Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac Potassium 50 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 mg of diclofenac potassium.

Excipient with known effect:
Each tablet contains 0.24 mg of lecithin soya (E322)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Reddish brown, circular, coated, biconvex.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Short-term treatment of all grades of pain and inflammation in following acute conditions:

- Post traumatic pain, inflammation and swelling, e.g. due to sprains.
- Acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendonitis, tenosynovitis, bursitis.
- 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 associated menorrhagia.
- Migraine attacks.
- Acute gout.
- Painful syndromes of the vertebral column.
- Non-articular rheumatism.
- As an adjuvant in severe painful inflammatory infections of the ear, nose or throat, e.g. pharyngotonsillitis, otitis. In keeping with general therapeutic principles, the underlying disease should be treated with basic therapy, as appropriate. Fever alone is not an indication.

4.2 Posology and method of administration

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

Adults
The recommended daily dose is 100-150mg in two or three divided doses. For milder cases, 75-100 mg daily in two or three divided doses is usually sufficient. The recommended maximum daily dose of diclofenac is 150 mg.
In migraine an initial dose of 50 mg should be taken at the first signs of an impending attack.
In cases where pain relief within 2 hours after the first dose is not sufficient, a further dose of 50 mg may be taken.
If needed, further doses of 50 mg may be taken at intervals of 4-6 hours, not exceeding a total dose of 200 mg per day.

Paediatric population
Diclofenac Potassium tablets are not recommended for children under 14 years of age.

For children over 14 years of age, the recommended daily dose of diclofenac suppositories and tablets 12.5 to 25 mg is 75-100 mg in three or four divided doses.
The use of diclofenac potassium in migraine attacks has not been established in children.

Elderly
Although the pharmacokinetics of diclofenac 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 (see section 4.4) and the patient should be monitored regularly for GI bleeding during NSAID therapy.

Method of administration
For oral administration.
To be taken preferably with or after food.
The tablets should be swallowed whole with liquid.

4.3 Contraindications

- Hypersensitivity to diclofenac potassium or 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 NSAIDs therapy.

Active, or history of recurrent peptic ulcer / haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Like other NSAIDs, diclofenac is also contraindicated in patients in whom attacks of asthma, acute rhinitis or urticaria are precipitated by acetylsalicylic acid / aspirin, or other non- steroidal anti-inflammatory drugs.
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Severe hepatic and renal failure (see section 4.4).
- During the last trimester of pregnancy (see section 4.6)
- This product contains soya. If you are allergic to peanut or soya, do not use this medicinal product.
- Women of childbearing potential who are not using effective contraception (see sections 4.4, 4.6 and 4.8)

4.4 Special warnings and precautions for use

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

Like other NSAIDs, diclofenac potassium may mask the signs and symptoms of infection due to its pharmacodynamic properties.

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.

In women of childbearing potential (see also section 4.3) diclofenac potassium must not be used unless they use effective contraception and have been advised of the risks of taking the product if pregnant (see section 4.6).

Respiratory disorders:
Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

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.

Cardiovascular, Renal and Hepatic Impairment:
The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, the elderly or those recovering from major surgery. Renal Function should be monitored in these patients (see also section 4.3). Effects on renal function are usually reversible on withdrawal of diclofenac potassium.

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 diclofenac in such cases. Discontinuation of therapy is usually followed by recovery to the pre-treatment state.

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, 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 potassium should be discontinued. Hepatitis may occur without prodromal symptoms. Caution is called for when using diclofenac potassium in patients with hepatic porphyria, since it may trigger an attack.

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 risk 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.

Appropriate monitoring and advice are required for patients with a history of hypertension 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 daily) and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Gastrointestinaleffects:
GI 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 GI events. They generally have more serious consequences in the elderly. When GI bleeding or ulceration occurs in patients receiving diclofenac potassium, the treatment 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 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 patients 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 GI 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/aspirin, or other medicinal products likely to increase gastrointestinal risk (see below and 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.

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.

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 (see section 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 section 4.8).

SLE and mixed connectivetissue 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).

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 section 4.8). Patients appear to be at the highest risk for 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 Potassium 50mg Film-coated Tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Hypersensitivity reactions:
As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can 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.

Impaired femalefertility:
The use of Diclofenac Potassium tablets 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 Potassium tablets should be considered.

Haematologicaleffects:
During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.
As with other NSAIDS, diclofenac potassium may temporarily inhibit platelet aggregation (see section 4.5). 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. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. This is particularly important in the elderly.
Use of diclofenac is only recommended for short term treatment.

4.5 Interaction with other medicinal products and other forms of interactions

Other analgesics (including cyclooxygenase-2 selective inhibitors) and corticosteroids: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of gastrointestinal adverse effects (see section 4.4).

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 (see section 4.4).

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

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 increase plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

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 is increased.

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

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

Anticoagulants and anti-platelet 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, 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.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients already receiving an NSAID.

