1.3.1 SUMMARY PRODUCT CHARACTERISTICS (SmPC)

1 Name of the Finished Medicinal Product:

1.1 Product Name: Diclofenac Injection 75mg/ml

1.2 Strength : 75 mg/ml

1.3 Pharmaceutical Form: Injection

2 Qualitative and Quantitative Compositions:

Qualitative Declaration:
Active component
INN Name: Diclofenac Sodium
Quantitative Declaration:
Each ml contains:
Diclofenac Sodium BP..... 75 mg
Benzyl Alcohol BP……2% v/v
Water for Injections BP……..Q.S.

Sr. No.	Content Name	Quality Standard	Qty Per ml
1.	Diclofenac Sodium	BP	75.00 mg
2.	Benzyl Alcohol	BP	0.02 ml
3.	Diethylene Glycol Monoethyl Ether	BP	200.00 mg
4.	Sodium Metabisulfite	BP	1.00 mg
5.	Disodium Hydrogen Phosphate Dihydrate	BP	2.00 mg
6.	Sodium Hydroxide	BP	q.s.
7.	Hydrochloric Acid	BP	q.s.
8.	Water for Injections	BP	q.s. to 1.00 ml

BP - British Pharmacopoeia

3 Pharmaceutical Form: Injection
A clear, colourless to yellowish liquid.

4 Clinical Particulars:

4.1 Therapeutic Indications:

Intramuscular Injection

Treatment of:

- Exacerbations of inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, spondylarthritis, painful syndromes of the vertebral column, non-articular rheumatism
- Acute attacks of gout
- Renal colic
- Post-traumatic and post-operative pain, inflammation and swelling
- Severe migraine attacks

	Intravenous Infusion Treatment or prevention of post-operative pain in a hospital setting
4.2	**Posology and Method of Administration** Diclofenac Injection 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. ***Intramuscular Injection*** Adult: 75 mg once daily, injected into the gluteal muscle, may increase to 75 mg bid in severe conditions. The 1ml injection can also be administered alternatively in the deltoid muscle. Especially suitable in obese patients and convenient for women. ***Intravenous infusion*** Immediately before starting an intravenous infusion, Diclofenac Injection must be diluted with saline 0.9% or glucose 5% infusion solution buffered with sodium bicarbonate according to the instructions given in section (Instructions for use and handling) **Method of Administration in special cases:** ***Postoperative Pain*** **-** Adult: 75 mg 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 150 mg within any period of 24 hours. ***Prophylaxis of Postoperative Pain*** **-** Adult: A loading dose of 25 mg to 50 mg should be infused after surgery over 15 minutes to 1 hour, followed by a continuous infusion of about 5 mg per hour up to a maximum daily dose of 150 mg.
4.3	**Contra-indications:** • Known hypersensitivity to the active substance or to any of the excipients. • Active gastric or intestinal ulcer, bleeding or perforation. • 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, Urticaria, or acute Rhinitis are precipitated by Acetylsalicylic Acid or other NSAIDs.
4.4	**Special warning and precautions for use:** Gastric or intestinal ulceration with associated bleeding has been reported. Therapy with Diclofenac Injection should be discontinued immediately in such cases. 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. Discontinue Diclofenac Sodium immediately if rash occurs. As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with Diclofenac without earlier exposure to the drug. 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. Diclofenac Injection may mask the signs and symptoms of infection due to its Pharmacodynamic Properties.

4.5	**Interaction with other drugs, other forms of interactions:** The following interactions include those observed with Diclofenac Sodium enteric-coated tablets and/or other Pharmaceutical forms of Diclofenac. ***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. Concomitant treatment with Potassium-sparing drugs may be associated with increased serum Potassium levels, which should therefore be monitored frequently. ***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 isolated 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. ***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*** Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin 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. ***Quinolone antibacterials*** There have been isolated reports of convulsions which may have been due to concomitant

