1. NAME OF THE MEDICINAL PRODUCT

Econac 100 mg suppositories
Diclofenac Sodium 100 mg suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One suppository contains 100 mg diclofenac sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories for rectal use

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

- arthritic conditions: rheumatoid arthritis, osteo-arthritis, ankylosing spondylitis, acute gout,
- acute musculo-skeletal disorders such as periarthritis (for example frozen shoulder), tendinitis, tenosynovitis, bursitis,
- other painful conditions resulting from trauma, including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.

4.2 Posology and method of administration

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

Posology

Adults
One 100mg suppository may be given as a once daily treatment usually at night.
Where necessary therapy may be combined with tablets up to a total maximum dose of 150 mg diclofenac per day.

Special population
Elderly patients
Although the pharmacokinetics of Diclofenac Sodium are not impaired to any clinically relevant extent in elderly patients, non-steroidal anti-inflammatory drugs should be used with particular caution in such patients who, generally, are more prone to adverse reactions. In particular, it is recommended that the lowest effective dosage be used in frail, elderly patients or those with a low body weight (see also Precautions) and the patient should be monitored for GI bleeding during NSAID therapy.

Renal impairment

Diclofenac is contraindicated in patients with severe renal impairment (see section 4.3). No specific studies have been carried out in patients with renal impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate renal impairment (see section 4.3 and 4.4).

Hepatic impairment

Diclofenac is contraindicated in patients with severe hepatic impairment (see section 4.3). No specific studies have been carried out in patients with hepatic impairment, therefore, no specific dose adjustment recommendations can be made. Caution is advised when administering diclofenac to patients with mild to moderate hepatic impairment (see section 4.3 and 4.4).

Paediatric population
Children (aged 1 - 12 years):
Diclofenac Sodium 100 mg suppositories are not suitable for children.

Method of administration:

Not to be taken by mouth, as per rectal administration only.

The suppositories should be inserted well into the rectum. It is recommended to insert the suppositories after passing stools.

4.3 Contraindications

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

- Active, gastric or intestinal ulcers, 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 or cardiac failure (see section 4.4).
- Like other non-steroidal anti-inflammatory drugs (NSAIDs), diclofenac is also contraindicated in patients in whom attacks of asthma, angioedema, urticaria or acute rhinitis are precipitated by ibuprofen, acetylsalicylic acid or other nonsteroidal anti-inflammatory drugs.
- Proctitis
- Established congestive heart failure (NYHA II-IV), ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

4.4 Special warnings and precautions for use

General

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2 and GI and cardiovascular risks below).

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

Caution is indicated in the elderly on basic medical grounds. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight (see section 4.2).

As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur in rare cases with diclofenac without earlier exposure to the drug (see section 4.8). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to diclofenac.

Like other NSAIDs, Diclofenac Sodium 100 mg suppositories may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Gastrointestinal effects:

Gastrointestinal bleeding, haematemesis, melaena, 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 Sodium 100 mg suppositories, 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, is higher with increasing NSAID doses, and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation.

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

To reduce the risk of GI toxicity in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly, the treatment should be initiated and maintain at the lowest effective dose.

Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant use of medicinal products containing low dose acetylsalicylic acid (ASA)/ aspirin, or other medicinal products likely to increase gastrointestinal risk (See section 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding).

Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, such as warfarin, anti-platelet agents such as acetylsalicylic acid or selective serotonin-reuptake inhibitors (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).

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 Sodium 100 mg suppositories.

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. Diclofenac Sodium 100 mg Suppositories should be discontinued at the first appearance of skin rash, mucosal lesions or any other signs of hypersensitivity.

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).

Cardiovascular and cerebrovascular effects
Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration. As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

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

Clinical trial and epidemiological data consistently point towards increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.

Patients 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.

Haematological effects:
Use of Diclofenac Sodium 100 mg suppositories is recommended only for short term treatment. During prolonged treatment with Diclofenac, as with other NSAIDs, monitoring of the blood count is recommended. Diclofenac may reversibly inhibit platelet aggregation (see section 4.5). Patients with defects of haemostasis, bleeding diathesis or haematological abnormalities should be carefully monitored.

