IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0743/010/002
Case No: 2032080

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

Trinity-Chiesi Pharmaceuticals

Cheadle Royal Business Park, **Highfield**, **Cheadle**, **SK8 3GY**, **United Kingdom**

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

BREXIDOL 20mg 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 **25/01/2007** until **13/08/2007**.

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

Brexidol 20 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg piroxicam (as betadex)

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet

Pale yellow, hexagonal tablet with a median score line on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

As an anti-inflammatory analgesic in the treatment of:

- arthritis and related disorders (e.g., rheumatoid arthritis, osteoarthritis, ankylosing spondylitis)
- acute musculoskeletal disorders (e.g., bursitis, tendinitis)
- acute gout
- primary dysmenorrhoea
- post-operative pain

4.2 Posology and method of administration

Route of Administration

For oral use
Two equivalent halves of a tablet (10 mg as piroxicam), are obtained by placing the tablet on a hard surface, with the score fracture line upwards and pressing it in half using the thumb.

Dosage Recommendations

Adults
The recommended dose is one tablet (20 mg piroxicam), as one single daily dose, preferably with or after food.

Children
The use of piroxicam in children is not recommended.

The Elderly
In elderly patients, it may be necessary to reduce the dosage (half a tablet), and limit the duration of treatment. Again, it is preferable to take the dose with or after food.

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 and the patient should be monitored for

gastrointestinal bleeding for 4 weeks following initiation of NSAID therapy (see section 4.4).

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

4.3 Contraindications

Brexidol 20 mg tablets should not be given to patients with:
- known hypersensitivity to any of the constituents or piroxicam
- a history of, or active, peptic ulceration or recurrent peptic ulceration
- a history of hypersensitivity reactions (eg., bronchospasm, asthma, rhinitis, urticaria), in response to piroxicam, aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs
- porphyria

Brexidol is contra-indicated in children.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration. Patients on prolonged therapy with NSAIDs should undergo regular medical supervision to monitor for adverse events.

To avoid the risk of increased side effects, piroxicam should not be given with other non-steroidal anti-inflammatory agents.

Elderly patients are at increased risk of the serious consequences of adverse effects of NSAIDs. They tend to be susceptible to gastrointestinal bleeding and they are also likely to suffer from impaired hepatic, renal or cardiac function.

Therefore, NSAIDs should only be given after other forms of treatment have been carefully considered. Prolonged use of NSAIDs in the elderly is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

Piroxicam should be used with caution in patients with a history of gastrointestinal disease or inflammatory bowel disease and should be withdrawn if peptic ulceration or gastrointestinal bleeding occurs.

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 in such patients, should occur prior to the initiation of therapy and regularly thereafter. NSAIDs should be given with care to patients with heart failure or hypertension since oedema has been reported in association with NSAID administration.

Piroxicam may cause a decrease in platelet aggregation and prolongation of bleeding time. This effect should be kept in mind when bleeding times are determined.

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Caution is required if piroxicam is administered to patients suffering from or with a previous history of bronchial asthma since NSAIDs have been reported to cause bronchospasm in such patients.

There are reports of reversible elevation of blood urea, nitrogen and creatinine.

In rare cases, NSAIDs may cause interstitial nephritis, glomerulitis papillary necrosis and nephrotic syndrome. They inhibit synthesis of renal prostaglandin that plays a supportive role in maintaining renal perfusion in patients with reduced blood volume and renal blood flow. In such patients, administration of a NSAID may precipitate overt renal decompensation, which is followed by recovery to the pre-treatment state upon discontinuation of NSAID therapy. Patients at greatest risk of such a reaction are those with congestive heart failure, liver cirrhosis, nephrotic syndrome or overt renal disease. Such patients should be monitored carefully whilst receiving NSAID therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the drugs mentioned below because, as with other NSAIDs, piroxicam has the potential to induce the following interactions.

Anti-hypertensives
There may be a reduction in the effect of anti-hypertensives.

Diuretics
Piroxicam may cause sodium, potassium and fluid retention, and may interfere with the natriuretic action of diuretic drugs causing a reduction in the diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension, to avoid a possible worsening of these conditions.

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

Concomitant administration of antacids had no effect on piroxicam plasma levels, nor did concurrent therapy of piroxicam with digoxin or digitoxin affect the plasma levels of either drug.

