Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diclo 75mg prolonged release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 75 mg of Diclofenac Sodium in a prolonged release formulation.
Excipients: each tablet contains lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Round, flat, two-layered pink and white coloured, prolonged release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and spondylarthritis, psoriatic arthropathy, painful syndrome of the vertebral column, non-articular rheumatism
- Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendonitis, tenosynovitis, bursitis;
- Other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery;
- Post-traumatic and post-operative pain, inflammation, and swelling, e.g. following dental or orthopaedic surgery.
- Painful and/or inflammatory conditions in gynaecology, e.g. primary dysmenorrhoea or adnexitis and menorrhagia.
- Acute gout

4.2 Posology and method of administration

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

For oral administration. The tablets should be swallowed whole with liquid, preferably with meals and must not be divided or chewed.

Adults: The recommended initial daily dose is one or two tablets daily.

The recommended maximum dose is 150mg.
In milder cases, as well as for long-term therapy, 75mg is usually sufficient.

Where the symptoms are most pronounced during the night or in the morning, Diclo 75mg prolonged release tablets should preferably be taken in the evening.

Elderly (patients aged 65 or above): Although the pharmacokinetics of Diclo 75 prolonged release tablets are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs (NSAIDs) should be used with particular caution in such patients who generally are more prone to adverse reactions. In particular it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight and the patient should be monitored for GI bleeding during NSAID therapy (see section 4.4 Special warnings and precautions for use).

Children: Because of their dosage strength, Diclo 75mg prolonged release tablets are not suitable for children and adolescents

Renal impairment
Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3).

No specific studies have been carried out in patients with renal impairment; therefore, no specific dose adjustment recommendations can be made.

Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

Hepatic impairment
Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3).

No specific studies have been carried out in patients with hepatic impairment; therefore, no specific dose adjustment recommendations can be made.

Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.3 and 4.4).

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active gastric or intestinal ulcer, bleeding or perforation
- History of gastrointestinal bleeding or perforation, related 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 section 4.6).
- Hepatic failure
- Chronic Kidney Disease Grade 5 (GFR <15)
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease
- Like other non-steroidal anti-inflammatory (NSAIDs) diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid/aspirin 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; see also gastrointestinal, cardiovascular and cerebrovascular effects outlined below).

The concomitant use of diclofenac with systemic NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided due to the absence of any evidence demonstrating synergistic benefits and the potential for additive undesirable effects (see section 4.5).

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dosage be used in frail elderly patients or those with a low body weight (see section 4.2).

As with other nonsteroidal anti-inflammatory drugs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Like other NSAIDs, Diclo 75mg prolonged release tablets may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Gastrointestinal effects
Gastrointestinal bleeding, ulceration and 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 Diclo 75mg prolonged release tablets, the drug 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 section 4.8). The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses in patient with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3).

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

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. 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 GI risk (see below and section 4.5).

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

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemiccorticosteroids, anticoagulants such as warfarin, anti-platelet agents such as aspirin or selective serotonin-reuptake inhibitors (see section 4.5).

NSAIDs, including diclofenac, may be associated with increased risk of gastro-intestinal anastomotic leak. Close medical surveillance and caution are recommended when using diclofenac after gastro-intestinal surgery.

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

Hepatic effects
Close medical surveillance is required when prescribing Diclo 75mg prolonged release tablets to patients suffering with 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 Diclo 75 mg prolonged release tablets, 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), Diclo 75 prolonged release tablets 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 section 4.3). Monitoring of renal function is recommended as a precautionary measure when using Diclo 75 mg prolonged release tablets in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

Skin effects
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 including diclofenac (see section 4.8). 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. Diclo 75 mg prolonged release tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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)

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or congestive heart failure (NYHA-1), as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that the use of diclofenac particularly at high dose (150mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). To minimize the potential risk of an adverse cardiovascular event in patients taking a NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

Patients with congestive heart failure (NYHA-1) and 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 re-evaluated periodically.

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.

Haematological effects
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of blood counts is recommended.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation. Patients with defects in 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 disease 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), Quinckes'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.

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

4.5 Interaction with other medicinal products and other forms of interactions

The following interactions include those observed with diclofenac prolonged release tablets and/or other pharmaceutical forms of diclofenac.

Observed Interactions to be considered

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as 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 concentration of lithium. Monitoring of 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 (see section 4.4).

Ciclosporin*:* Diclofenac, like other NSAID's, may increase the nephrotoxicity of ciclosporin due to effects on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Drugs known to cause hyperkalemia*:* Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increase serum potassium levels, which should therefore be monitored frequently (see section 4.4)

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

Anticipated Interactions to be considered

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4). Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

Anticoagulants and antiplatelet agents*:* Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4). 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 (SSRI's)*:* Concomitant administration of systemic NSAIDs including diclofenac and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and special precautions for use).

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 agent 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.

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.

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

4.6 Fertility, 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, cardiac malformation, and/or 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 should not be given unless clearly necessary. If diclofenac 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 oligo-hydroamniosis;

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 is contraindicated during the third trimester of pregnancy.

Lactation
Like other NSAIDs, diclofenac passes into the breast milk but in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant (see section 5.2).