Pre-existing asthma

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

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

Female fertility:
The use of Diclofenac Sodium 100 mg suppositories 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 Sodium 100 mg suppositories 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 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. Monitoring of the serum digoxin level is recommended.

Diuretics and antihypertensive agents: Like other NSAIDS, concomitant use of Diclofenac Sodium 100 mg Suppositories with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors) may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity.

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

Anticoagulants and anti-platelet agents:
Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulants concomitantly (see section 4.4). Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required.

As with other non-steroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation.

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

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

Antidiabetics: Clinical studies have shown that Diclofenac Sodium 100 mg suppositories 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. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

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

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.

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

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

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

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

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

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

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 or 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 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 organogenetic period.

From the 20th week of pregnancy onward, diclofenac use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, diclofenac should not be given unless clearly necessary. If Diclofenac is used by a woman attempting to conceive, or during the 1st and 2nd trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to diclofenac for several days from gestational week 20 onward. Diclofenac should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

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

- cardiopulmonary toxicity (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 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, Diclofenac is contra-indicated during the third trimester of pregnancy (see section 4.3).

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 (see section 5.2).

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. (See also section 4.4).

4.7 Effects on ability to drive and use machines

Patients who experience visual disturbances, dizziness, vertigo, somnolence central nervous system disturbances, drowsiness or fatigue while taking NSAIDS should refrain from driving or operating machinery.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common: (>1/10); common

(≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); Not known: 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 reactions**
Blood and lymphatic system disorders	Very rare	Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), Agranulocytosis.
Immune system disorders	Rare	Anaphylactic, anaphylactoid reactions (including hypotension and shock) and hypersensitivity.
	Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	Common	Headache, dizziness.
	Rare	Somnolence, tiredness
	Very rare	cerebrovascular accident, aseptic meningitis, convulsion, memory impairment, anxiety, tremor, paraesthesia, taste disturbances.
	Not known	Hallucination, confusion, disturbances of sensation
Eye disorders	Very rare	Visual disturbance, vision blurred, diplopia.
	Not known	Optic Neuritis
Ear and labyrinth disorders	Common	Vertigo.
	Very rare	Tinnitus, hearing impaired.
Cardiac disorders	Very rare	cardiac failure, myocardial infarction. chest pain Palpitations
	Not known	Kounis syndrome
Vascular disorders	Very rare	Hypertension, vasculitis, hypotension
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 with or without bleeding or perforation (sometimes fatal particularly in the elderly), gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastritis,
	Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, Stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
	Not known	Ischaemic colitis
Hepatobiliary disorders	Common	Transaminases increased.
	Rare	Hepatitis, jaundice, liver disorder.
	Very rare	Hepatic failure, Fulminant hepatitis, hepatic necrosis.
Skin and subcutaneous tissue disorders	Common	Rash.
	Rare	Urticaria.
	Very rare	Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), Generalised Bullous fixed drug eruptions, eczema, erythema, erythema multiforme, dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
	Not known	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	Impotence.
General disorders and administration site conditions	Rare	Application site irritation, oedema,
	Not known	Malaise

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 for Contraindications and Special warnings and special precautions for use).

Reporting of suspected adverse reactions
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly 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.

By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms
There is no typical clinical picture resulting from diclofenac over dosage. Over dosage can cause symptoms like headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, dizziness, disorientation, excitation, coma, drowsiness, tinnitus, fainting, or convulsions. In rare cases of significant poisoning acute renal failure and liver damage are possible.

Management
Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults gastric lavage should be considered within one hour of 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: Nonsteroidal anti-inflammatory drugs (NSAIDs), ATC Code- M01AB05

Mechanism of Action
Diclofenac Sodium 100 mg suppositories are a non-steroidal agent with marked analgesic/anti-inflammatory properties. It is an inhibitor of prostaglandin

synthetase, (cyclo-oxygenase). Diclofenac sodium *in vitro* does not suppress proteoglycan biosynthesis in cartilage at concentrations equivalent to the concentrations reached in human beings.

