DICLOFENAC SODIUM 50 MG CAPLETS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diclofenac sodium 50 mg caplets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains 50 mg diclofenac sodium.

3. PHARMACEUTICAL FORM

Caplet

Plain yellow bconvex caplet with a break line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of:

- Inflammatory and degenerative forms of rheumatism such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis including spondylarthritis
- Periarthritis humeroscapularis
- Painful postoperative and post-traumatic inflammation, and swelling, e.g. following dental or orthopaedic surgery
- Primary dysmenorrhoea
- Diseases accompanied by fever, especially for short term use as adjuvant in chemotherapy in inflammatory infections

Fever as such is not an indication

Since the formulation of this medicinal product is a delayed release formulation, the product is not indicated when a quick onset of efficacy (relief of pain) is required.

4.2 Posology and method of administration

General information

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

Posology

Adults

There is no general dosage information for adults. For the dose regimen in adults we refer to the paragraphs containing specific information per indication.

Rheumatoid arthritis

The initial dose for adults is 150 mg daily as a rule, the maintenance dose is 75-100 mg daily. For the treatment of juvenile rheumatoid arthritis a daily dose of 1.5 till 2 mg per kg bodyweight divided in 2 to 3 doses is recommended.

Osteoarthritis

Depending on the severity of the pain the initial dose amounts to 100-150 mg daily, the maintenance dose is usually 75-100 mg daily.

Periarthritis humeroscapularis

Depending on the severity of the pain the initial dose amounts to 150 mg daily. Thereafter the dose is diminished depending on the symptoms.

Painful postoperative and posttraumatic inflammation and swelling

As a rule the initial dose amounts to 150 mg daily. Thereafter the dose is diminished depending on the symptoms.

Symptomatic treatment of primary dysmenorrhoe

In primary dysmenorrhoe the dose should be individually adjusted.

In general the dose varies between 50 and 150 mg daily.

The initial dose amounts to 50-100 mg. This dose may be raised in the course of several menstrual cycles up to a maximum of 200 mg daily.

Treatment should be started upon appearance of the first symptoms and, depending on the symptomatology, continued for a few days.

Diseases accompanied by fever, especially for short term use as adjuvant in chemotherapy in inflammatory diseases

A low dose of 0.5 mg/kg body weight daily, divided into 2-3 doses is recommended.

Special populations

Renal impairment

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

No specific studies have been conducted in patients with impaired renal function; therefore, no specific dose adjustment is recommended. Caution is advised when diclofenac is administered to patients with mild to moderate renal impairment (see section 4.4).

Hepatic impairment

Diclofenac is contraindicated in patients with severe hepatic impairment or liver failure (see section 4.3).

No specific studies have been conducted in patients with impaired liver function; therefore, no specific dose adjustment is recommended. Caution is advised when diclofenac is administered to patients with mild to moderate liver impairment (see section 4.4).

Paediatric population

There is no general dosage information for children. For the dose regimen in children we refer to the paragraph containing specific information on the indication rheumatoid arthritis.

Diclofenac sodium caplets of 50 mg are not suitable for use in children due to the dose strength.

Elderly

Elderly patients should be treated with the lowest possible effective dose (see also section 4.4).

Method of administration

The total daily dose should be divided into 2 or 3 doses.

The caplets should be swallowed whole with at least half a glass (200 ml) of liquid.

The caplets can be taken at meal times.

4.3 Contraindications

" Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

" Active gastric or intestinal ulcer, bleeding, or perforation (see also section 4.4)

" History of gastrointestinal bleeding or perforation, related to previous NSAID therapy (see sections 4.4 and 4.8)

" Active or history of recurrent peptic ulcer/hemorrhage (two or more distinct episodes of proven ulceration or bleeding) (see section 4.4 and 4.8)

" Last trimester of pregnancy (see section 4.6)

" Severe hepatic impairment and liver failure (see section 4.4)

" Severe renal impairment and renal failure (see section 4.4)

" Like other NSAIDs, diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAIDs (see sections 4.4 and 4.8).

