidence that Diclofenac Sodium had a teratogenic potential in mice, rats or rabbits. Diclofenac Sodium had no influence on the fertility of parent animals in rats. Except for minimal foetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected. Administration of NSAIDs (including Diclofenac Sodium) inhibited ovulation in the rabbit and implantation

and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of Diclofenac Sodium were associated with dystocia, prolonged gestation, decreased foetal survival, and intrauterine growth retardation in rats. The slight effects of Diclofenac Sodium on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Lactose monohydrate
- Maize starch
- Poly vinyl pyrrolidone
- Poly ethylene glycol
- Silicon dioxide fumed
- Magnesium stearate
- Isopropyl alcohol
- Purified water
- Hydroxypropyl methyl cellulose

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu blister, pack size is 30’s.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

No special requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

BP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

009744

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

08th May, 1988

10. DATE OF REVISION OF THE TEXT

ڈکلوران ۵۰ ملی گرام ٹیبلٹ
(ڈکلوفینک سوڈیم)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ
کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Dicloran® SR 100

(Diclofenac Sodium)

WARNING: 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 NSAIDs therapy. Although minor upper GI problem s (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, 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.

1. NAME OF THE PRODUCT

Dicloran® SR 100 (Diclofenac Sodium) Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Dicloran® SR 100 Tablets

Each sustained release film coated tablet contains:

Diclofenac Sodium BP.....100mg

3. PHARMACEUTICAL FORM

Tablet

Appearance: Yellow to dark yellow round biconvex film coated tablet.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Used for relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout and following some surgical procedures.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

As a general recommendation, the dose should be individually adjusted. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Established cardiovascular disease or significant cardiovascular risk factors: Treatment with **Dicloran® SR 100** is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischaemic 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 **Dicloran® SR 100** only after careful consideration and only at doses ≤100mg daily if treated for more than 4 weeks.
Adults: One 100mg tablet a day.
Elderly: Care should be used when treating patients who are frail or have a low body weight as they will in general be more susceptible to adverse reactions. The lowest effective dose should be used in these patients. The standard adult dose may be used for other elderly patients.
Children: Not suitable for use in children.
Method of administration: Oral, tablets should be swallowed whole preferably with food.

4.3. CONTRAINDICATIONS:

- Contraindicated in patients known to be hypersensitive to Diclofenac Sodium.
- Contraindicated in patients who when taking aspirin or other non-steroidal anti-inflammatory drugs suffer attacks of asthma, urticaria or acute rhinitis.
- Should not be used in patients with active or suspected peptic ulcer or gastrointestinal bleeding
- Contraindicated in patients with bone marrow depression.
- Severe cardiac failure.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

- Patients with a history of gastrointestinal ulceration, haematemesis or melaena should be carefully observed.
- Care should be taken when treating patients with ulcerative colitis, Crohn's disease, haematological abnormalities or bleeding diathesis.
- Caution is recommended in elderly patients and those with renal or hepatic impairment. Monitoring of renal function, hepatic function and blood counts should be performed on long-term NSAID patients, as a precautionary measure.
- Diclofenac sodium may trigger an attack in patients with hepatic porphyria.
- Patients should not drive or operate machinery if they experience dizziness or other central nervous system disturbances.
- Caution in patients who must restrict their sodium intake.

- Diclofenac should be stopped if liver function tests show abnormalities which persist or worsen, or if liver disease develops or if other symptoms such as eosinophilia or rash occur.
- 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 sign of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.

Cardiovascular effects: Treatment with NSAIDs including Diclofenac Sodium, particularly at high dose and in long term, may be associated with an increased risk of serious cardiovascular thrombotic events (including myocardial infarction and stroke). Treatment with Diclofenac Sodium is generally not recommended in patients with established cardiovascular disease (congestive heart failure, established ischaemic 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 Sodium only after careful consideration and only at doses ≤ 100mg daily when treatment continues for more than 4 weeks. As the cardiovascular risks of Diclofenac Sodium 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 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.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

- Diclofenac Sodium may increase plasma concentrations of lithium, digoxin and methotrexate.
- Concomitant use of diclofenac sodium and other NSAIDs may increase the frequency of side effects.
- Diclofenac Sodium may increase ciclosporin nephrotoxicity as a result of their effect on renal prostaglandins.
- There is an increased risk of convulsions if quinolone antibiotics are given while Diclofenac Sodium is being taken, and caution is advised when considering their use.
- Increased serum potassium levels may result when Diclofenac Sodium is given concomitantly with potassium-sparing diuretics. Serum potassium levels should therefore be monitored.

