SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Econac SR 75 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Diclofenac sodium 75 mg

Excipient(s) with known effect
Each tablet contains 61.1 mg Lactose monohydrate

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Prolonged release tablet.

Light-pink, round, convex tablets embossed on one side with “Delta” (Δ) symbol.
Diameter = 9 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults and elderly

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

(i) arthritic conditions: rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout.

(ii) acute musculoskeletal 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

Posology

Adult population

The recommended dose is one tablet once or twice daily (maximum daily dose is 150mg).

Elderly

The pharmacokinetics of Econac SR 75 mg Tablets is not impaired in elderly patients, and the standard adult dose may be used. 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 for GI bleeding for 4 weeks following initiation of NSAID therapy.

Paediatric population

Econac SR 75 mg Tablets are not recommended for use in children as dosage recommendations and indications for use in this group of patients have not been established.

Method of Administration

The tablets should be swallowed whole with liquid, to be taken preferably with or after food.

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 gastrointestinal bleeding or perforation, relating to previous NSAID therapy. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)

• Last trimester of pregnancy (see section 4.6).

• 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 Econac SR 75mg 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 gastrointestinal bleeding and perforation, which may be fatal (See section 4.2).

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, Econac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

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 a high dose (150mg daily) and in long-term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)

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 daily 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/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 gastro-intestinal 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 patient 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, anti-platelet agents such as aspirin or selective serotonin-reuptake inhibitors (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 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 (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.

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 reactions:

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 the 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. Econac SR 75mg Tablets should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

Haematological effect:

Care should be taken when treating patients with haematological abnormalities, or bleeding diathesis. Use of Econac SR 75 mg 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 other NSAIDs, Diclofenac 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.

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 infertility, withdrawal of Diclofenac should be considered (see section 4.6).

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

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 the serum lithium level is recommended.

Digoxin: If used concomitantly, Diclofenac 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 Diclofenac with diuretics or antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect. Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

Concomitant treatment with potassium-sparing drugs may be associated with increased serum potassium levels, which should therefore be monitored frequently (see section 4.4).

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.

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 Econac 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 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.

Mifepristone: NSAIDs should not be used for 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 antiprostaglandin 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 concentration 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, Diclofenac Sodium 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 Sodium should not be given unless clearly necessary. If Diclofenac Sodium 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Diclofenac Sodium for several days from gestational week 20 onward. Diclofenac Sodium 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, which may progress to renal failure with oligo-hydroamniosis (see above);

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 Sodium is contraindicated during the third trimester of pregnancy (see section 4.3).

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 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 dizziness drowsiness, fatigue and visual disturbances, vertigo or other central nervous system disturbances after 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 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.

System Organ Class	Frequency	Adverse effects
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	Rare	Anaphylactic and anaphylactoid reactions (including hypotension and shock) and hypersensitivity.
	Very rare	Angioneurotic oedema (face oedema).
Psychiatric disorders	Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder. Anxiety

Nervous system disorders	Common	Headache, dizziness.
	Rare	Somnolence.
	Very rare	Cerebrovascular accident, meningitis aseptic *, convulsion, memory impairment, tremor Paraesthesia, dysgeusia.
Eye disorders	Very rare	Visual impairment, vision blurred, diplopia.
Ear and labyrinth disorders	Common	Vertigo.
	Very rare	Tinnitus, hearing impaired.
Cardiac disorders	Very rare	cardiac failure, myocardial infarction, chest pain and palpitations.
	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	gastrointestinal ulcer **, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena and gastritis
	Very rare	Colitis *** constipation, stomatitis (including ulcerative stomatitis) mouth ulceration, glossitis, oesophageal disorder, crohn's disease, large intestinal stricture, pancreatitis.
	Not known	Ischaemic colitis
Hepatobiliary disorders	Common	Transaminases increased.
	Rare	Hepatitis, jaundice, liver disorder.
	Very rare	hepatic failure, hepatitis fulminant, hepatic necrosis.
Skin and subcutaneous	Common	Rash.

tissue disorders	Rare	Urticaria.
	Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis ****), dermatitis bullous, eczema, erythema multiforme, dermatitis exfoliative alopecia, photosensitivity reaction, purpura, henoch-Schonlein purpura, pruritus
	Not known	Fixed drug eruption, Generalised bullous fixed drug eruption
Renal and urinary disorders	Very rare	Renal failure acute, haematuria, proteinuria, nephrotic syndrome, tubulointerstitial nephritis, renal papillary necrosis.
Reproductive system and breast disorders	Not known	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),
****Toxic epidermal necrolysis includes Lyell's syndrome

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:
Yellow Card Scheme
Website: 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 non-steroidal, anti-inflammatory drug (NSAID) with analgesic/anti-inflammatory and antipyretic properties, ATC code: M01AB05

Mechanism of action
It is an inhibitor of prostaglandin synthetase, (cyclooxygenase).

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
After ingestion of the Diclofenac slow release tablet, the active principle is slowly released into the gastrointestinal contents. Once released from the tablet, Diclofenac is rapidly absorbed from the gastrointestinal tract but is subject to first-pass metabolism. Peak plasma concentrations occur about 6 - 8 hours after administration of the prolonged release tablets when taken with a meal. Food and antacids decrease the rate but not the extent of absorption of Diclofenac.

Distribution
The active substance is 99.7% protein bound, mainly albumin
Diclofenac enters the synovial fluid, and peak synovial fluid concentrations at steady state exceed plasma concentrations. Furthermore, elimination from the synovial fluid is slower than from plasma.

Biotransformation
Diclofenac and its metabolites cross the placenta and traces of Diclofenac have been found in the milk of lactating women. The half-life for the terminal elimination phase is 1-2 hours. 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 they remain higher for up to 12 hours.

Elimination
Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in unchanged form. The remainder of the dose is excreted via the bile in metabolised form.

Characteristics in patient
In patients with impaired renal function, no accumulation of Diclofenac has been reported.
However, half-life of Diclofenac may be prolonged in patients with severe renal impairment

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 gastrointestinal 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 monohydrate
Magnesium stearate
Hypromellose
Cellulose, microcrystalline
Povidone
Talc
Iron oxide red (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

PP-container with PE lids: Pack sizes:	28, 56, 100 tablets
HDPE-container with PE lids: Pack sizes:	28, 56, 100 tablets

Al/Al blister: Pack sizes:	10, 20, 28, 30, 50, 56, 60, 90, 100 tablets
Al/PVDC blister: Pack sizes:	10, 20, 28, 30, 50, 56, 60, 90, 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd
Dashwood House,
69 Old Broad Street,
London, EC2M 1QS,
United Kingdom

8. MARKETING AUTHORISATION NUMBER

PL 12762/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/02/2009

10 DATE OF REVISION OF THE TEXT

05/09/2025