Anticoagulants, Sulphonamides and Hydantoins
Piroxicam is highly protein bound, and therefore, it might be expected to displace other protein bound drugs eg., anticoagulants, sulphonamides and hydantoins such as phenytoin. Patients must be monitored closely for change in dosage requirements when giving Brexidol to patients already receiving other highly protein bound drugs.

It is considered unsafe to take NSAIDs in combination with warfarin or heparin unless under direct medical supervision. Bleeding has been reported rarely when piroxicam has been administered to patients being treated with coumarin-type anticoagulant drugs. Such patients should be monitored closely if Brexidol and oral anticoagulants are administered together.

Other Analgesics
Human studies have shown that concomitant administration of piroxicam and aspirin reduced the plasma levels of piroxicam to about 80 % of the normal value.

The use of piroxicam with aspirin or its concurrent use with other NSAIDs, increases the potential for adverse reactions and therefore concomitant use of two or more NSAIDs is not recommended.

Cimetidine
There is some evidence that a slight but significant increase in absorption of piroxicam may occur following administration of cimetidine - with no significant changes in elimination rate constants or half-life. It is unlikely that this small increase in absorption is of clinical significance.

Lithium
NSAIDs, including piroxicam, have been reported to decrease the elimination of lithium. It is recommended that the levels of lithium are monitored when initiating, adjusting or discontinuing treatment with piroxicam.

Quinolone Antibiotics
Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Mifepristone

In common with other NSAIDs, piroxicam should be avoided for at least 8 to 12 days following mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Methotrexate
There is decreased elimination of methotrexate with NSAIDs.

Ciclosporin
NSAIDs may increase cyclosporin nephrotoxicity as a result of their effect on renal prostaglandins.

Corticosteroids
There is increased risk of gastrointestinal bleeding with corticosteroids.

Aminoglycosides
Reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations have been reported.

Probenecid
Reduction in metabolism and elimination of NSAID and metabolites occurs with probenecid.

Oral Hypoglycaemic Agents
Inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia is known to occur with oral hypoglycaemic agents.

4.6 Pregnancy and lactation

Although no teratogenic effects have been demonstrated in animal toxicology studies, the use of NSAIDs during pregnancy should, if possible, be avoided. Congenital abnormalities have been reported in association with NSAID administration in man. However, these are low in frequency and do not appear to follow any discernible pattern.

Piroxicam inhibits prostaglandin synthesis and release through a reversible inhibition of the cyclo-oxygenase enzyme. This effect, as with other NSAID, is associated with an increased incidence of dystocia and delayed parturition in pregnant animals when drug administration was continued into late pregnancy. NSAIDs are also known to induce closure of the ductus arteriosus in infants and therefore, use in late pregnancy should be avoided.

A study indicates that piroxicam is found in breast milk at about 1 % to 3 % of the maternal plasma concentrations. No accumulation of piroxicam occurred in milk relative to that in plasma during treatment for up to 52 days. Brexidol is not recommended for use in nursing mothers because clinical safety in neonates has not been established.

4.7 Effects on ability to drive and use machines

Piroxicam can alter the state of alertness to such an extent that driving vehicles or performing activities which require quick reflexes (such as operating machinery), may be affected.

Since swollen eyes, blurred vision and eye irritation have been reported in association with the use of piroxicam, and dizziness, drowsiness or headaches are possible side effects associated with taking NSAIDs, patients should be warned to take care when undertaking such activities.

Although routine ophthalmology and slit-lamp examinations have not shown evidence of ocular changes such examinations should be performed if these symptoms develop.

4.8 Undesirable effects

Gastrointestinal
Gastrointestinal symptoms associated with piroxicam administration are the most common side effects, but in most cases do not interfere with continuation of therapy. These include ulcerative stomatitis, anorexia, epigastric or abdominal discomfort or pain, nausea, constipation, flatulence, diarrhoea and indigestion, vomiting, dyspepsia, melaena

and haematemesis.

Gastric ulceration, duodenal ulcer and gastrointestinal perforation and gastrointestinal bleeding, in rare cases fatal, have been reported with piroxicam. Long-term administration of piroxicam in a dose of 30 mg per day or more carries an increased risk of gastrointestinal side effects.

Hypersensitivity Reactions
There are rare reports of piroxicam causing cutaneous hypersensitivity reactions such as rash or pruritus, urticaria, angioedema, onycholysis or alopecia. As with other NSAIDs, epidermal necrolysis (Lyell's disease), Stevens-Johnson syndrome or vesiculo-bullous reactions may occur rarely.