- Care is required when giving anticoagulants with Diclofenac Sodium as it may reversibly inhibit platelet aggregation.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the hypoglycaemic effect of antidiabetic agents; dosage adjustments of the diabetic agent may be necessary; glipizide and glyburide may not be affected as much as the other oral antidiabetic agents, however, caution with concurrent use is recommended. Diclofenac Sodium has also been reported to decrease the effects of antidiabetic agents, leading to hyperglycaemia.

4.6. FERTILITY, PREGNANCY AND LACTATION:

The use of diclofenac sodium is not advisable in pregnancy and lactation.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Not applicable.

4.8. UNDESIRABLE EFFECTS:

- Common side effects include nausea, headaches, diarrhoea, epigastric pain, anorexia, dyspepsia, flatulence, abdominal cramps, vertigo and dizziness.
- Skin rashes and eruptions have occasionally been reported and rarely urticaria.
- Isolated effects on the central nervous system include drowsiness, tiredness, impaired hearing, insomnia, irritability, anxiety etc.
- Occasional effects on the kidney include acute renal insufficiency, urinary abnormalities (eg. haematuria, proteinuria), nephrotic syndrome, papillary necrosis and interstitial nephritis.
- Effects on the liver include occasional reports of elevation of serum aminotransferase enzymes (ALT, AST) and rarely liver function disorders.
- Leucopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia and agranulocytosis have rarely been reported.
- Hypersensitivity reactions (anaphylactic/anaphylactoid systemic reactions, hypotension, and bronchospasm) have rarely been reported.
- Many of these cardiovascular effects may occur secondary to NSAID-induced renal function impairment: angina pectoris, irregular heartbeat, congestive heart failure, increased blood pressure and nose bleeds.
- Cases of hair loss, bullous eruptions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and photosensitivity reactions have been reported.
- **Cardiac Disorders:** ***Uncommon*:*** Myocardial infarction, cardiac failure, palpitations, chest pain.

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

4.9. OVERDOSE:

Clinical features: Gastrointestinal symptoms (e.g. abdominal pain, nausea, vomiting); central nervous system effects (e.g. lethargy, drowsiness) and renal effects have been reported. More serious effects such as gastrointestinal haemorrhage, acute renal failure, convulsions and coma have also been reported.

Treatment for overdosage: Gastric lavage and treatment with activated charcoal should be used as soon as possible after overdosage in order to prevent absorption of the drug. Further treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic products, non-steroids, acetic acid derivatives and related substances.

ATC code: M01A B05.

As an analgesic, Diclofenac Sodium 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 sensitize pain receptors to mechanical or chemical stimulation.

Mechanism of action: Diclofenac Sodium is a non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. It inhibits the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Diclofenac Sodium probably produce antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating and heat loss. The central action probably involves reduction of prostaglandin activity in the hypothalamus.

5.2. PHARMACOKINETICS:

Dicloran®SR 100 tablets are slow release preparations designed to release Diclofenac Sodium over a period of time.

Absorption: Diclofenac Sodium is rapidly absorbed after oral administration. Although orally administered Diclofenac Sodium is almost completely absorbed, it is subject to first-pass metabolism so that only 50 to 60% of the drug reaches the systemic circulation in the unchanged form.

Distribution: Diclofenac penetrates synovial fluid. It was detected in the synovial fluid 2 hours after a dose and the concentration remained relatively constant for the next 9 hours. It also readily crosses the placenta. Diclofenac is

excreted in breast milk. In one study, long-term use of 150mg per day produced concentrations of 100 nanograms per mL in the breast milk. An infant of 4 to 5kg consuming one liter per day would therefore ingest approximately 0.03mg/kg per day.

Protein Binding: Diclofenac Sodium is highly protein bound. At therapeutic concentrations it is more than 99% bound to plasma proteins.

Half-life: The terminal plasma half-life is about 1 to 2 hours.