" Active bleedings or bleeding disorders

" Blood dyscrasias

" Bone marrow depression

" 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 gastrointestinal and cardiovascular risks below). Diclofenac sodium should be administered with caution to patients suffering from systemic lupus erythematosus and mixed connective tissue disease.

The use of diclofenac sodium, as with any medicinal product known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or are undergoing investigation of infertility, withdrawal of diclofenac sodium should be considered.

Gastrointestinal (GI) effects

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have 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 GI disorders or with a history suggestive of gastric or intestinal ulceration, bleeding or perforation (see section 4.8). The risk of GI bleeding is higher with increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

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) or other medicinal products likely to increase gastrointestinal 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). Caution is recommended 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 medicinal products such as acetylsalicylic acid (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).

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.

Skin reactions

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, 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. Diclofenac should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

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

Hepatic effects

Close medical surveillance is required when prescribing diclofenac to patients with impaired hepatic function, as their condition may be exacerbated.

As with other NSAIDs, including diclofenac, values of one or more liver enzymes may increase. During prolonged treatment with diclofenac, regular monitoring of hepatic function is indicated as a precautionary measure. If abnormal liver function tests persist or worsen, if clinical signs or symptoms consistent with liver disease develop, or if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur with use of diclofenac without prodromal symptoms.

Caution is called for when using diclofenac in patients with hepatic porphyria, since it may trigger an attack.

Renal effects

As fluid retention and oedema have been reported in association with NSAID therapy, including diclofenac, particular caution is called for in patients with impaired cardiac or renal function, history of hypertension, the elderly, patients receiving concomitant treatment with diuretics or medicinal products that can significantly impact renal function, and in those patients with

substantial extracellular volume depletion from any cause, e.g. before or after major surgery. 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.

When NSAIDs including diclofenac are combined with diuretics, ACE inhibitors or angiotensin II receptor antagonists, the risk of worsening of renal function, including possible acute renal failure may be increased in some patients, especially when renal function is compromised (see section 4.5).

Cardiovascular and cerebrovascular effects

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

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 (150 mg daily) and in long term treatment.

Patients with congestive heart failure (NYHA I) or significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration (see section 4.3 for which cardiovascular patients diclofenac should not be prescribed).

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 be alert for signals and symptoms of severe arterial thrombotic events (e.g. chest pain, shortness of breath, weakness, delayed speaking) that may occur without warning signs. Patients should be instructed to consult a doctor immediately in these cases.

Haematological effects

During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended.

Like other NSAIDs, diclofenac may temporarily inhibit platelet aggregation and prolong bleeding time. Patients with defects of haemostasis should be carefully monitored.

Elderly

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.

Elderly patients are more likely to suffer from impaired renal, cardiovascular or hepatic function, so careful supervision is required.

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

Interaction with NSAIDs

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).

Masking signs of infection

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

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications. To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of [Nationally completed name, 50 mg, gastro-resistant tablet] in case of varicella infection.

Diclofenac sodium caplets contains sodium, lactose and hydrogenated castor oil

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

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains hydrogenated castor oil, which may cause stomach upset and diarrhoea.

4.5 Interaction with other medicinal products and other forms of interaction

A. Observed interactions to be considered Potent CYP2C9 inhibitors

Caution is recommended when co-prescribing diclofenac with CYP2C9 inhibitors (such as fluconazole, amiodarone, voriconazole and sulfinpyrazone), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism. Co-administration of voriconazole resulted in 78% and 114% increase in diclofenac AUC and Cmax, respectively.

Lithium

If used concomitantly, diclofenac may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin

If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive medicinal products

NSAIDs including diclofenac may reduce the effect of diuretics and antihypertensive medicinal products. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. When NSAIDs including diclofenac are combined with diuretics, ACE inhibitors or angiotensin II receptor antagonists, the risk of worsening of renal function, including possible acute renal failure (which is usually reversible) may be increased in some patients, especially when renal function is compromised (e.g. dehydrated or elderly patients). Therefore, the combination should be administered with caution, especially in the elderly. 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 NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. In addition, it has been reported that ciclosporin can enhance the plasma concentrations of diclofenac by about 100%. Therefore, diclofenac should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Medicinal products known to cause hyperkalaemia

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).