	use of Quinolones and NSAIDs.
4.6	**Usage in pregnancy& Lactation** **Pregnancy** The use of Diclofenac in pregnant women has not been studied. Therefore, Diclofenac Sodium should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweights the risk to the foetus. As with other NSAIDs, use of Diclofenac during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductusarteriosus. Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/foetal development, parturition or postnatal development. **Lactation** 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. **Renal impairment** Caution should be exercised. **Hepatic impairment** Caution should be exercised.
4.7	**Effects on ability to drive and operate machine:** Patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking Diclofenac Sodium should refrain from driving or using machines.
4.8	**Undesirable effects:** ***Dermatological*** Occasional - rashes or skin eruptions. Cases of hair loss, bullous eruptions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported. Patients experiencing Visual disturbances, Dizziness, Vertigo, Somnolence or other Central Nervous System disturbances while taking Diclofenac Sodium, should refrain from driving or using machines. The following undesirable effects include those reported with Diclofenac Sodium 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: Angioneuroticoedema (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, Aseptic meningitis, taste disturbances, Cerebrovascular accident. ***Eye disorders*** Very rare: Visual disturbance, Vision blurred, Diplopia. ***Ear and labyrinth disorders*** Common: Vertigo. Very rare: Tinnitus, Hearing impaired. ***Cardiac disorders*** Very rare: Palpitations, Chest pain, Cardiac failure, Myocardial infarction. ***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, Anorexia. Rare: Gastritis, Gastrointestinal haemorrhage, Haematemesis, Diarrhoeahaemorrhagic, Melaena, Gastrointestinal ulcer (with or without bleeding or perforation). Very rare: Colitis (including Haemorrhagic colitis and Exacerbation of ulcerative colitis or Crohn's disease), Constipation, Stomatitis, Glossitis, Oesophageal disorder, Diaphragm-like Intestinal strictures, and Pancreatitis. ***Hepatobiliary disorders*** Common: Transaminases increased. Rare: Hepatitis, Jaundice, Liver disorder. Very rare: Fulminant hepatitis. ***Skin and Subcutaneous tissue disorders*** Common: Rash. Rare: Urticaria. Very rare: Bullous eruptions, Eczema, Erythema, Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis (Lyell's syndrome), Dermatitis exfoliative, Loss of hair, Photosensitivity reaction, Purpura, Allergic purpura, Pruritus. ***Renal and Urinary disorders*** Very rare: Acute renal failure, Haematuria, Proteinuria, Nephrotic syndrome, Interstitial 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.
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	**Pharmacodynamics Properties:** **Pharmacotherapeutic Group (ATC Code) :**M01AB05 ***Mechanism of Action*** Diclofenac Sodium 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. ***Clinical Pharmacology*** *Pharmacodynamic effects* In Rheumatic diseases, the Anti-inflammatory and Analgesic properties of Diclofenac Sodium elicit a clinical response characterized 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 injections are particularly suitable for initial treatment of inflammatory and degenerative rheumatic diseases, and of painful conditions due to inflammation of non-rheumatic origin.
5.2	**Pharmacokinetic Properties:** ***Absorption*** After administration of 75 mg Diclofenac by intramuscular injection, absorption sets in immediately. The amount absorbed is in linear proportion to the size of the dose. 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 behavior 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. ***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 (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 ±56 ml/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.
5.3	**Pre-clinical Safety Data:** The acute and sub acute toxicity study has been conducted in two animal species Swiss Albino Mice and Wistar rats as per the recommended clinical dose. The test results of Acute and Sub Acute Toxicity study in both the species did not show any lethality after administration of test compound once with 10 times of intended therapeutic dose. The result of the sub acute study indicated that the safety of test compound administered at three dose (therapeutic, 3 (Average) and 10 (highest) times of the therapeutic dose) levels. There were no preterminal deaths till the end of experiment with no significant Changes recorded in physical, Physiological, Hematological, Biochemical and Histopathological parameters under experimental conditions in Wistar rats and Swiss Albino Mice.
6	**Pharmaceuticals Particulars:**
6.1	**List of Excipients:** Benzyl Alcohol BP Diethylene Glycol Monoethyl Ether BP Sodium Metabisulfite BP Disodium Hydrogen Phosphate Dihydrate BP Sodium Hydroxide BP Hydrochloric Acid BP Water for Injection BP

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:** 24 months
6.4	**Special Precaution for Storage:** Store below 30^0C. Protect from light. Do not refrigerate.
6.5	**Nature and Contents of Container:** Diclofenac Injection 75 mg/ml is packed in 1 ml clear glass ampoule. 5 such ampoules available in a tray are packed in a carton along with pack insert.
6.6	**Disposal and other handling of the product:** ***Instructions for use and handling*** To be injected either intramuscularly by deep intragluteal injection into the upper outer quadrant, or intravenously by slow infusion after dilution in accordance with the following instructions. Each ampoule is for single use only. The solution should be used immediately after opening. Any unused contents should be discarded. Depending on the intended duration of infusion (see Dosage and administration), mix 100 to 500 mL of isotonic saline (sodium chloride 0.9 % solution) or glucose 5 % solution buffered with sodium bicarbonate injectable solution (0.5 mL of 8.4 % or 1 mL of 4.2 % or a corresponding volume of a different concentration) taken from a freshly opened container; add the contents of one Diclofenac Injection ampoule to this solution. Only clear solutions should be used. If crystals or precipitates are observed, the infusion solution should not be used.
7	**Registrant:** **Marketing Authorization Holder:** **M/s PHILLIPS PHARMACEUTICALS (NIGERIA) LTD.** Address : Afprint Industrial Estate, Plot 122-132, Apapa Oshodi Expressway Lagos Country : Nigeria. Telephone : +234 806761764 Fax : --- E-mail : --- **Manufacturing Site Address:** **M/s THEMIS MEDICARE LIMITED** Sector 6A, Plot No. 16, 17 & 18, IIE, SIDCUL, Haridwar – 249 403, Uttarakhand, INDIA. Telephone: 91-1334-239321/22 Fax: 91-334-239217 E-mail: hwdgmtech@themismedicare.com
8	**Date of Revision of the Text:** Not Applicable
9	**Dosimetry (if applicable):** Not Applicable
10	**Instruction for preparations of Radiopharmaceutical (if applicable):** Not Applicable