5.2 Pharmacokinetic properties

Absorption

Diclofenac is rapidly and efficiently absorbed after conventional oral, rectal or intramuscular administration.

Maximal plasma concentrations after rectal administration are attained after approximately thirty minutes. Peak plasma concentrations and area under the plasma concentration-time curve (AUC) are linearly related to a dose over the range of 25 - 150 mg, regardless of administration route; after oral, rectal or intramuscular doses no accumulation occurred after repeated doses.

In elderly patients of more than 62 years of age and patients aged 2 - 7 years with juvenile rheumatoid arthritis peak plasma concentrations, time to peak plasma concentrations (tmax) and AUC values are similar to those produced in adult patients without arthritic conditions.

Distribution

Highest concentrations of Diclofenac are found in descending order in the liver, bile, kidneys, blood, heart and lungs.

Diclofenac passes into the synovial fluid of patients with osteoarthritis and rheumatoid arthritis, where higher concentrations are maintained compared with plasma concentrations.

Even though Diclofenac has a relatively short elimination half-life in plasma (1.5 hours), the drug persists in synovial fluid.

Diclofenac, like all NSAIDs, is $\geq$ 99.5 % bound to human serum proteins, specifically to albumin. The volume of distribution of diclofenac in healthy subjects is 0.12 to 0.17 L/kg and that of the central compartment 0.04 L/kg.

Biotransformation

Diclofenac is metabolized in the liver by conjugation. The principal metabolite in humans, 4’-hydroxydiclofenac, which has about 1/40 of the activity of the parent compound against adjuvant-induced arthritis.

5'-hydroxydiclofenac and 4', 5'-dihydroxydiclofenac do not have any pharmacologic activity. Drug disposition in patients with hepatic impairment is comparable to that in normal subjects.

Elimination

Diclofenac is eliminated by urinary and biliary excretion of glucuronide and sulfate conjugates of the metabolites.

Urinary excretion of 4'-hydroxydiclofenac accounts for 20 % to 30 % of the dose. Biliary excretion of this metabolite accounts for 10 % to 20 %. The other metabolites excreted in urine each account for 10 % to 20 % of the dose; smaller amounts are excreted in the bile.

Approximately 90 % of an oral dose of diclofenac is excreted within 96 hours. The mean elimination half-life of the unchanged drug is 1.2 to 1.8 hours. Elimination rates in renally impaired patients are comparable to those in other patients. The steady state concentrations of the total metabolites in patients with severe renal impairment are four times higher than in subjects with normal renal function, but exert no additional pharmacological effects.

Bioavailability

The relative bioavailability of the suppositories compared to the reference product is 96.4 %.

The 90 % confidence intervals are for:

- AUC $o-\infty$: 90.5 - 102.7
- C_{max}: 77.0 - 93.4

5.3 Preclinical safety data

Acute Toxicity

The study of acute toxicity in various animal models did not reveal any special sensitivity.

Chronic Toxicity

The chronic toxicity was examined in rats, dogs and monkeys. Ulceration in the gastrointestinal tract was observed and produced complications, i.e. peritonitis, anemia and leucocytosis.

Mutagenic and Carcinogenic Potential

A mutagenic effect of diclofenac seems to be excluded by the results of in-vitro and in-vivo tests. Studies on carcinogenicity in rats did not show any evidence of tumour-developing activities.

Reproduction Toxicology

The embryotoxic potential of diclofenac was studied in 3 animal models (rat, mouse and rabbit). Fetal death and retardation of growth resulted in doses in the toxic range. Malformations have not been observed. The gestation period and duration of parturition were prolonged by diclofenac. The effect on fertility was not examined. Doses below the maternal-toxic range did not reveal any influence on the postnatal development of the descendants.

PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hard fat

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years

6.4. Special precautions for storage

Do not store above 25°C.

6.5. Nature and contents of container

PVC/PE strips with 10 suppositories

6.6 Special precautions for disposal

See section 4.2

7. MARKETING AUTHORISATION HOLDER

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

8. Marketing Authorisation Number

PL 10972/0069

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/11/2010

10 DATE OF REVISION OF THE TEXT

09/09/2025