2.16 Summary Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT: PINNACLE DICLOFENAC INJECTION (Diclofenac Sodium Injection 75mg/3ml)

2. Composition:
Each ampoule (3ml) contains:
Diclofenac sodium BP..... 75 mg

3. PHARMACEUTICAL FORM
Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Acute exacerbations of rheumatoid arthritis and osteoarthrosis; acute back pain; acute gout; post-operative pain, relief of pain in acute trauma and fractures and renal colic.

4.2 Posology and method of administration
Route of administration: intramuscular injection.

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 alternate buttock be used for the second injection. Diclofenac Sodium Injection should not be given for more than 2 days; if necessary, treatment can be continued with tablets. Diclofenac Sodium Injection should not be administered by the intravenous route.

Renal colic: 1 x 75 mg ampoules intramuscularly. A further ampoule may be administered after 30 minutes if necessary. The total daily dose should not exceed 150 mg.

Elderly: Although the pharmacokinetics of diclofenac are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients as the elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lower dose should be used and the patients should be monitored for GI bleeding during NSAID therapy. (See also 4.4 Special warnings and special precautions for use).

Children: Diclofenac Sodium Injection is not recommended for use in children.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

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• Known hypersensitivity to the active substance sodium metabisulphite 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 (see 4.6).
• Severe hepatic, renal and cardiac failure (see 4.4).
• Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
• Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac 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 warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The concomitant use of Diclofenac Sodium Injection 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.

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.

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug.

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

The sodium metabisulphite present in solution for injection can also lead to isolated severe hypersensitivity reactions and bronchospasm.

Gastro-intestinal effect:
Gastrointestinal bleeding, ulceration or perforation which can be fatal has 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 occurs in patients receiving Diclofenac Sodium Injection, the medicinal product should be withdrawn.

As with all NSAIDs, including diclofenac, close medical surveillance is imperative and particular caution should be exercised when prescribing Diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see 4.8).

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

To reduce the risk of GI toxicity in patient with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly, the treatment should be initiated and maintain at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) 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 such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see 4.5).

Close medical surveillance and caution should also be exercised in patients with ulcerative colitis or Crohn's disease, as their condition may be exacerbated (see 4.8).

Hepatic effects: Close medical surveillance is required when prescribing Diclofenac 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, 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 should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using Diclofenac 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 (see 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

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.

Skin effects
Serious skin reactions, 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, (see 4.8). 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 injection should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Cardiovascular and cerebrovascular effects:
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be reevaluated periodically.

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.

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

Haematological effects:
Use of Diclofenac injection is recommended only for short term treatment. During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, Diclofenac may temporarily inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

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 is used parenterally in patients with bronchial asthma because symptoms may be exacerbated.
SLE and mixed connective tissue disease:
In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8 Undesirable effects).

Female fertility:
The use of diclofenac may impair female fertility and is not recommended in women attempting to conceive. In women who may have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of diclofenac should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

The following interactions include those observed with Diclofenac gastroresistant 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 via inhibition of vasodilatory prostaglandin synthesis. 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 potassiumsparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see 4.4).

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see 4.4).

Anti-coagulants and antiplatelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see 4.4). 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 SSRI may increase risk of gastrointestinal bleeding (see 4.4).

Antidiabetics: Clinical studies have shown that Diclofenac Sodium Injection 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: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. 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 antibiotics: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions.

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

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Potent 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 concentration and exposure to diclofenac due to inhibition of diclofenac metabolism.

Cardiac glycosides: Concomitant use of cardiac glycosides and NSAIDs in patients may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Mifepristone: NSAIDs should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

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 Pregnancy and lactation
Pregnancy:
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%.

The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. During the first and second trimester of pregnancy, diclofenac sodium should not be given unless clearly necessary. If diclofenac sodium is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligohydroamniosis; the mother and the neonate, at the end of pregnancy, to:
- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, diclofenac sodium is contraindicated during the third trimester of pregnancy.