Quinolone antibacterials

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

B. **Anticipated interactions to be considered Other NSAIDs and corticosteroids**

Concomitant administration of diclofenac together with other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4). Concomitant administration of acetylsalicylic acid decreases the plasma concentration of diclofenac, without compromising clinical efficacy.

Anticoagulants and anti-platelet medicinal products

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. Close monitoring of such patients is therefore recommended.

Selective serotonin reuptake inhibitors (SSRIs)

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

Antidiabetics

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

Phenytoin

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

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.

Colestipole and colestyramine

Colestipole/colestyramine may delay or reduce the absorption of diclofenac. It is therefore recommended that diclofenac should be taken at least 1 hour before, or 4 to 6 hours after, the administration of colestipole/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 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 inhibitors 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 (see sections 4.3 and 5.3).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

This medicinal product has no or negligible influence on the ability to drive and use machines. However, patients experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Adverse drug reactions from clinical trials and/or spontaneous or literature cases (Table below) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by 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 to <1/10); uncommon (?1/1,000 to <1/100); rare (?1/10,000 to <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 diclofenac gastro-resistant caplets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Table: Adverse drug reactions

Blood and lymphatic system disorders

Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis

Immune system disorders

Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock)

Very rare: Angioedema (including face oedema)

Psychiatric disorders

Very rare: Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, anxiety

Nervous system disorders

Common: Headache, dizziness

Rare: Somnolence

Very rare: Paraesthesia, memory impairment, convulsion, tremor,meningitis aseptic, dysgeusia, cerebrovascular accident

Eye disorders

Very rare: Decreased vision, vision blurred, diplopia

Ear and labyrinth disorders

Common : Vertigo

Very rare: Tinnitus, hearing impaired

Cardiac disorders

Uncommon*: Myocardial infarction, cardiac failure, palpitations, chest pain

Vascular disorders

Very rare: Hypertension, vasculitis

Respiratory, thoracic and mediastinal disorders

Rare: Asthma (including dyspnoea)

Very rare: Pneumonitis

Gastrointestinal disorders

Common: Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain,flatulence, decreased 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, glossitis, oesophageal disorder, intestinal diaphragm disease, pancreatitis

Frequency not known :Ischaemic colitis

Hepatobiliary disorders

Common: Transaminases increased

Rare: Hepatitis, jaundice, liver disorder

Very rare: Hepatitis fulminant, hepatic necrosis, hepatic failure

Skin and subcutaneous tissue disorders

Common: Rash

Rare: Urticaria

Very rare: Dermatitis bullous, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, alopecia, photosensitivity reaction, purpura, Henoch-Schönlein purpura, pruritus

Renal and urinary disorders

Very rare: Renal failure acute, haematuria, proteinuria, nephrotic syndrome, tubulo-interstitial nephritis, renal papillary necrosis

General disorders and administration site conditions

Rare: Oedema

* The frequency reflects data from the long-term treatment with high-dose diclofenac (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 (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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

There is no typical clinical picture resulting from diclofenac overdose. Overdose can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs, including diclofenac, essentially consists of supportive measures and symptomatic treatment. Supportive measures and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastrointestinal disorder, and respiratory depression.

Special measures such as forced diuresis, dialysis or haemoperfusion are probably of no help in eliminating NSAIDs, including diclofenac, due to the high protein binding and extensive metabolism.

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: Antiinflammatory and antirheumatic products, non-steroids,

ATC code: M01AB05

Mechanism of action

Diclofenac sodium caplets 50 mg contains the prostaglandin synthetase inhibitor diclofenac sodium. This is a phenylacetic acid derivative with anti-inflammatory, analgesic and antipyretic properties. Inhibition of prostaglandin biosynthesis (demonstrated in experiments), is considered fundamental to its mechanism of action. Prostaglandins play a major role in causing of inflammation, pain and fever.

