SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Enstar XL 100mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 100mg of the active substance Diclofenac sodium

Excipient(s) with known effect

Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off white, Circular, biconvex tablets with D4 embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In the management of chronic conditions, such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

4.2 Posology and method of administration

For oral administration.

Adults: One tablet once daily, taken whole with liquid, preferably at meal times.

Elderly: The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children: Diclofenac sodium is not recommended for use in children as dosage recommendations and indications for use in this group of patients have not been established.

To be taken preferably with or after food.

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active, gastric or intestinal ulcer, bleeding or perforation.
- History of upper gastrointestinal bleeding or perforation, related to previous NSAID's therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Last trimester of pregnancy (see section 4.6).
- Severe hepatic, renal and cardiac failure (see section 4.4).
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), Diclofenac is also contraindicated in patients in whom attacks of asthma, urticaria, angioedema or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other NSAIDs.

4.4 Special warnings and precautions for use

In all patients:
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).

Monitoring of renal function, hepatic function (elevation of liver enzymes may occur) and blood counts should be performed on long-term NSAID patients, as a precautionary measure.
The concomitant use of Enstar XL 100mg tablets 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).

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.

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

General:

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

Like other NSAIDs, diclofenac may mask the signs and symptoms of the 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.

Cardiovascular and cerebrovascular effects:
Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly at high dose (150 mg daily) and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

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

As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Gastro-intestinal 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 and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

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.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment. Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors (SSRIs) or anti-platelet agents such as acetylsalicylic acid (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Diclofenac, the treatment should be withdrawn.

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).

Patients with a history of haematemesis or melaena should be carefully observed.

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 Enstar XL 100mg Tablets 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, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (e.g. eosinophilia, rash), Enstar XL 100mg Tablets should be discontinued.

Hepatitis may occur with 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 NSAIDs 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 therapy is usually followed by recovery to the pre-treatment state.

The importance of prostaglandins in maintaining renal blood flow should be taken into account in patients with impaired cardiac or renal function, those being treated with diuretics or recovering from major surgery.

Effects on renal function are usually reversible on withdrawal of diclofenac.

Skin effects:

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, 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 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. Enstar XL 100mg Tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.

Haematological effects:

Care should be taken when treating patients with haematological abnormalities, or bleeding diathesis. Use of Enstar XL 100mg Tablets is recommended only for short term treatment. During prolonged treatment with diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Like with NSAIDs Enstar XL 100mg Tablets may temporarily

inhibit platelet aggregation. Patients with defects of haemostasis should be carefully monitored.

Pre-existing asthma:
In patients with asthma, seasonal allergic rhinitis, swelling of the nasal mucosa (i.e. nasal polyps), chronic obstructive pulmonary diseases or chronic infections of the respiratory tract (especially if linked to allergic rhinitis-like symptoms), reactions on NSAIDs like asthma exacerbations (so-called intolerance to analgesics / analgesics-asthma), Quincke's oedema or urticaria are more frequent than in other patients. Therefore, special precaution is recommended in such patients (readiness for emergency). This is applicable as well for patients who are allergic to other substances, e.g. with skin reactions, pruritus or urticaria.

Like other drugs that inhibit prostaglandin synthetase activity, diclofenac and other NSAIDs can precipitate bronchospasm if administered to patients suffering from, or with a previous history of bronchial asthma.

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).

Impaired 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 fertility, withdrawal of diclofenac should be considered (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

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

Lithium: If used concomitantly, Enstar XL 100mg Tablets may raise plasma concentrations of lithium. Monitoring of the serum lithium level is recommended.

Digoxin: If used concomitantly, Enstar XL 100mg Tablets may raise plasma concentrations of digoxin which may exacerbate cardiac failure, reduce GFR. Monitoring of the serum digoxin level is recommended.

Other NSAIDs and corticosteroids:
Concomitant use of diclofenac with other systemic NSAIDs (including aspirin) or corticosteroids may increase the risk of adverse effects in particular increasing the frequency of GI side effects (see section 4.4).

Diuretics and antihypertensive agents:
Like other NSAIDs, concomitant use of Enstar XL 100mg Tablets 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 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).

Anticoagulants and antiplatelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly. Close monitoring of such patients is therefore recommended. As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

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

Antidiabetic agents:
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 or after treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increased.

Ciclosporin:
Diclofenac, like other NSAIDs, may ~~i~~ncrease 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.

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

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

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

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

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

Potent CYP2C9 inhibitors:
Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as sulfinpyrazone and voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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.

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 inhibitor during the organogenetic period. From the 20th week of pregnancy onward, Enstar XL 100mg tablets 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, Enstar XL 100mg tablets should not be given unless clearly necessary. If Enstar XL 100mg Tablets are 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Enstar XL 100mg tablets for several days from gestational week 20 onward. Enstar XL 100mg tablets 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 (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)

- renal dysfunction (see above)

the mother and the neonate, at the end of the 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, Enstar XL 100mg Tablets are contraindicated during the third trimester of pregnancy (see section 4.3 and 5.3).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Patients may experience undesirable effects such as visual disturbances, dizziness, vertigo, somnolence, central nervous system disturbances, drowsiness or fatigue while taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse reactions associated with diclofenac obtained from clinical studies and post marketing surveillance are tabulated below according to the system organ classes in MedDRA and are ranked under the 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, <1/1000); very rare (<1/10,000); not known: cannot be estimated from available data.