These reactions may also consist of respiratory tract reactivity comprising of asthma, aggravated asthma, bronchospasm or dyspnoea.

There may be other non-specific allergic reactions and anaphylaxis.

Other hypersensitivity reactions such as vasculitis and serum sickness have been rarely reported.

Dermatological Reaction
Photosensitivity reactions occur infrequently.

Renal
Rarely, NSAIDs may cause interstitial nephritis, glomerulo-nephritis, nephrotic syndrome and renal failure.

Haematological Reactions
Decreases in haemoglobin and haematocrit in the absence of obvious gastrointestinal bleeding have occurred and anaemia has been reported, as have thrombocytopenia, non-thrombocytopenic purpura (Henoch-Schoenlein), leucopenia and eosinophilia. There are rare reports of aplastic anaemia, haemolytic anaemia and epistaxis.

Hepatic
Changes in various liver function parameters have been seen with piroxicam and, as with other NSAIDs, some patients may show an increase in serum transaminase concentration during piroxicam treatment; also, severe hepatic reactions, including jaundice and cases of fatal hepatitis have occurred.

Even though such events are rare, where abnormal liver function tests persist or worsen or clinical signs consistent with liver disease develop, or there are systemic manifestations (such as a rash or eosinophilia), treatment should be discontinued.

Cardiovascular
As with other NSAIDs, oedema (mainly of the ankle), has been reported in some patients; the possibility of precipitating congestive cardiac failure in the elderly or those with compromised cardiac function should be remembered.

Equally, elderly, frail or debilitated patients require careful supervision because they may tolerate side effects less well; the elderly require caution since they are more likely to have impaired renal, hepatic or cardiac function.

Neurological and Special Senses
CNS effects including dizziness, headache, somnolence, insomnia, depression, nervousness, hallucinations, mood alterations, dream abnormalities, mental confusion, paraesthesias, vertigo, visual disturbances, optic neuritis, tinnitus, malaise, fatigue and drowsiness have all been reported.

Palpitations, metabolic abnormalities such as hypoglycaemia, weight increase or decrease and anecdotal cases of positive ANA or hearing impairment have all been reported.

4.9 Overdose

Symptoms
The most likely symptoms of overdose are headache, vomiting, drowsiness, dizziness and fainting.

Management
In the event of an overdose with Brexidol, supportive and symptomatic management is necessary and may include gastric lavage and the use of oral activated charcoal to reduce absorption of piroxicam. The correction of severe electrolyte abnormalities may need to be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Brexidol is an inclusion complex of piroxicam and beta-cyclodextrin (piroxicam betadex). It is a non-steroidal anti-inflammatory drug.

The faster dissolution characteristics of piroxicam betadex (about 100 % in 10 minutes) with respect to piroxicam alone, results in a quicker absorption of the active ingredient and promotes a more rapid onset of analgesic action (see Pharmacokinetics).

5.2 Pharmacokinetic properties

As a NSAID, piroxicam is well absorbed after oral administration and is extensively metabolised by the liver with elimination occurring via the kidneys.

The drug has a plasma half-life of about 50 hours with the maintenance of plasma levels for up to 24 hours. Steady state levels are reached in 7 to 12 days and maintained with little change for up to a year of treatment.

The absorption of piroxicam from piroxicam betadex is more rapid than that of piroxicam alone, so that the time taken to reach the maximum plasma concentration (T_{max}), is much shorter; clinically this is reflected by a more rapid onset of acute analgesia after single doses.

Studies on healthy volunteers demonstrated that, after single oral administration at equivalent doses (20 mg as piroxicam), piroxicam from piroxicam betadex was absorbed at least 2 times faster than it was as the plain drug. The maximum plasma concentration (C_{max}) of piroxicam was reached within 30 to 60 minutes with piroxicam betadex and was higher than that obtained after 2 hours with plain piroxicam.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicology, genotoxicology and toxicology of reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Crospovidone
Sodium starch glycollate
Colloidal hydrated silica
Pregelatinised starch
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

The tables are enclosed in opaque blisters composed of 250 µm PVC coated with 40 g m^{-2} PVDC and 25 µm aluminium coated with 18 to 20 g m^{-2} PVDC.

The blisters are boxed in cardboard cartons containing 20 tablets.

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

Trinity Chiesi Pharmaceuticals Ltd
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8 MARKETING AUTHORISATION NUMBER

PA 743/10/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 1992
Date of last renewal: 14th August 2002

10 DATE OF REVISION OF THE TEXT

October 2006