Lactation:

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

Fertility
As with other NSAIDs, the use of Diclofenac 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 should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: 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); Not known: cannot be estimated from the available data.

The following undesirable effects include those reported with either short-term or long-term use.

Table 1

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- Angioneurotic oedema (including face oedema).

Psychiatric disorders

Very rare-Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.

Nervous system disorders

Common- Headache, dizziness.

Rare- Somnolence, tiredness.

Very rare- Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident.

Unknown-Confusion, hallucinations, disturbances of sensation, malaise.

Eye disorders

Very rare- Visual disturbance, vision blurred, diplopia.

Unknown-Optic neuritis.

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, hypotension, 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, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).

Very rare-Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, Stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.

Hepatobiliary disorders

Common- Transaminases increased.
Rare- Hepatitis, jaundice, liver disorder.
Very rare-Fulminant hepatitis, hepatic necrosis, hepatic failure.

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.

Reproductive system disorders

Not known-Impotence.

General disorders and administration site conditions

Common- Injection site reaction, injection site pain, injection site induration
Rare-Oedema Injection site necrosis.

Infections and infestations

Very rare-Injection site abscess.

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment. (see section 4.3 and 4.4 for Contraindications and Special warnings and special precautions for use).

4.9 Overdose

Symptoms:

There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms such as headache, nausea, vomiting**,** epigastric pain, gastrointestinal haemorrhage, diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting 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 haemo-perfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patients clinical condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: analgesic, anti-inflammatory and antipyretic
ATC Code: M01AB05

Mechanism of action
Diclofenac Sodium Injection contains diclofenac sodium, a non-steroidal compound with pronounced antirheumatic, antiinflammatory, 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.

Pharmacodynamic effects
In rheumatic diseases, the anti-inflammatory and analgesic properties of Diclofenac Sodium Injection 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 Injection 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 Injection has also been shown to have a beneficial effect in migraine attacks.

In post-traumatic and post-operative inflammatory conditions, Diclofenac Sodium Injection 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 Injection significantly reduces the need for opioids.

Diclofenac Sodium Injection ampoules 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, and mean peak plasma concentrations of about 2.5 micrograms/mL (8 micromol/L) are reached after about 20 minutes. When 75 mg diclofenac is administered as an intravenous infusion over 2 hours, mean peak plasma concentrations are about 1.9 micrograms/mL

(5.9micromol/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 gastroresistant 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 (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

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'-methoxydiclofenac), 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.

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

Pharmacokinetics in special patient groups
No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed. However, in a few elderly patients a 15-minute intravenous infusion resulted in 50% higher plasma concentrations than expected from the data on young healthy subjects.

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-state plasma levels of the hydroxy metabolites are about 4 times higher than in normal subjects. However, the metabolites are ultimately cleared through the bile.

In patients with chronic hepatitis or non-decompensated cirrhosis, the kinetics and metabolism of diclofenac are the same as in patients without liver disease.

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. In standard preclinical animal studies, there was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. Except for minimal fetal effects at maternally toxic doses, the prenatal, perinatal and postnatal development of the offspring was not affected.

Administration of NSAIDs (including diclofenac) 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 were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of diclofenac 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
Propylene glycol
Benzyl alcohol
Anhydrous sodium sulfite
Water for Injection

6.2 Incompatibilities
Diclofenac Sodium Injection should not be mixed with other injection solutions.

6.3 Shelf life

36 months

6.4 Special precautions for storage
Store below 30°C in a dry place. Do not refrigerate or freeze.
Keep out of reach of children.

6.5 Nature and contents of container
Diclofenac sodium Injection is supplied in packs of 5 or 10 or 20 x 3ml glass ampoules (Type I) with blue spot on neck along with a pack insert.

6.6 Special precautions for disposal
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Pinnacle Health Pharmaceutical & Stires Limited

8. MARKETING AUTHORISATION NUMBER(S)
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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
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10. Date of revision of the text
Will be assigned after approval.