Biotransformation: Diclofenac Sodium undergoes first-pass metabolism. It is metabolised to 4'-hydroxydiclofenac, 5- hydroxydiclofenac, 3'-hydroxydiclofenac and 4',5-dihydroxydiclofenac.

Elimination: It is excreted in the form of glucuronide and sulphate conjugates, mainly in the urine but also in the bile. About 40-65% of dose undergoes renal elimination and about 35% of dose undergoes biliary/faecal elimination. Little or none is eliminated unchanged via the renal or biliary systems.

5.3. PRECLINICAL SAFETY DATA:

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Lactose spray dried
- Methocel
- Silicon dioxide fumed
- Poly vinyl pyrrolidone
- Talcum powder
- Magnesium stearate
- Simethicone
- Titanium dioxide
- Poly ethylene glycol
- Tartrazine yellow lake color
- Purified water

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu blister, pack size is 30's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

BP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

009743

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

08th May, 1988

10. DATE OF REVISION OF THE TEXT

ڈکلوران ایس۔آر۔۱۰۰

(ڈکلوفینک سوڈیم) ٹیبلٹ

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

Dicloran®
(Diclofenac Sodium)

1. NAME OF THE PRODUCT
Dicloran® (Diclofenac Sodium) 75mg Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Dicloran® 75mg Injection
Each 3ml contains:
Diclofenac Sodium BP.....75mg

3. PHARMACEUTICAL FORM
Solution for Injection

Appearance: Clear to slightly colored solution free from any visible particles.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Intramuscular injection: Treatment of:
- Renal colic and biliary colic.
- Severe migraine attacks when other forms of Diclofenac Sodium are considered unsuitable.

Intramuscular injection: Treatment or prevention of post-operative pain in a hospital setting.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Diclofenac Sodium should only be prescribed when the benefits are considered to outweigh the potential risks. After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used. Adverse effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.
Dosage:
General population: Diclofenac Sodium solution for injection should not be given for more than 2 days; if necessary, treatment can be continued with Diclofenac Sodium tablets or suppositories.
Special populations:
Paediatric population: Because of their dosage strength, the ampoules of Diclofenac Sodium solution for injection are not suitable for children and adolescents.
Geriatric population (Patients aged 65 or above): No adjustment of the starting dose is generally required for elderly patients However, caution is

indicated on basic medical grounds, especially for frail elderly patients or those with a low body weight.

Patients with established cardiovascular disease or significant cardiovascular risk factors: Treatment with Diclofenac Sodium solution for injection is generally not recommended in patients with established cardiovascular disease or uncontrolled hypertension. If needed, patients with established cardiovascular disease, uncontrolled hypertension or significant risk factors for cardiovascular disease should be treated with Diclofenac Sodium solution for injection only after careful consideration and only at doses ≤100mg daily initial treatment with Diclofenac Sodium solution for injection continues e.g. with Diclofenac Sodium tablets or suppositories for more than 4 weeks.

Patients with renal impairment: Diclofenac Sodium is contraindicated in patients with renal failure.

Patients with hepatic impairment: Diclofenac Sodium is contraindicated in patients with hepatic failure.

Method of administration:

Intramuscular injection: The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site (which may result in muscle weakness, muscle paralysis, hypoaesthesia and Embolia cutis medicamentosa (Nicolau syndrome)). The dose is generally one 75mg ampoule daily, given by deep intragluteal injection into the upper outer quadrant using aseptic technique. In severe cases (e.g. colic), the daily dose can exceptionally be increased to two injections of 75mg, separated by an interval of a few hours (one into each buttock). Alternatively, one ampoule of 75mg can be combined with other pharmaceutical forms of Diclofenac Sodium (e.g. tablets, suppositories) up to a total maximum daily dose of 150mg. In migraine attacks, clinical experience is limited to initial use of one ampoule of 75mg administered as soon as possible, followed by suppositories up to 100mg on the same day if required. The total dose should not exceed 175mg on the first day.

Intravenous infusion: Diclofenac Sodium solution for injection must not be given as an intravenous bolus injection. Immediately before starting an intravenous infusion, Diclofenac Sodium solution for injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate. Two alternative dosage regimens of Diclofenac Sodium solution for injection are recommended. For the treatment of moderate to severe post-operative pain, 75mg should be infused continuously over a period of 30 minutes to 2 hours. If necessary, treatment may be repeated after a few hours, but the dose should not exceed 150mg within any period of 24 hours. For the prevention of post-operative pain, a loading dose of 25mg to 50mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5mg per hour up to a maximum daily dose of 150mg.

