IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0711/009/004
Case No: 2025679

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

Rowex Ltd

Bantry, **Co. Cork**, **Ireland**

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

Diclac 150 mg Prolonged-release Tablets

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 **04/10/2006** until **26/05/2009**.

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

Diclac 150 mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150mg Diclofenac Sodium.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Round, flat, two - layered pink and white coloured, prolonged release tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the symptomatic treatment of osteoarthritis

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, 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, strains, dislocations, orthopaedic, dental and other minor surgery;
(iv) in the management of dysmenorrhoea and associated menorrhagia.

4.2 Posology and method of administration

As a general recommendation, the dose should be individually adjusted and the lowest effective dose given for the shortest possible duration.

Route of Administration:
Oral.

Recommended Dosage Schedule:
Adults: Diclac Prolonged Release tablet 150 mg: One tablet daily, swallow whole with liquid, do not chew.

Elderly: Although the pharmacokinetics of Diclac 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 section 4.4.

Children: Not recommended.

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

4.3 Contraindications

- Known hypersensitivity to the active substance or to any of the excipients
- History of gastrointestinal bleeding or perforation related to previous NSAID's therapy
- Active or history of recurrent gastric or intestinal ulcer, bleeding or perforation
- Last trimester of pregnancy (see section 4.6 Pregnancy and Lactation)
- Severe hepatic, renal or cardiac failure (see section 4.4 Special warnings and special precautions for use
- Like other non-steroidal anti-inflammatory drugs (NSAID's), diclofenac is also contra-indicated in patients in whom attacks of asthma, urticaria, or acute rhinitis are precipitated by acetylsalicylic acid or other NSAID's.

4.4 Special warnings and precautions for use

Warnings

Gastrointestinal bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs and may oc 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 patien receiving diclofenac, the medicinal product should be withdrawn.

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, including diclofenac (see section 4.8 Undesirable effects).
Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurrin the majority of cases within the first month of treatment. Diclofenac should be discontinued at the first appearance of s rash, musosal lesions or any other sign of hypersensitivity.

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

Like other NSAIDs, diclofenac may mask the signs and symptoms of infection due to its pharmacodynamic properties.

Precautions

General

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.

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

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 oede 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.

Gastrointestinal effects

As with all NSAIDs, close medical surveillance is imperative and particular caution should be excerised when prescribi diclofenac in patients with symptoms indicative of gastrointestinal (GI) disorders or with a history suggestive of gastric intestinal ulceration, bleeding or perforation (see section 4.8 Undesirable effects). The risk of GI bleeding is higher witl increasing NSAID doses and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly.

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 maintained at the lowest effective dose.

Combination therapy with protective agents (e.g. proton pump inhibitors or misoprostol) 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.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especiall GI bleeding). Caution is recommended in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as systemic corticosteroids, anticoagulants, anti-platelet agents or selective serotonin-reupta inhibitors (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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 Undesirable effects).

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, 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 o worsen, if clinical signs or symptoms consistent with liver disease develop, of if other manifestations occur (e.g. eosinophilia, rash), diclofenac should be discontinued. Hepatitis may occur 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, 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 Contraindications).

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.

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.

Haematological effects

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 or haemostatis shoul be carefully monitored.

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

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 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 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 Special warnings and special precautions for use).

Other NSAIDs and corticosteroids: Concomitant administration of diclofenac and other systemic NSAIDs or corticosteroids may increase the frequency of gastrointestinal undesirable effects (see section 4.4 Special warning and special precautions for use).

Anticoagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding (see section 4.4 Special warnings and special precautions for use). Although clinical investigations do not appear to indicate that diclofenac affects the action of anticoagulants, there are isolated 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 NSAID and SSRIs may increase the risk of gastrointestinal bleeding (see section 4.4 Special warnings and special precautions for use).

Antidiabetic: Clinical studies have shown that diclofenac 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: Caution is recommended when NSAIDs 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 effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Quinolone antimicrobials: There have been isolated reports of convulsions which may have been due to concomitant use of quinolones and NSAIDs.

