**IRISH MEDICINES BOARD ACT 1995**

**MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998**

**(S.I. No.142 of 1998)**

**PA1046/007/002**
Case No: 2034402

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Winthrop Pharmaceuticals UK Limited**

**One Onslow Street**, **Guildford**, **Surrey**, **GU1 4YS**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Diclofenac Sodium 50 Milligram Tablets Gastro-Resistant**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **05/07/2007** until **12/07/2008**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Diclofenac Sodium 50mg Gastro-Resistant Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Diclofenac sodium 50 mg.

For excipients, see 6.1.

## 3 PHARMACEUTICAL FORM

Gastro-resistant tablet.

Biconvex, mustard brown coloured gastro resistant coated tablets with S/27 on one side and plain on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

In the symptomatic management of rheumatoid arthritis including juvenile chronic arthritis, osteoarthrosis, ankylosing spondylitis, psoriatic arthropathy, low back pain, and acute musculoskeletal disorders including periarthritis, tendinitis, tenosynovitis, bursitis, sprains, strains, dislocations and in acute gout.

In the management of post operative pain and inflammation in orthopaedic, dental and other minor surgery.

### 4.2 Posology and method of administration

Route of Administration
Oral.

Adults
The usual total daily dosage is 75-150mg in divided doses.

Elderly
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 are generally more prone to adverse reactions. In particular, it is recommended that the lowest effective dose be used in frail elderly patients or those with a low body weight. (See also Precautions.)

Children
The usual total daily dose is 1 to 3mg/kg in divided doses.

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

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

## 4.3 Contraindications

Use in patients hypersensitive to diclofenac or any of the other excipients.

Use in patients with active or suspected peptic ulceration or peptic ulcer disease, or with gastrointestinal bleeding.

Use in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.

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

Severe heart failure

## 4.4 Special warnings and precautions for use

The use of Diclofenac sodium with concomitant NSAIDs including cyclooxygenase-2-selective inhibitors should be avoided.

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

Renal: Patients with renal, cardiac or hepatic impairment and the elderly should be kept under surveillance, since the use of NSAIDs may result in deterioration of renal function. The lowest effective dose should be used and renal function monitored prior to the initiation of treatment 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 Sodium.

Hepatic: 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 Sodium should be discontinued. Hepatitis may occur without prodromal symptoms. Use of Diclofenac Sodium with hepatic porphyria may trigger an attack.

Haematological: Diclofenac Sodium may reversibly inhibit aggregation (see anticoagulants in Interactions) and should be used with caution in patients with intracranial haemorrhage, bleeding diathesis or haematological abnormalities.

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. This is particularly important in the elderly.

Gastrointestinal: Close medical surveillance is imperative in patients with symptoms indicative of gastrointestinal disorders, with a history suggestive of gastrointestinal ulceration, with ulcerative colitis or with Crohn’s disease.

Gastrointestinal bleeding or ulceration/perforation, haematemesis and melaena have in general 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 gastrointestinal bleeding or ulceration occurs in patients receiving Diclofenac Sodium the drug should be withdrawn.

Gastrointestinal bleeding, ulceration and performation : GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3),and in the elderly. 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 4.5)

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

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (see section 4.5)

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

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8 - undesirable effects).

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

Hepatic: Close medical surveillance is also imperative in patients suffering from severe impairment of hepatic function.

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.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 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 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

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 cardiovascular risks below)

Cardiovascular and cerebrovascular

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 (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).

The use of diclofenac sodium 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 sodium should be considered.

## 4.5 Interaction with other medicinal products and other forms of interaction

Lithium and Digoxin: Diclofenac Sodium may increase plasma concentrations of lithium and digoxin.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4)

Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).

**It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision.** Although clinical investigations do not appear to indicate that Diclofenac Sodium has an influence on the effects of anticoagulants, there are isolated reports of an increased risk of haemorrhage with the combined use of diclofenac and anticoagulant therapy. 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 high dose can reversibly inhibit platelet aggregation.

Anti-platelet agents and selective serotonin reuptake (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4)

Antidiabetic Agents: Clinical studies have shown that Diclofenac Sodium can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents.

Ciclosporin: Cases of nephrotoxicity have been reported in patients receiving concomitant ciclosporin and NSAIDs, including Diclofenac Sodium. This might be mediated through combined renal antiprostaglandin effects of both the NSAID and ciclosporin.