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

Blood and lymphatic system disorders

Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder, anxiety.
Not known	Confusional state
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, tremor, meningitis aseptic*, dysgeusia, cerebrovascular accident.
Not known	Hallucinations, sensory disturbance
Eye disorders	
Very rare	Visual impairment, vision blurred, diplopia.
Not known	Optic neuritis.
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 syndrome
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer** sometimes fatal particularly in the elderly).

Very rare	Colitis***, constipation, stomatitis (including ulcerative stomatitis), mouth ulceration, glossitis, oesophageal disorder, Crohn's disease, large 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, alopecia, photosensitivity reaction, purpura, Henoch-Schönlein purpura, pruritus.
Not known	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.
Reproductive system and breast disorders	
Very rare	Erectile dysfunction
General disorders and administration site conditions	
Rare	Generalised oedema.
Not known	Malaise.

* Meningitis aseptic (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus and mixed connective tissue disease) with symptoms of stiff neck, headache, nausea, vomiting, fever or disorientation
** Gastrointestinal ulcer could be with or without bleeding or perforation
*** Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis)

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, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting or convulsions. In the event of significant poisoning acute renal failure and liver damage are possible. Other complications that might be encountered include hypotension, respiratory depression, and gastro-intestinal irritation.

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

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

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.

Renal and liver function should be closely monitored.
Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diclofenac is a non-steroidal, anti-inflammatory drug (NSAID) with analgesic/anti-inflammatory and antipyretic properties

ATC code: M01AB05

Mechanism of action
The exact mechanism of action of diclofenac has not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Diclofenac inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase, an enzyme that catalyses formation of prostaglandin precursors (endoperoxides) from arachidonic acid.

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

5.2 Pharmacokinetic properties

Absorption

The same amount of active substance is released and absorbed from SR 75mg and XL 100mg tablets as from enteric-coated tablets. Mean peak plasma concentrations of diclofenac are reached at 4 hours, 0.508 ± 0.185µg/ml (0.5µg/mL ≡1.6µmol/L) or 0.4 ± 0.184µg/ml (0.4µg/mL ≡1.25µmol/L) after XL 100mg or SR 75mg, respectively. SR 75mg and XL 100mg are modified release preparations and plasma concentrations of diclofenac of 13ng/mL (40nmol/L) can be recorded at 24 hours (XL 100mg) and 16 hours (SR 75mg) after administration. Absorption is unaffected by food.

Bioavailability:

The systemic availability of diclofenac from the sustained release formulations is on average 82% of that achieved with the same dose of enteric-coated tablets (possibly due to release rate dependent first-pass metabolism). As a result of the slower release of active substance, peak plasma concentrations are lower than for the equivalent enteric-coated tablets.

Pharmacokinetic behaviour does not change on repeated administration. Accumulation does not occur, provided the recommended dosage intervals are observed. Trough levels of diclofenac in the plasma after XL 100mg daily or SR 75mg twice daily are around 22ng/ml or 25ng/ml (70nmol/l or 80nmol/l), respectively.

Distribution

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

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been attained. The apparent half-life for elimination from the synovial fluid is 3-6 hours. Two hours after reaching the peak plasma values, concentrations of the active substance are already higher in the synovial fluid than they are in the plasma and remain higher for up to 12 hours.

Diclofenac was detected in a low concentration (100 ng/mL) in breast milk in one nursing mother. The estimated amount ingested by an infant consuming breast milk is equivalent to a 0.03 mg/kg/day dose (see section 4.6 Pregnancy and lactation).

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.

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

Elderly: No relevant age-dependent differences in the drug's absorption, metabolism, or excretion have been observed, other than the finding that in five elderly patients, a 15 minute iv infusion resulted in 50% higher plasma concentrations than expected with young healthy subjects.

Patients with renal impairment: In patients suffering from renal impairment, no accumulation of the unchanged active substance can be inferred from the single-dose kinetics when applying the usual dosage schedule. At a creatinine clearance of less than 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

Diclofenac Sodium was considered to be unsafe in patients with acute porphyria because it has been shown to be porphyrinogenic in animals or in vitro systems.

Dog Oral LD50: 59 mg/kg	No toxic effects noted
Mouse Oral LD50: 125 mg/kg	No toxic effects noted
Rat Oral LD50: 53 mg/kg	Behavioural (altered sleep time, ataxia),

	lungs, thorax or respiration (respiratory stimulation)
Rabbit Oral LD50: 157 mg/kg	No toxic effects noted

(Registry of toxic effects of chemical substances 1985-6)

Multiple dose studies were performed in rats, dogs and monkeys. At toxic doses there were gastro-intestinal ulcers and disorders in the blood picture in all species. Genetic toxicology studies with diclofenac sodium show that diclofenac is not a mutagen. Carcinogenicity studies have been conducted in mice and rats. No carcinogenic effect has been seen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Magnesium stearate
Hydrogenated vegetable oil Type I (Sterotex)
Povidone K30
Talc

6.2 Incompatibilities

None known.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in a dry place.

6.5 Nature and contents of container

1. Blister packs (Aluminium/Polyvinylchloride): 20, 21, 28, 30 tablets

2. Polypropylene bottles with Low-density polyethylene caps: 56, 100, 250 & 500 tablets

3. High-density polyethylene bottles with Low-density polyethylene screw caps: 56, 100, 250 & 500 tablets

6.6 Special precautions for disposal

Not relevant.

7 MARKETING AUTHORISATION HOLDER

Ennogen IP Ltd
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8 MARKETING AUTHORISATION NUMBER(S)

PL 55612/0120

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