Antidiabetic agents: Clinical studies have shown that diclofenac potassium 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 to the dosage of hypoglycaemic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of systemic NSAIDs, including diclofenac, and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

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

Medicinal products that inhibit the CYP2C9 enzyme: The metabolism of diclofenac is catalysed by the CYP2C9 enzyme. Simultaneous treatment with medicinal products that inhibit this enzyme (e.g. fluconazole, sulfinpyrazone and voriconazole) is likely to lead to higher plasma concentration of diclofenac. Medicinal products that induce CYP2C9 (e.g. rifampicin, carbamazepine or barbiturates) may reduce the plasma concentration of diclofenac to sub-therapeutic levels.

Bile acid-binding anion exchangers: With simultaneous administration of diclofenac and colestipol or colestyramine the absorption of diclofenac decreased by approx. 30 and 60% respectively. Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol or colestyramine.

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 and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk of 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 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-hydroamnios 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 in small amounts. Therefore, diclofenac should not be administered during breast feeding in order to avoid undesirable effects in the infant.

Women of childbearing potential
Women of childbearing potential must be informed about the risk of teratogenicity prior to treatment with diclofenac-misoprostol. Treatment must not be initiated until pregnancy is excluded, and women should be fully counselled on the importance of adequate contraception while undergoing treatment. If pregnancy is suspected, treatment must be immediately discontinued (see section 4.3, 4.4 and 4.8).

4.7 Effects on ability to drive and use machines

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

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 (can not be estimated from the available data).

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). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of coilitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

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

Blood and lymphatic system disorders	
Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic anaemia 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, nightmares, irritability, psychotic disorders
Nervous system disorders	
Common	Headache, dizziness
Rare	Somnolence
Very rare	Paraesthesias, memory impairment, convulsions, 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
Not Known	Kounis sydrome
Vascular disorders	
Very rare	Hypertension, vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Bronchospasm
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)
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	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, pruritis
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis

General disorders and administration site conditions	

Rare	Oedema
Congenital, familial and genetic disorders	
Common	Foetal malformation

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

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 doses (150 mg daily) and in long term treatment (see sections 4.3 and 4.4).

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 16762517. Website: www.hpr a.i e; 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 nausea, vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure, liver damage, hypotension, and respiratory depression and possibly coagulation disorders are possible.

Therapeutic measures

Management of acute poisoning with NSAIDS consists essentially 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. Frequent or prolonged convulsions should be treated with intravenous diazepam.

Special measures such as forced diuresis, dialysis, or haemoperfusion are probably unlikely to be helpful in accelerating the eliminating NSAIDs due to the 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: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances (NSAID) (ATC code: M01A B05).

Mode of action: Diclofenac potassium is a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin synthetase (cyclo-oxygenase).

Diclofenac potassium in vitro does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings. Diclofenac Potassium tablets have a rapid onset of action which makes them particularly suitable for the treatment of acute painful and inflammatory conditions.

In migraine attacks, diclofenac potassium has been shown to be effective in relieving the headache and in improving the accompanying nausea and vomiting symptoms.

5.2 Pharmacokinetic properties

Absorption: Diclofenac is rapidly and completely absorbed from Diclofenac Potassium tablets. The absorption sets in immediately after administration and the same amount is absorbed as from an equivalent dose of diclofenac sodium gastro-resistant tablets. Mean peak plasma concentrations of 3.8µmol/L are attained after 20-60 minutes after ingestion of one

tablet of 50mg. Ingestion together with food has no influence on the amount of diclofenac absorbed although onset and rate of absorption may be slightly delayed.

The amount absorbed is in linear proportion to the size of the dose.

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 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.

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 $\pm$ 56 ml/min (mean value $\pm$ 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.

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

Diclofenac did not influence fertility of the parent animals (rats) nor the pre- peri-, and postnatal development of the offspring. No teratogenic effects were detected in mice, rats and rabbits. No mutagenic effects could be demonstrated in various in vitro and in vivo experiments, and no carcinogenic potential was detected in long-term studies in rats and mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal anhydrous
Sodium starch glycolate Type A
Povidone
Maize starch
Calcium hydrogen phosphate anhydrous
Magnesium stearate

Coating:
Polyvinyl alcohol partially hydrolysed
Titanium dioxide (E171)
Talc
Lecithin soya (E322)
Iron oxide red (E172)
Xanthan gum (E145)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

Blister: Store in the original package in order to protect from moisture.
Container: Keep the container tightly closed in order to protect from moisture.

6.5 Nature and contents of container

Al/Al Blister or PP Tablet Container with LDPE Cap with desiccant

Pack sizes: 7, 14, 21, 28, 30, 50, 56, 60, 84, 100 or 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/138/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th August 2009
Date of last renewal: 28th August 2014

10 DATE OF REVISION OF THE TEXT

November 2019