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.

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.

Other NSAIDs and Steroids: Co-administration of Diclofenac Sodium with other systemic NSAIDs and steroids may increase the frequency of unwanted effects. Concomitant therapy with aspirin lowers the plasma levels of each, although no clinical significance is known.

Diuretics: Various NSAIDs are liable to inhibit the activity of diuretics. 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

Diclofenac sodium tablets 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 may result in premature closure of the ductus arteriosus if given in the last trimester of pregnancy.

Following oral doses of 150mg daily, traces of active substances 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 CNS disturbances while taking NSAIDs should refrain from driving or operating machinery.

## 4.8 Undesirable effects

If serious side effects occur, Diclofenac Sodium 50mg Tablets should be withdrawn.

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

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4) Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 - Special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed

Gastro-intestinal tract:

Occasional: Epigastric pain, other gastro-intestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal cramps, dyspepsia, flatulence, anorexia).

Rare: Gastro-intestinal bleeding (haematemesis, melaena, bloody diarrhoea), gastro-intestinal ulcers with or without bleeding or perforation.

Isolated cases: Aphthous stomatitis, glossitis, oesophageal lesions, lower gut disorders (e.g. non-specific haemorrhagic colitis and exacerbations of ulcerative colitis or Crohn’s proctocolitis, colonic damage and stricture formation), pancreatitis, constipation.

*Central Nervous System:*

Occasional: Headache, dizziness or vertigo.

Rare: Drowsiness, tiredness.

Isolated cases: Disturbances of sensation, paraesthesia, memory disturbance, disorientation, insomnia, irritability, convulsions, depression, anxiety, nightmares, tremor, psychotic reactions, aseptic meningitis.

*Special senses:*

Isolated cases: Disturbances of vision (blurred vision, diplopia), impaired hearing, tinnitus, taste disturbances.

*Skin:*

Occasional: Rashes or skin eruptions.

Rare: Urticaria.

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.

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (ver rare).

*Kidney:*

Rare: Oedema.

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:*

Isolated cases: Thrombocytopenia, leucopenia, agranulocytosis, haemolytic anaemia, aplastic anaemia.

*Hypersensitivity:*

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

Isolated cases: Vasculitis, pneumonitis.

*Cardiovascular system:*

Isolated cases: Palpitations, chest pain, hypertension, congestive heart failure.

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of diclofenac, particularly high doses (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) (see section 4.4)

## 4.9 Overdose

There is no specific antidote to Diclofenac Sodium Tablets, and the treatment is symptomatic. Symptomatology of overdose with Diclofenac Sodium Tablets is not well defined; hypotension, convulsions, respiratory depression, gastrointestinal, renal and hepatic effects are possible.

Immediate treatment consists of forced emesis or gastric lavage to recover undigested tablets, and treatment with activated charcoal.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

ATC code: M01A B05, Anti-inflammatory and antirheumatic products, non-steroids.

Diclofenac sodium is a non-steroidal anti-inflammatory agent and inhibitor of PG synthetase.

## 5.2 Pharmacokinetic properties

The drug is well absorbed with peak plasma levels achieved between 1 and 4 hours. It is extensively metabolised in the liver and excreted through bile and urine. The drug is strongly protein-bound. It has a half life of 1 to 2 hours.

## 5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose (crystalline)
Maize starch
Povidone K25
Microcrystalline cellulose
Silicon dioxide
Magnesium stearate

Coating Constituents

Hypromellose
Macrogol 400

Opaspray M-1-6140 [contains titanium dioxide (E171), iron oxide yellow (E172), hypromellose]

Eudragit L30D [contains methacrylic acid copolymer Type C, polysorbate 80, sodium laurilsulfate]

Macrogol 8000
Polysorbate 80
Talc
Antifoam silicone 1510

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

4 years

## 6.4 Special precautions for storage

Do not store above 30°C.

## 6.5 Nature and contents of container

The tablets are contained in PVC/aluminium foil blisters and enclosed in cardboard cartons in pack sizes 28, 30, 56, 60, 84 and 100.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Winthrop Pharmaceuticals UK Limited
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Trading as:
Winthrop Pharmaceuticals UK Limited
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# 8 MARKETING AUTHORISATION NUMBER

PA 1046/7/2

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13 July 1993

Date of Last Renewal: 13 July 2003

# 10 DATE OF REVISION OF THE TEXT

July 2007