Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac 100 mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac Sodium 100 mg

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablet.

White, circular, biconvex tablets, diameter 12.0 mm with a Greek Delta symbol embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Relief of all grades of pain and inflammation in conditions such as:

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

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

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

Dysmenorrhoea and associated menorrhagia.

For the symptomatic treatment of osteoarthritis.

4.2 Posology and method of adminstration

Dosage

Route of administration: oral.

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

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest effective dosage of diclofenac compatible with adequate safe clinical control should be employed. (See also Special warning and precautions, Section 4.4).

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Children: Not recommended.

4.3 Contraindications

Patients with active or suspected peptic ulceration, peptic ulcer disease or gastro-intestinal bleeding.

Previous sensitivity to diclofenac or other ingredients of the preparation.

Patients with a history of hypersensitivity reactions (e.g. Bronchospasm, rhinitis, urticaria) in response to Diclofenac Retard 100 mg Tablets, aspirin or other non-steroidal anti-inflammatory drugs.

4.4 Special warnings and special precautions for use

Undesirable effects may be reduced by using the minimum effective dose for the shortest possible duration. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Gastro-intestinal: Diclofenac Retard 100 mg Tablets should be used with caution in patients with a history of peptic ulceration of inflammatory disease. Patients with ulcerative colitis or Crohn's disease, bleeding diathesis or haematological abnormalities should also be treated with caution. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving diclofenac the drugs should be withdrawn.

Hypersensitivity reactions: As with other non-steroidal anti-inflammatory drugs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Renal: In patients with renal, cardiac or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function. Assessment of renal function should occur prior to the initiation of therapy and regularly thereafter.

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.

Hepatic: Close medical surveillance is imperative in patients suffering from severe impairment of hepatic function. If abnormal liver function tests persist or worsen, clinical signs or symptoms consistent with liver disease develop or if other manifestations occur (eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur without prodromal symptoms. Use of diclofenac in patients with hepatic porphyria may trigger an attack.

Haematological: As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis (see anticoagulants in 'drug interaction').

Long-term treatment: All patients who are receiving non-steroidal anti-inflammatory agents should be monitored as a precautionary measure e.g. renal function, hepatic function (elevation of liver enzymes may occur) and blood counts. Elderly patients are particularly susceptible to adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

4.5 Interaction with other medicinal products and other forms of interaction

It is considered unsafe to take NSAIDs in combination with Warfarin or heparin unless under direct medical supervision.

Care should be taken in patients treated with any of the following drugs as interactions have been reported.

Anti-hypertensives: reduced anti-hypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium.

Methotrexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Other NSAIDS: avoid concomitant use of two or more NSAIDs.

Corticosteroids: increased risk of gastrointestinal bleeding.

Aminoglycosides: reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

Oral hypoglycaemic agents: inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

4.6 Pregnancy and lactation

Although animal studies have not demonstrated teratogenic effects, diclofenac should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dosage should be used.

Use of prostaglandin synthetase inhibitors during the third trimester of pregnancy may result in premature closure of the ductus arteriosus or uterine inertia and should therefore be avoided.

Following oral administration of diclofenac, traces of active substance have been detected in breast milk in trace quantities unlikely to have any undesirable effects on the infant.

4.7 Effects on ability to drive and use machines

Patients who experience dizziness or other central nervous system disturbances while taking NSAIDs should refrain from driving or operating machinery.

4.8 Undesirable effects

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

Gastro-intestinal tract:
Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).
Rare: Gastro-intestinal bleeding, peptic ulcer (with or without bleeding or perforation), bloody diarrhoea.
In isolated cases: Lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn’s proctocolitis), pancreatitis, aphthous stomatitis, glossitis, oesophageal lesions, constipation.

Central nervous system:
Occasional: Headache, dizziness, or vertigo.
Rare: Drowsiness, tiredness.
In isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, disturbance of vision (blurred vision, diplopia), impaired hearing, tinnitus, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions. Taste alteration disorders.

Skin:
Occasional: Rashes or skin eruptions.
Rare: Urticaria.

In isolated cases: Bullous eruptions, eczema, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome, (acute toxic epidermolysis), erythroderma (exfoliative dermatitis), loss of hair, photosensitivity reactions, purpura including allergic purpura.

Kidney:
In isolated cases: Acute renal insufficiency, urinary abnormalities (e.g. haematuria, proteinuria), interstitial nephritis, nephrotic syndrome, papillary necrosis.

Liver:
Occasional: Elevation of serum aminotransferase enzymes (ALT, AST).
Rare: Liver function disorders including hepatitis (in isolated cases fulminant) with or without jaundice.

Blood:
In isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

Other organ systems:
Rare: Oedema, hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).
Isolated cases: Impotence (association with diclofenac intake is doubtful), palpitation, chest pain, hypertension.

4.9 Overdose

Management of acute poisoning with NSAIDs essentially consists of supportive and symptomatic measures. There is no typical clinical picture resulting from diclofenac overdosage.
The following therapeutic measures may be taken:
1. Absorption should be prevented as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal;
2. Supportive and symptomatic treatment for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression.
Specific therapies such as forced diuresis, dialysis or haemoperfusion are unlikely to be of help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diclofenac is a non-steroidal agent with marked analgesic, anti-pyretic and anti-inflammatory properties. It is an inhibitor of 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

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism, only 50-60% of the drug reaching the systemic circulation in the unchanged form.

The active substance is more than 99% protein bound. The plasma half-life for the terminal elimination phase is 1-2 hours.

Diclofenac enters the synovial fluid, where maximum concentrations are measured 2-4 hours after the peak plasma values have been obtained. 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. Diclofenac has also been detected in the breast milk following oral administration (see section 4.6).

Metabolites include 4-hydroxy diclofenac, 5-hydroxy diclofenac, 3-hydroxy diclofenac and 4,5-dihydroxy diclofenac. The metabolites are excreted in the form of glucuronide and sulphate conjugates. 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.

In patients with impaired renal function, no accumulation of diclofenac has been reported.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrogenated vegetable oil
Lactose
Magnesium stearate
Povidone
Talc

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

Blister packs (A1/PVC), PP-container with LDPE cap (Securitainer), HDPE-container with LDPE cap (Scanstar).

Pack sizes: 28, 30, 56, 100 tablets.

6.6 Instructions for use and handling

None.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 476/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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