4.3. CONTRAINDICATIONS:

- Known hypersensitivity to the active substance, sodium metabisulphite or to any of the excipients.
- Active gastric or intestinal ulcer, bleeding or perforation.
- Last trimester of pregnancy.
- Hepatic failure.
- Renal failure (GFR <15mL/min/1.73m^2).
- Severe cardiac failure.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac Sodium is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

General:

Patients on long-term treatment should be reviewed regularly with regards to efficacy, adverse effects, the development of risk factors and the on-going need for therapy. Consideration should be given to monitoring blood pressure, haemoglobin levels and renal function.

Cardiovascular thrombotic events: Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. Patients with previous myocardial infarction (within the last 6 to 12 months) should not use diclofenac. Treatment with Diclofenac Sodium is generally not recommended in patients with established cardiovascular disease (e.g. congestive heart failure, established Ischaemic 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, hyperlipidemia, diabetes mellitus and smoking) should be treated with Diclofenac Sodium 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 reevaluated periodically, especially when treatment continues for more than 4 weeks. Prescribers should inform the individual patient of the possible increased risk when prescribing diclofenac for patients at high risk of cardiovascular events. Physicians and patients should remain alert for such events, even in the absence of previous cardiovascular symptoms. Patients should be informed about the signs and/or symptoms of

cardiovascular toxicity and the steps to take should they occur. Patients should 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 warning. Patients should be instructed to see a physician immediately in case of such an event. 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 of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive 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, therefore caution is advised in patients with fluid retention or heart failure.

Gastrointestinal effects: Gastrointestinal bleeding, ulceration or perforation, which may increase with dose or duration of use and which can be fatal, have been reported with all NSAIDs, including diclofenac, and may occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. They generally have more serious consequences in the elderly. If gastrointestinal bleeding or ulceration occur in patients receiving Diclofenac Sodium, the treatment should be discontinued. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac Sodium in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation. The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. 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. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events. NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using Diclofenac Sodium after gastrointestinal surgery. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

Severe skin reactions: Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS), have been reported very rarely in association with the use of NSAIDs, including Diclofenac Sodium. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity, and Diclofenac Sodium should be discontinued. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac, without earlier exposure to the drug. The sodium metabisulphite in the solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: DRESS syndrome has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS syndrome typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS syndrome may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such

signs or symptoms are present, discontinue the NSAID and evaluate the patient immediately.

Masking signs of infections: Like other NSAIDs, Diclofenac Sodium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

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.

Injection site reactions: Injection site reactions have been reported after the administration of Diclofenac Sodium intramuscularly, including injection site necrosis and embolia cutis medicamentosa, also known as Nicolau Syndrome (particularly after inadvertent subcutaneous administration). Appropriate needle selection and injection technique should be followed during IM administration of Diclofenac Sodium.

Haematological effects: During prolonged treatment with Diclofenac Sodium, as with other NSAIDs, monitoring of the blood count is recommended. Like other NSAIDs, Diclofenac Sodium may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Geriatric patients: Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight.

Interactions with other NSAIDs: The concomitant use of Diclofenac Sodium with systemic NSAIDs including cyclooxygenase-2 selective inhibitors, should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

The following interactions include those observed with Diclofenac Sodium solution for injection and/or other pharmaceutical forms of diclofenac.

Observed interactions to be considered:

CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

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.

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects.

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding.

Antidiabetics: Clinical studies have shown that diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However, there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy. There have also been isolated reports of metabolic acidosis when diclofenac was co-administered with metformin, especially in patients with pre-existing renal impairment.

Methotrexate: Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin and Tacrolimus: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of cyclosporin and tacrolimus due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin and tacrolimus.

Drugs known to cause hyperkalaemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Quinolone antibacterials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

CYP2C9 inducers: Caution is recommended when co-prescribing diclofenac with CYP2C9 inducers (such as rifampicin), which could result in a significant decrease in plasma concentration and exposure to diclofenac.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility:

Female fertility: As with other NSAIDs, the use of Diclofenac Sodium may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of Diclofenac Sodium should be considered.