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 or other central nervous system disturbances while taking NSAIDs should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table 1) are listed by MedRA system order class. Within each system organ class, the adverse drug reactions are ranked under heading of frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, 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 most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4, Special warnings and precautions for use). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

The following undesirable effects include those reported with diclofenac prolonged-release tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leucopoenia, 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, convulsions, anxiety, tremor, meningitis aseptic, dysgeusia, cerebrovascular accident.
Eye disorders	
Very rare	Visual impairment (blurred vision, diplopia).
Ear and labyrinth disorders	
Common Very rare	Vertigo. Tinnitus, hearing impaired.
Cardiac disorders	
Uncommon*	Palpitations, chest pain, cardiac failure, myocardial infarction.
Not known	Kounis syndrome
Vascular disorders	
Very rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare Very rare	Asthma/bronchospasm (including dyspnoea). Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, decrease appetite.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, 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 (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Not known	Ischaemic colitis
Hepatobiliary disorders	
Common Rare Very rare	Transaminases increased. Hepatitis with or without jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rashes.
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, Henoch-Schonlein purpura, pruritus.
Renal and urinary disorders	

Very rare	Acute renal failure, haematuria, proteinuria, nephritic syndrome, interstitial nephritis, tubule-interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Edema

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

Clinical trial 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 doses (150mg daily) and in long term treatment (see section 4.3 and 4.4*)*.

Oedema, Hypertension and cardiac failure have been reported in association with NSAID treatment.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL-Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

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, consists essentially of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably unlikely to be helpful in accelerating the elimination of NSAIDs, including diclofenac, because of their high protein binding and extensive metabolism.

Activated charcoal may be considered after ingestion of a potentially toxic overdose, and gastric decontamination (e.g. vomiting, gastric lavage) after ingestion of a potentially life-threatening overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group; non-steroidal anti-inflammatory and antirheumatic products, non steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05)

Mechanism of action
Diclofenac 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.

Pharmacodynamic effects

In rheumatic diseases, the anti-inflammatory and analgesic properties of diclofenac 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.

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

Diclofenac prolonged-release tablets are particularly suitable for patients in whom a daily dose of 75mg is appropriate to the clinical picture. The possibility of prescribing the medicinal product in a single daily dose considerably simplifies long-term treatment and helps to avoid the possibility of dosage errors.

There is limited clinical trial experience of the use of diclofenac in Juvenile Rheumatoid Arthritis (JRA)/Juvenile Idiopathic Arthritis (JIA) paediatric patients. In a randomized, double-blind, 2-week, parallel group study in children aged 3-15 years with JRA/JIA, the efficacy and safety of daily 2-3 mg/kg BW diclofenac was compared with acetylsalicylic acid (ASS, 50-100 mg/kg BW/d) and placebo – 15 patients in each group. In the global evaluation, 11 of 15 diclofenac patients, 6 of 12 aspirin and 4 of 15 placebo patients showed improvement with the difference being statistically significant ($p < 0.05$). The number of tender joints decreased with diclofenac and ASS but increased with placebo. In a second randomized, double-blind, 6-week, parallel group study in children aged 4-15 years with JRA/JIA, the efficacy of diclofenac (daily dose 2-3 mg/kg BW, n=22) was comparable with that of indomethacin (daily dose 2-3mg/kg BW, n=23).

5.2 Pharmacokinetic properties

Absorption:
Judged by urinary recovery of unchanged diclofenac and its hydroxylated metabolites, the same amount of diclofenac is released and absorbed from diclofenac prolonged-release tablets as from gastro-resistant tablets. However, the systemic availability of diclofenac from diclofenac prolonged-release tablets is on average about 82% of that achieved with the same dose of diclofenac administered in the form of gastro-resistant tablets (possibly due to release-rate dependent "first pass" metabolism). As a result of a slower release of the active substance from diclofenac prolonged-release tablets, peak concentrations attained are lower than those observed following the administration of gastro-resistant tablets.

Mean peak concentrations of 0.5 micrograms/mL or 0.4 micrograms/mL (1.6 or 1.25 micromol/L) are reached on average 4 hours after ingestion of a prolonged-release tablet of 100 mg or 75 mg.

Food has no clinically relevant influence on the absorption and systemic availability of diclofenac prolonged-release tablets.

On the other hand, mean plasma concentrations of 13 ng/mL (40 nmol/L) can be recorded at 24 hours (16 hours) after administration of diclofenac prolonged-release tablets 100 mg (75 mg).

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

Trough concentrations are around 22 ng/mL or 25 ng/mL (70 nmol/L or 80 nmol/L) during treatment with diclofenac prolonged-release tablets 100 mg once daily or 75 mg twice daily.

The amount absorbed is linearly related to the dose strength. Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

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 the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma, and 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, 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 263 ± 56mL/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.

Special Populations
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-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.

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.

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. 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 (see sections 4.3 Contraindications and 4.6 Fertility, pregnancy and lactation).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Hypromellose
Microcrystalline cellulose
Calcium hydrogen phosphate dihydrate
Maize starch
Sodium starch glycollate
Colloidal anhydrous silica
Magnesium stearate
Red ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in original container in order to protect from light and/or moisture.

6.5 Nature and contents of container

Blisters of both polypropylene/aluminium foil and PVC/PVDC/aluminium foil. Packs of 60 tablets, sample packs of 10 tablets are also available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/106/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 May 1999
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10 DATE OF REVISION OF THE TEXT

November 2019