Pharmacodynamic effects

In rheumatic diseases the anti-inflammatory and analgesic properties of diclofenac sodium 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 painfull postoperative inflammations and swelling, diclofenac rapidly relieves both spontaneous pain and pain on movement and reduces inflammation and swelling.

Clinical studies have also revealed that, in primary dysmenorrhoea, diclofenac sodium is capable of relieving the pain and reducing the extent of bleeding.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is completely absorbed from the gastro-resistant caplets after their passage through the stomach. Although absorption is rapid, its onset may be delayed due to the gastro-resistant coating of the tablet.

Mean peak plasma concentrations of 1.5 microgram/ml (5 micromol/l) are attained on average 2 hours after ingestion of one tablet of 50 mg.

The passage of a tablet through the stomach is slower when ingested with or after a meal than when it is taken before a meal. The amount of diclofenac absorbed remains the same. For this reason diclofenac sodium caplets 50 mgshould preferably be ingested before meals.

Since about half the active substance is metabolised during its first passage through the liver (first pass effect), the absolute oral bioavailability is approximately 50%.

Pharmacokinetic behaviour does not change after repeated administration. No accumulation occurs provided the recommended dosage intervals are observed.

The plasma concentrations attained in children given equivalent doses (mg/kg body weight) are similar to those obtained in adults.

Distribution

Diclofenac is bound to serum proteins at a rate of 99.7%, mainly to albumin (99.4%).

The apparent volume of distribution calculated is 0.12-0.17 l/kg.

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 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 and its metabolites cross the placenta and traces of diclofenac have been found in the milk of lactating women (100 ng/ml). The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose.

Biotransformation

The biotransformation of diclofenac takes place partly by glucuronidation of the intact molecule, but mainly by single and multiple hydroxylation and methoxylation, resulting in several phenolic metabolites (3'-hydroxy-, 4'-hydroxy, 5'-hydroxy, 4',5'-dihydroxy-, 3'-hydroxy-4'-methoxy-diclofenac), most of which are converted to glucuronide conjugates. Two of these phenolic metabolites are biologically active, but to a smaller 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. One metabolite, 3'-hydroxy-4'-methoxy-diclofenac has a much longer plasma half-life. However, this metabolite is virtually inactive.

About 60% of the administered dose is excreted in the urine in the form of metabolites from one of these processes; less than 1% is excreted as unchanged substance. The remainder of the dose is eliminated as metabolites through the bile in the faeces.

Linearity/non-linearity

The amount absorbed is linearly related to the size of the dose.

Special populations

No relevant age-dependent differences in the absorption, metabolism or excretion of the active substance have been observed.

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 dose schedule. At a creatinine clearance of below 10 ml/min, the theoretical steady-state plasma levels of hydroxy-metabolites are about 4 times higher than in normal subjects.

However, the metabolites are ultimately cleared through the bile.

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans in the intended therapeutic doses. These data are based on conventional studies of acute and repeated dose toxicity, genotoxicity, mutagenicity and carcinogenicity.

In studies on reproduction toxicity the following results were found: 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 foetal survival, and intrauterine growth retardation in rats.

Diclofenac had no influence on the fertility of parent animals in rats, showed no evidence of a teratogenic potential in standard embryo-foetal developmental studies in mice, rats or rabbits, and did not affect the prenatal, perinatal and postnatal development of the offspring with the exception of foetal effects at maternally toxic doses.

The 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 and 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Microcrystalline cellulose

Lactose monohydrate

Magnesium stearate

Maize starch

Povidone K30

Sodium starch glycolate type A

Hypromellose

Polyoxyl hydrogenated castor oil

Yellow iron oxide (E 172)

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

The caplets are packed in PVC/ Aluminium blisters and inserted in a carton of 1 x 10's

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Auscel laboratories limited

Plot 40799 Shinco road

Rayfield , Jos, Plateau State.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

Not applicable