Male fertility: There is no human data on the effect of Diclofenac Sodium on male fertility.

Pregnancy: Diclofenac has been shown to cross the placental barrier in humans. Use of NSAIDs, including diclofenac, can cause uterine inertia, premature closure of the foetal ductus arteriosus and foetal renal impairment leading to oligohydramnios. Because of these risks, Diclofenac Sodium should not be used during the first two trimesters of pregnancy unless the expected benefits to the mother outweigh the risks to the foetus. In addition, Diclofenac Sodium should not be used during the third trimester of pregnancy. Risk of foetal renal impairment with subsequent oligohydramnios has been observed when NSAIDs (including diclofenac) were used from the 20th week of pregnancy onwards. There are no studies on the effects of Diclofenac Sodium during labour or delivery. As with other NSAIDs, use of diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia.

Breast-feeding: Like other NSAIDs, diclofenac passes into the breast milk in small amounts. Therefore, Diclofenac Sodium should not be administered during breast-feeding in order to avoid undesirable effects in the infant.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients who experience visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness, or fatigue while taking NSAIDs should refrain from driving or operating machinery.

4.8. UNDESIRABLE EFFECTS:

The corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000). The following undesirable effects include those reported with Diclofenac Sodium solution for injection and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Infections and infestations: ***Very rare:*** Injection site abscess.

Blood and lymphatic system disorders: ***Very rare:*** Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.

Immune system disorders: ***Rare:*** Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock). ***Very rare:*** Angioedema (including face oedema).

Psychiatric disorders: ***Very rare:*** Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders: ***Common:*** Headache, dizziness. ***Rare:*** Somnolence. ***Very rare:*** Paraesthesia, memory impairment, convulsion, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident.

Eye disorders: ***Very rare:*** Visual impairment, blurred vision, diplopia.

Ear and labyrinth disorders: ***Common:*** Vertigo. ***Very rare:*** Tinnitus, impaired hearing.
Cardiac disorders: ***Uncommon:*** Myocardial infarction, cardiac failure, palpitations, chest pain. ***Frequency unknown:*** Kounis syndrome.
Vascular disorders: ***Very rare:*** Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders: ***Rare:*** Asthma (including dyspnoea). ***Very rare:*** Pneumonitis.
Gastrointestinal disorders: ***Common:*** Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decreased appetite. ***Rare:*** Gastritis, gastrointestinal haemorrhage, haematemesis, melaena, haemorrhagic diarrhoea, gastrointestinal ulcer (with or without bleeding gastrointestinal stenosis or perforation which may lead to peritonitis). ***Very rare:*** Colitis (including haemorrhagic colitis, ischemic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis.
Hepatobiliary disorders: ***Common:*** Transaminases increased. ***Rare:*** Hepatitis, jaundice, liver disorder. ***Very rare:*** Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissues disorders: ***Common:*** Rash. ***Rare:*** Urticaria. ***Very rare:*** Bullous dermatitis, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), exfoliative dermatitis, alopecia, photosensitivity reaction, Henoch-Schonlein purpura, pruritus. ***Unknown:*** Drug reaction with eosinophilia with systemic symptoms (DRESS).
Renal and urinary disorders: ***Very rare:*** Acute kidney injury (acute renal failure), haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions: ***Common:*** Injection site reaction, injection site pain, injection site induration. ***Rare:*** Oedema, injection site necrosis.
Injection site reactions: Embolia cutis medicamentosa (Nicolau syndrome).

4.9. OVERDOSE:

Symptoms: There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.
Therapeutic measures: Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression. Special

measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances.

ATC code: M01A B05.

In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac Sodium elicit a clinical response characterised by marked relief from signs and symptoms such as pain at rest, pain on movement, morning stiffness, and swelling of the joints, as well as by an improvement in function. Diclofenac Sodium has also been found to exert a pronounced analgesic effect in moderate and severe pain of non-rheumatic origin, an effect which sets in within 15 to 30 minutes. Diclofenac Sodium has also been shown to have a beneficial effect in migraine attacks. In post-traumatic and post-operative inflammatory conditions, Diclofenac Sodium rapidly relieves both spontaneous pain and pain on movement and reduces inflammatory swelling and wound oedema. When used concomitantly with opioids for the management of post-operative pain, Diclofenac Sodium significantly reduces the need for opioids. Diclofenac Sodium ampoules are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.

