SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac Tablets BP 50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each enteric-coated tablet contains Diclofenac Sodium 50 mg.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Light-brown film coated biconvex tablet.

4.1 Therapeutic indications

Relief of all grades of pain and inflammation in a wide range of conditions, including:

(i) arthritic conditions: rheumatoid arthritis, osteo-arthritis, ankylosing spondylitis, acute gout,

(ii) acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,

(iii) other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

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.
To be taken preferably with or after food.

Adults: 75-150 mg daily in two or three divided doses.

The recommended maximum daily dose is 150 mg.

Special populations

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 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 also section 4.4) and the patient should be monitored regularly for GI bleeding during NSAID therapy.

Cardiovascular and significant cardiovascular risk factors

Diclofenac is contraindicated in patients with established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (see section 4.3 Contraindications).

Patients with congestive heart failure (NYHA-I) or significant risk factors for cardiovascular disease should be treated with diclofenac only after careful consideration. Since cardiovascular risks with diclofenac may increase with dose and duration of exposure, the lowest effective daily dose should be used and for the shortest duration possible (see section 4.4 Special warnings and precautions for use).

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).

Paediatric population

For children over 14 years of age, the recommended daily dose is 75-100 mg in two or three divided doses. Diclofenac tablets are not recommended for children under 14 years of age.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients.

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, perforation or bleeding).

Last trimester of pregnancy (see section 4.6)

Severe hepatic, renal or cardiac failure (see section 4.4).

Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, acute rhinitis or angioedema are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs.

Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

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 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 (see section 4.5).

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 (see section 4.2).

As with other NSAIDs including diclofenac, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug (see section 4.8). 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, Diclofenac 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 as it contains lactose.

The tablets contain methyl and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

This medicine contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium free'.

Gastrointestinal effects

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, 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 section 4.8).

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses including diclofenac 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 (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. proton pump inhibitors or misoprostol) 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 (see section 4.5).

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 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 these condition may be exacerbated (see section 4.8).

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.

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 (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 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.

Skin effects

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, **and generalised bullous fixed drug eruption** have been reported very rarely in association with the use of **diclofenac** (see section 4.8). Patients appear to be at 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 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular and cerebrovascular effects

Patients with congestive heart failure (NYHA-I) or 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.

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure (NYHA-I) as fluid retention and oedema have been reported in association with NSAID therapy including diclofenac.

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.

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

Use of Diclofenac tablets 50mg are 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 reversibly inhibit platelet aggregation (see anticoagulants in section 4.5). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities 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.

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.

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).

Female fertility

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 (see section 4.6).

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 interaction

The following interactions include those observed with Diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac.

Lithium: If used concomitantly, diclofenac may raise plasma concentrations 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 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 (see section 4.4).

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

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs (including aspirin) or corticosteroids may increase the frequency of gastrointestinal undesirable effects bleeding or ulceration (see section 4.4). Avoid concomitant use of two or more NSAIDs (see section 4.4).

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 reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly (see section 4.4). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

Selective serotonin reuptake inhibitors (SSRIs): Concomitant administration of SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics: Clinical studies have shown that Diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of both hypoglycaemic and hyperglycaemic effects necessitating changes in the dosage of the antidiabetic agents during treatment with diclofenac. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Methotrexate: 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 treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

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

Quinolone antibacterials:. There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs. Convulsions may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

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 voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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

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

Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostaglandin 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 (a NSAID).

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.
From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, 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 or second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (with premature constriction 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 (see section 4.3 and 5.3).

Lactation

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

Female 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 (see also section 4.4).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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, neutropenia, leucopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis
Immune system disorders	
Rare Very rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock) Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmares, irritability, psychotic disorder.
Nervous system disorders	
Common Rare Very rare Not known	Headache, dizziness. Somnolence, tiredness. Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis taste disturbances, cerebrovascular accident. Disturbances of sensation, confusion, hallucinations, malaise
Eye disorders	
Very rare Not known	Visual disturbance, vision blurred diplopia. Optic neuritis.
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, hypotension.
Respiratory, thoracic and mediastinal disorders	
Rare Very rare Not known	Asthma (including dyspnoea). Pneumonitis. Bronchospasm
Gastrointestinal disorders	
Common Rare Very rare Not known	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain flatulence, anorexia. Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation, (sometimes fatal, particularly in the elderly). Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, oesophageal lesions, diaphragm-like intestinal strictures, pancreatitis, colonic damage. Ischaemic colitis
Hepatobiliary disorders	
Common Rare Very rare Not known	Transaminases increased. Hepatitis, jaundice, liver disorder. Fulminant hepatitis, hepatic necrosis, hepatic failure Abnormal liver function.
Skin and subcutaneous tissue disorders	
Common Rare Very rare Not known	Rash Urticaria 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. **Fixed drug eruption, Generalised bullous fixed drug eruption**
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary

	necrosis. Acute renal insufficiency.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence

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

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).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antiinflammatory and Antirheumatic products, Non-steroids; Acetic Acid Derivatives and Related Substances

ATC Code: M01AB05

Diclofenac is a non-steroidal agent with marked analgesic, anti-inflammatory and anti-pyretic properties. It is an inhibitor of prostaglandin synthetase, (cyclo-oxygenase).

Diclofenac sodium *in-vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

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

Bioavailability

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

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed.

Distribution

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

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 (see section 4.6).

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

The total systemic clearance of diclofenac in plasma is 263 ± 56 mL/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.

Repeated oral administration of Diclofenac tablet for 8 days in daily doses of 50 mg t i d does not lead to accumulation of diclofenac in the plasma.

About 60% of the administered dose is excreted in the urine in the form of the glucuronide conjugate of the intact molecule and as metabolites, most of which are also converted to glucuronide conjugates. Less than 1% is excreted as unchanged substance. The rest of the dose is eliminated as metabolites through the bile in the faeces.

Characteristics in patients

The age of the patient has no influence on the absorption, metabolism or excretion of diclofenac.

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 <10 mL/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

There are no pre-clinical data of relevance to the prescriber that are additional to that already included in other sections of the SPC.

6.1 List of excipients

Core ingredients:
Povidone
Maize starch
Lactose
Magnesium stearate
Purified talc

Coating ingredients:
Methacrylic Acid-Ethyl Acrylate Copolymer (1:1) Dispersion 30 per cent
Hypromellose
Yellow Iron Oxide (E172)
Red Iron Oxide (E172)
Titanium Dioxide (E171)
Sodium Hydroxide
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Disodium Edetate (E385)

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in container provided. Do not store above 25°C

6.5 Nature and contents of container

Aluminium foil/PVC blister packs in a cardboard carton containing 28, 50, 84 and 100 tablets. (Not all pack sizes may be marketed).

Polypropylene container with a polyurethane foam insert and tamper-evident cap containing 50 and 100 tablets.

6.6 Special precautions for disposal

None.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0220

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