Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diclofenac 50 mg Stada Gastro-resistant Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains diclofenac sodium 50 mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.

Light-brown circular, biconvex, gastro-resistant tablets, 8mm x 4.3mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Diclofenac 50mg Stada Gastro-resistant Tablets are indicated for the relief of all grades of pain and inflammation in a range of conditions, including:

1. arthritic conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, psoriatic arthropathy.
2. acute musculo-skeletal disorders such as periarthritis (e.g. frozen shoulder), tendinitis, tenosynovitis, bursitis.
3. other painful conditions resulting from trauma including fracture, low back pain, sprains, strains, dislocations, orthopaedic, dental and other minor surgery.
4. the management of dysmenorrhoea and associated menorrhagia.

4.2 Posology and method of adminstration

For oral use only.

Adults: The recommended dose is 75-150 mg daily in two or three divided doses, taken whole with liquid.

Elderly: NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also Section 4.4. The lower strength Diclofenac preparations may therefore be appropriate.

Children: The recommended dose is 1-3 mg/kg daily in divided doses.

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

4.3 Contraindications

Patients with a history of hypersensitivity reactions (e.g. bronchospasm, rhinitis, urticaria) in response to Diclofenac, aspirin or nonsteroidal anti-inflammatory drugs.
Patients with peptic ulceration, or gastro-intestinal bleeding.

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 effects.

Elderly patients are particularly susceptible to the adverse effects of NSAIDs. Prolonged use of NSAIDs in the elderly is not recommended. When prolonged therapy is required, patients should be reviewed regularly.

Gastro-intestinal: Diclofenac should be used with caution in patients with a history of peptic ulceration or inflammatory bowel disease.

Gastro-intestinal bleeding or ulceration/perforation, haematemesis and melaena in general have more serious consequences in the elderly. They can occur at any time during treatment with or without warning symptoms or a previous history. In the rare instances where gastro-intestinal bleeding or ulceration occurs in patients receiving Diclofenac the drug should be withdrawn.

Hypersensitivity reactions: As with other NSAIDs, allergic reactions, including anaphylactic/anaphylactoid reactions, can also occur without earlier exposure to the drug.

Renal: 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 use 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 formation, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

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

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:

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate. Cases of serious toxicity have been reported when methotrexate and NSAIDs 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.

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

Anti-hypertensives: Reduced anti-hypertensive effect.

Other NSAIDs: Avoid concomitant use of two or more NSAIDs.

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. Clinical studies have shown that Diclofenac can be given together with oral antidiabetic agents without influencing their clinical effect.

Cyclosporin: Increased risk of nephrotoxicity with NSAIDs. This might be mediated through the combined renal antiprostaglandin effects of both NSAIDs and cyclosporin.

Quinolone antimicrobials: 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.

Corticosteroids: Increased risk of gastro-intestinal bleeding.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Various NSAIDs are liable to inhibit the activity of loop-type diuretics in particular. Concomitant treatment with potassium-sparing diuretics may be associated with increased serum potassium levels, hence serum potassium should be monitored.

4.6 Pregnancy and lactation

No teratogenic effects have been observed in animal studies. However, due to lack of evidence of safety, Diclofenac should not be prescribed during pregnancy, unless there are compelling reasons for doing so. The lowest effective dose should be used.

Use of prostaglandin synthetase inhibitors may result in premature closure of the ductus arteriosus or uterine inertia; such drugs are therefore not recommended during the last trimester of pregnancy.

Following oral doses of 50mg Diclofenac every 8 hours, traces of active substance have been detected in breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

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. The following side-effects have been reported:

Frequency estimate: frequent: >10%, occasional: >1 ≤10%, rare: >0.001% ≤1%, isolated cases: <0.001%.

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:
Rare: oedema
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.

Cardiovascular system:
Isolated cases: palpitations, chest pain, hypertension, congestive heart failure.

Hypersensitivity:
Rare: hypersensitivity reactions (e.g. bronchospasm, anaphylactic/anaphylactoid systemic reactions including hypotension).

Other organ systems:
Isolated cases: Impotence (association with Diclofenac intake is doubtful).

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 therapeutic measures to be taken are: absorption should be prevented as soon as possible after overdosage by means of gastric lavage and treatment with activated charcoal; supportive and symptomatic treatment should be given for complications such as hypotension, renal failure, convulsions, gastro-intestinal irritation, and respiratory depression; specific therapies such as forced diuresis dialysis or haemoperfusion are probably of no help in eliminating NSAIDs due to their high rate of protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, ATC code M01 AB05

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 form 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 form 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 Pregnancy and lactation).

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

Tablet core
Maize starch
Microcrystalline cellulose
Lactose monohydrate
Povidone K30
Colloidal anhydrous silica
Magnesium stearate

Tablet coat
Poly (methacrylate, methylmethacrylate)
O-Acetyltriethylcitrate
Hypromellose
Macrogol 6000
Macrogol 400
Talc
Titanium dioxide (E171)
Ferric oxide red (E172)
Ferric oxide yellow (E172)
Magnesium stearate

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

A1/PVC blisters. Pack sizes of 20, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Swallow whole. Do not chew.

7 MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastraβe 2-18
61118 Bad Vilbel
Germany

8 MARKETING AUTHORISATION NUMBER

PA 593/8/5

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th February 2000
Date of last renewal: 18th February 2005

10 DATE OF REVISION OF THE TEXT

October 2005