Mechanism of action: Diclofenac Sodium contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, anti-inflammatory, analgesic, and antipyretic properties. Inhibition of prostaglandin biosynthesis, which has been demonstrated in experiments, is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing inflammation, pain, and fever. Diclofenac sodium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to those reached in humans.

5.2. PHARMACOKINETICS:

Absorption: After administration of 75mg diclofenac by intramuscular injection, absorption sets in immediately, and mean peak plasma concentrations of about 2.5µg/mL (8µmol/L) are reached after about 20 minutes. When 75mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9µg/mL (5.9µmol/L). Shorter infusions result in higher peak plasma concentrations, while longer infusions give plateau concentrations proportional to the infusion rate after 3 to 4 hours. In contrast, plasma concentrations decline rapidly once peak levels have been reached

following intramuscular injection or administration of gastro-resistant tablets or suppositories. The area under the concentration curve (AUC) after intramuscular or intravenous administration is about twice as large as it is following oral or rectal administration, because about half the active substance is metabolised during its first passage through the liver ("first pass" effect) when administered via the oral or rectal routes. Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

Distribution: 99.7% of diclofenac is bound to serum proteins, mainly to albumin 99.4%). The apparent volume of distribution calculated is 0.12 to 0.17 L/kg. Diclofenac enters the synovial fluid, where maximum concentrations are measured 2 to 4 hours after peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3 to 6 hours. Two hours after reaching peak plasma values, concentrations of the active substance are already higher in the synovial fluid than in the plasma, and they remain higher for up to 12 hours. Diclofenac was detected in a low concentration (100ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03mg/kg/day dose.

Biotransformation: Biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-,4'-hydroxy-,5-hydroxy-,4',5-dihydroxy- and 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a much smaller extent than diclofenac.

Elimination: Total systemic clearance of diclofenac from plasma is 263 ± 56mL/min (mean value ±SD). The terminal half-life in plasma is 1 to 2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1 to 3 hours. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive. About 60% of the administered dose is excreted in the urine as the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Linearity/non-linearity: The amount absorbed is in linear proportion to the size of the dose.

5.3. PRECLINICAL SAFETY DATA:

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed

no specific hazard for humans at the intended therapeutic doses. Reproductive and developmental studies in animals demonstrated that diclofenac administration during organogenesis did not produce teratogenicity despite the induction of maternal toxicity and foetal toxicity in mice at oral doses up to 20mg/kg/day (0.41 times the maximum recommended human dose [MRHD] of Diclofenac Sodium, 200mg/day, based on body surface area (BSA) comparison), and in rats and rabbits at oral doses up to 10mg/kg/day (0.41 and 0.81 times, respectively, the MRHD based on BSA comparison). In animal studies, NSAIDS, including diclofenac, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth. Diclofenac administered to male and female rats at 4mg/kg/day (approximately 0.16 timesthe MRHD based on BSA comparison) did not affect fertility.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Benzyl alcohol
- Propylene glycol
- Sodium hydroxide
- Mannitol
- Sodium metabisulphite
- Water for Injection

6.2. INCOMPATIBILITIES:

As a rule, Diclofenac Sodium solution for injection should not be mixed with other injection solutions. Infusion solutions of sodium chloride 0.9 % or glucose 5 % without sodium bicarbonate as an additive present a risk of supersaturation, possibly leading to formation of crystals or precipitates. Infusion solutions other than those recommended should not be used.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and freezing. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

3ml clear ampoule USP Type-1, pack size is 5’s.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

The following directions for intramuscular injection must be followed in order to avoid damage to a nerve or other tissue at the injection site. To be injected

either intramuscularly by deep intragluteal injection into the upper outer quadrant using aseptic technique, or intravenously by slow infusion after dilution. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.

6.7. DRUG PRODUCT SPECIFICATIONS:

SAMI's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufacturing & Release Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

Packing Site:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-140/A, S.I.T.E., Karachi-Pakistan
Mfg Lic. No. 000938

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

009748

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

08th May, 1988

10. DATE OF REVISION OF THE TEXT

ڈکلوران انجکشن
(ڈکلوفینک سوڈیم)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو دھوپ، گرمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔

انجکشن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں ہرگز استعمال نہ کریں۔