National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINALPRODUCT

JAWA DICLOFENAC INJECTION (Diclofenac Sodium Injection 75 mg/3 ml)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each ml contains:

Diclofenac Sodium BP…25 mg

Benzyl alcohol BP……4% w/v

(As preservative)

Water for Injections BP….q.s.

3. PHARMACEUTICALFORM

Solution for Injection

4. Clinical particulars

4.1 Therapeutic indications

Intramuscular use: Diclofenac sodium can be used in the symptomatic management of acute exacerbation of rheumatoid arthritis and osteoarthritis, in acute back pain, acute gout, post-operative pain, relief of pain in acute traumatic Musculo-skeletal disorders and fractures and renal colic.

Intravenous infusion: For treatment or prevention of post-operative pain in the hospital setting.

4.2 Posology and method of administration

Posology

Adults:

Intravenous use: One ampoule should be diluted in a minimum of 300 ml of normal saline and administered intravenously over a minimum of 30 minutes. A second dose may be administered8 hours after the first infusion.

A maximum of two doses may be given intravenously.

Intramuscular use: One ampoule once (or in severe cases twice) daily intramuscularly by deep intragluteal injection into the upper outer quadrant. If two injections daily are required it is advised that the alternative buttock be used for the second injection.

Renal colic: One 75 mg ampoule intramuscularly. A further ampoule may be administered after 30 minutes if necessary.

As with oral Diclofenac sodium the total daily dose should not exceed 150 mg. Diclofenac sodium Injection should not be given for more than 2 days; if necessary, treatment can be continued with capsules or suppositories.

Elderly: NSAIDS should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed.

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Children: Not suitable for children

Mode of Administration: Diclofenac Sodium injection 75mg/3ml, is used in intramuscular(intra-gluteal) injection.

4.3 Contraindications

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulcerationor bleeding).

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to diclofenac, aspirin, nonsteroidal anti-inflammatory drugs or any components of the preparation.

Severe heart failure

4.4 Special warnings and precautions for use

Undesirable effects may be minimized by using the lowest effective dose for the shortestduration necessary to control symptoms.

The use of Diclofenac sodium Injection with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Elderly: The elderly has an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Warnings:

Gastro-intestinal: Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of previous GI events.The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with hemorrhage or perforation, andin the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.

Patients with a history of GI toxicity especially when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

When GI bleeding or ulceration occurs in patients receiving Diclofenac sodium injection, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated.

Cardiovascular and cerebrovascular effects: Caution and appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150mg initiating daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with diclofenac after careful consideration. Similar consideration should be made before longer- term treatment of patient with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

Hypersensitivity reactions: As with other nonsteroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Serious skin reaction, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs. Patients appear to be at the 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. Diclofenac sodium should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The use of Diclofenac sodium Injection may impair the female fertility and is not recommended in women attempting to conceive. In woman who have difficulties conceiving or who areundergoing investigation of infertility, withdrawal of Diclofenac sodium Injection should be considered.

Like other NSAIDs, Diclofenac sodium Injection may mask the signs and symptoms of infectiondue to its pharmacodynamic properties.

Precautions

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDS may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored prior to the initiation of therapy and regularly thereafter.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with

diuretics or recovering from major surgery. Effects on renal function are usually reversible on withdrawal of Diclofenac sodium.

Hepatic: If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), Diclofenacsodium Injection should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Diclofenac sodium Injection in patients with hepatic porphyria may trigger an attack.

Haematological: As with other NSAIDs, Diclofenac may reversibly inhibit platelet aggregation. Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Long-term treatment: All patients who are receiving non-steroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. hepatic function (elevation of liver enzymesmay occur) and blood counts. This is particularly important in the elderly.

May cause toxic reactions and anaphylactic reactions in infants and children up to 3 years old.
Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Lithium and digoxin: Diclofenac sodium may increase plasma concentrations of lithium and digoxin.

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

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.

Anti-platelet agents and selective serotonin-reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

Antidiabetic agents: 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 adjustment tothe dosage of hypoglycaemic agents.

Cyclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant cyclosporin and NSAIDS, including Diclofenac sodium. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and cyclosporin.

Methotrexate: Cases of serious toxicity have been reported when methotrexate and NSAIDS aregiven within 24 hours of each other. This interaction is mediated through accumulation ofmethotrexate resulting from impairment of renal excretion in the presence of the NSAID. **Quinolone antimicrobials:** Convulsions may occur due to an interaction between quinolonesand NSAIDS. This may occur in patients with or without a previous history of epilepsy orconvulsions. Therefore, caution should be exercised when considering the use of a quinolone inpatients who are already receiving an NSAID.

Other NSAIDS and steroids: Co-administration of Diclofenac sodium with other systemic NSAIDS and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding.

Diuretics: Various NSAIDS are liable to inhibit the activity of diuretics. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored. Diuretics can increase the risk of nephrotoxicity of NSAIDs

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

Anti-hypertensives: reduced anti-hypertensive effect.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased eliminationof aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin II antagonist and agentsthat inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking Diclofenac sodium concomitantly with ACE inhibitors or angiotensin II antagonists.

Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

4.6 Pregnancy and Lactation

Although animal studies have not demonstrated teratogenic effects, Diclofenac sodium Injection should not be used in pregnancy or lactation unless considered essential by the physician and ifso the lowest effective dose should be used. Use of prostaglandin synthetase inhibitors in thethird trimester may result in premature closure of the ductus arteriosus. Traces of drug are detectable in breast milk but are not clinically significant.

4.7 Effects on ability to drive and use machines

Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

If serious side-effects occur, Diclofenac Sodium should be withdrawn.

Gastrointestinal tract:

Occasional: epigastric pain, other gastrointestinal disorders (eg nausea, vomiting, diarrhea, abdominal cramps/pain, dyspepsia, flatulence, anorexia, gastritis).

Rare: gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhea.

Isolated cases: lower gut disorders (eg non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn's disease), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Central Nervous System:

Occasional: headache, dizziness or vertigo. Rare: drowsiness, tiredness.

Isolated cases: disturbances of sensation (paraesthesiae, memory disturbance, disorientation, disturbance of vision, blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

Skin:

Occasional: injection site disorders eg local pain and induration, rashes or skin eruptions.

Rare: urticaria

Isolated cases: injection site abscesses and local necrosis have been reported with intramuscular use, bullous eruptions, eczema, erythema multiforme, StevensJohnson syndrome, lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney:

Isolated cases: acute renal insufficiency, urinary abnormalities (eg haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:

Occasional: elevation of serum aminotransferase enzymes (SGOT, SGPT).

Rare: liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood:

Isolated cases: thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Cardiovascular system:

Isolated cases: Oedema, palpitations, chest pain, hypertension, congestive heart failure.

Clinical and epidemiological data suggest that use of diclofenac, particularily at high dose(150mg daily) and in long term treatment may be associated with a small increased risk ofarterial thrombotic events (for example myocardial infarction or stroke).

Other organ systems:

Rare: oedema, hypersensitivity reactions (eg bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).

Isolated cases: impotence (association with Diclofenac sodium intake is doubtful), palpitation, chest pain, hypertension

4.9 Overdosage

Management of acute poisoning with diclofenac and other non-steroidal anti-inflammatory drugsconsists of supportive and symptomatic measures.

Therapeutic measures that can be taken include; supportive and symptomatic treatment for the complications of overdosage such as hypotension, renal failure, convulsions, gastro-intestinal irritation and respiratory depression; Forced diuresis or dialysis are probably of no help in eliminating diclofenac and other non-steroidal anti-inflammatory medicines due to their high rateof protein binding.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Diclofenac sodium is a phenylacetic acid derivative and a non-steroidal anti-inflammatory agent with analgesic, anti-inflammatory and anti-pyretic properties. Diclofenac is an inhibitor of cyclo-oxygenase and therefore reduces prostaglandin synthesis. Reduction in prostaglandin levelsreduces the inflammatory response by the body.

5.2 **PHARMACOKINETIC PROPERTIES**

Absorption:

Absorption is complete but onset is delayed until passage through the stomach, which may be affected by food which delays stomach emptying. The mean peak plasma diclofenac concentrations reached at about 2 hours (50mg dose produces 1.48 ± 0.65g/ml (1.5g/ml 5mol/l)).

Bioavailability:

About half of the administered diclofenac is metabolised during its first passage through the liver ("first-pass" effect), the area under the concentrations curve (AUC) following oral administration is about half that following an equivalent parenteral dose.

Distribution:

The active substance is 99.7% protein bound, mainly to albumin (99.4%).

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from thesynovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations ofthe active substance are already higher in the synovial fluid than they are in the plasma, and remain higher for up to 12 hours.

Metabolism:

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 , most of which are converted to glucuronide conjugates. Two phenolic metabolites are biologically active, but to a much lesser extent than diclofenac.

Elimination:

Total systemic clearance of diclofenac in plasma is 26356mL/min (mean value SD). The terminal half-life in plasma is 1-2 hours. Four of the metabolites, including the two active ones, also have short plasma half-lives of 1-3 hours.

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.

Characteristics in patients:

Elderly:

No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of <10mL/min, the calculated steady-stateplasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are u Patients with hepatic disease: In patients with chronic hepatitis or non-

decompensated cirrhosis,the kinetics and metabolism of diclofenac are the same as in patients without liver disease ultimately cleared through the bile.

5.3 **Preclinical safety data**

NOT APPLICABLE

6.0 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Benzyl alcohol

Disodium Edetate

Sodium

Metabisulphite

Mannitol

Propylene Glycol

Sodium Hydroxide

Water for Injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with othermedicinal products

6.3 SHELF LIFE

36 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC. Protect from light.
KEEP OUT OF THE REACH OF CHILDREN

6.5 NATURE AND CONTENTS OF CONTAINER

10 x 3 ml Plain Glass ampoule packed in a carton along with plastic tray and insert

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Not Applicable

7.0 APPLICANT

JAWA INTERNATIONALLTD.

JAWA HOUSE

COMPOUND, PLOT 6

ABIMBOLA WAY, ISOLO

INDUSTRIAL ESTATE,

ISOLO, LAGOS, NIGERIA

E-mail: spjawasil@gmail.com

8.0 MANUFACTURER

SWISS PARENTERALS LTD.
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