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

4.6 Pregnancy and lactation

Pregnancy

The use of diclofenac in pregnant women has not been studied. Therefore, diclofenac should not be used during the first two trimesters of pregnancy unless the potential benefit to the mother outweighs the risk to the foetus. As with other NSAIDs, use during the third trimester of pregnancy is contraindicated owing to the possibility of uterine inertia and/or premature closure of the ductus arteriosus (see section 4.3 Contraindications). Animal studies have not shown any directly or indirectly harmful effects on pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3 Preclinical safety data).

Lactation
Like any 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 experiencing visual disturbances, dizziness, vertigo, somnolence or other central nervous system disturbances while taking diclofenac, should refrain from driving or using machines.

4.8 Undesirable effects

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥ 1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

The following undesirable effects include those reported with diclofenac gastro-resistant tablets and/or other pharmaceutical forms of diclofenac, with either short-term or long-term use.

Blood and lymphatic disorders
Very rare: Thrombocytopenia, leukopenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis

Immune system disorders
Rare: Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock)
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
Very rare: Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis, taste disturbances, cerebrovascular accident

Eye disorders
Very rare: Visual disturbance, vision blurred, diplopia

Ear and labyrinth disorders
Common: Vertigo
Very rare: Tinnitus, hearing impaired

Cardiac disorders
Very rare: Palpitations, chest pain, cardiac failure, myocardial infarction

Vascular disorders
Very rare: Hypertension, 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: Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer (with or without bleeding or peforation)
Very rare: Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis, glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis

Hepatobiliary disorders
Common: Transaminases increased
Rare: Hepatitis, jaundice, liver disorder
Very rare: Fulminant hepatitis

Skin and subcutaneous tissue disorders
Common: Rash
Rare: Urticaria
Very rare: Bullous eruptions, eczema, erythema, erythema multiforme, Stephens-Johnson syndrome, toxic epiderm necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus

Renal and urinary disorders
Very rare: Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis

General disorders and administration site conditions
Rare: Oedema

4.9 Overdose

Symptoms
There is no typical clinical picture resulting from diclofenac overdosage. Overdosage can cause symptoms such as vomiting, gastrointestinal haemorrhage, diarrhoea, dizziness, tinnitus or convulsions. In the event of significant poisoni acute renal failure and liver damage are possible.

Therapeutic measures

Management of acute poisoning with NSAIDs 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 haemoperfusion are probably of no help in eliminating NSAIDs du to the high protein binding and extensive metabolism.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: Musculo-skeletal system.
Anti-inflammatory and anti-rheumatic products.
MO1AB05: Acetic acid derivatives and related substances

Diclac is 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 humans.

5.2 Pharmacokinetic properties

Diclofenac sodium is rapidly absorbed from the gut and is subject to first-pass metabolism. Tablets give peak plasma concentrations after 1-4 hours, suppositories within 1 hour and ampoules within half and hour. The active substance is 99.7% protein bound and plasma half-life for the terminal elimination phase is 1-2 hours. Approximately 60% of the administered dose is excreted via the kidneys in the form of metabolites and less than 1% in the unchanged form. The remainder of the dose is excreted via the bile in metabolised form. In patients with impaired renal function, no accumulation of Diclac has been reported.

5.3 Preclinical safety data

Preclinical data from acute and repeated dose toxicity studies, as well as from genotoxicity, mutagenicity, and carcinogenicity studies with diclofenac revealed no specific hazard for humans at the intended therapeutic doses. There was no evidence that diclofenac had a teratogenic potential in mice, rats or rabbits.

Diclofenac had no influence on the fertility of parent animals in rats. The prenatal, perinatal and post natal development of the offspring was not affected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Hypromellose
Microcrystalline cellulose
Calcium hydrogen phosphate dihydrate
Maize starch
Sodium starch glycolate
Colloidal anhydrous silica
Magnesium stearate
Red ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years in PVC/Alu packaging.
2 years in PP/Alu packaging.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Diclac 150mg Prolonged Release tablets are each packed in blisters of both polypropylene and polyvinylchloride and aluminium foil. Diclac Prolonged Release 150mg Tablets are available in packs of 30 tablets and sample packs of 10 tablets are also available.
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

Rowex Ltd.,
Bantry,
Co. Cork.

8 MARKETING AUTHORISATION NUMBER

PA 711/9/4

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th March 2000
Date of last renewal: 27th May 2004

10 DATE OF REVISION OF THE TEXT

September 2006