IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PPA0465/121/001A
Case No: 2077025

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

PCO Manufacturing Limited

Unit 10, Ashbourne Business Park, **Rath**, **Ashbourne**, **Co. Meath**, **Ireland**

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

Selectol 200 mg Film-coated 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 **10/02/2010**.

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

Selectol 200 mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg of celiprolol hydrochloride.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet. (Tablet)

Product imported from Belgium:
White, film-coated, heart-shaped tablet with a distinctive ‘S’ shaped logo on one side and ‘200’ and a breakline on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Uses:
Mild to moderate hypertension.
Management of angina pectoris.

4.2 Posology and method of administration

The route of administration is oral.

Recommended Dosage:
Adults: The usual dose is 200 mg once daily in the morning. In the case of an inadequate response the dose may be increased to 400 mg daily.
It is important to take Selectol one hour before or two hours after food with a glass of water. If the treatment is to be discontinued, reduce the dosage gradually over a period of 1-2 weeks.

Elderly patients: Although pharmacokinetics in elderly patients are not significantly different, due regard should be made for decreased renal and liver function in this age group.

*Patients with renal disease**:*** Adjustment of dosage is ussually unneccessary in patients with renal insufficiency with a creatinine clearance exceeding 30 ml/min. However, careful surveillance of such patients is recommended until steady state blood levels are achieved. A reduction in dosage may be necessary in patients with severe renal impairment.

Children: not recommended

4.3 Contraindications

1. Second or third degree atrioventicular block.
2. Severe bradycardia.

3. Uncontrolled or digitalis/diuretic-refractory heart failure.
4. Cardiogenic shock.
5. Acute episodes of asthma.
6. Untreated pheochromocytoma.
7. Hypersensitivity to celiprolol or to the components of the formulation.
8. Sick sinus syndrome (including sino-atrial block)

4.4 Special warnings and precautions for use

Sudden withdrawal of beta adrenoceptor blocking agents in patients with ischaemic heart disease may result in the appearance of anginal attacks of increased frequency or severity or deterioration in cardiac state. Discontinuation of therapy should be gradual.

The beta-blocker should only be used with caution in patients with controlled congestive cardiac failure or with a history of asthma. Evidence of recrudescence of either condition should be regarded as a signal to discontinue therapy.

Celiprolol may be used in patients with obstructive respiratory disorders provided that adequate supervision is maintained to permit any necessary adjustment of dosage of the bronchodilator employed.

The initial treatment of severe malignant hypertension should be so designed as to avoid reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

Patients with hepatic or renal insuffiency should be carefully monitored after treatment has commenced.

Cardiac Failure: in patients with well-controlled cardiac insufficiency, celiprolol requires strict medical surveillance. Symptoms of cardiac decompensation should be regarded as a signal to discontinue therapy.

First degree heart block: celiprolol should be given with caution in patients with first degree heart block.

Prinzmetal's angina: beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal's angina.

Peripheral circulatory disorders: due to its vasodilating activity, celiprolol may be used in patients with peripheral circulatory disorders (Raynauds disease or syndrome, intermittent claudication). Nevertheless, close monitoring of such patients is advisable.

Asthma and bronchospastic diseases: due to its beta 1 selective blocking and beta 2 agonist properties, celiprolol may be used with caution in controlled asthmatics and in patients with compensated chronic obstructive pulmonary disease.

Impaired Renal Function: see dosage and method of administration.

Treated pheochromocytoma: close blood pressure monitoring should be exercised.

Diabetes Mellitus: although celiprolol dose not interfere with the metabolism of carbohydrates, celiprolol as other beta blockers may mask the symptoms of hypoglycaemia. (see also section 4.5).

Allergic reactions have been observed with celiprolol which may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions induced by other drugs.

Drug-screening tests: celiprolol which may induce a positive reaction when drug-screening tests are conducted and patients should be informed about such a possibility.

Discontinuation of therapy should be gradual i.e. over 1-2 weeks

4.5 Interaction with other medicinal products and other forms of interaction

General anaesthesia: Selectol therapy must be reported to the anaesthesist prior to general anaesthesia. If it is decided to withdraw the drug before surgery, 48 hours should be allowed to elapse between the last dose and anaesthesia. Special care should be exercised when using anaesthetic agents such as ether, cyclopropane or thrichloroethylene which cause myocardial depression, where Selectol treatment is continued.

Celiprolol should be used with caution when co-administred with amiodarone.

Blood pressure should be closely monitored in case of co-administration of celiprolol and dihydropyridine derivates such as nifedipine. The risk of hypotension may be increased. There is also a risk of cardiac failure in patients with a latent or uncontrolled cardiac insufficiency.

Associations not recommended:

Verapamil: verapamil and celiprolol both slow A-V conduction and depress myocardial contractility through different mechanisms. Therefore, clinical signs and electrocardiogram should be carefully monitored during the treatment with this combination particularly when initiating therapy.

Floctafenine: In case of shock or hypotension due to floctafenine, beta-blockers make the drugs used for compensating these symptoms less effective.

Monoamineoxidase inhibitors (exception MOA-B inhibitors): co-administration of beta blockers with MAOI is not recommended.

Associations to be used with caution:

Class I antiarrhythmic agents (disopyramide, quinidine): risk of disturbances in rhythm and conduction. Therefore, clinical and ECG monitoring must be performed.

Calcium antagonists: diltiazem, bepridil, as they depress the myocardial contractibility and slow the A.V. conduction.

Insulin and oral antidiabetic drugs: beta-adrenergic blockade may prevent the appearance of signs of hypoglycemia, such as tachycardia. In diabetics treated by sulfonylureas, efficacy of the treatment may be increased and drug adjustment may be required.

Anesthetic drugs: celiprolol therapy must be reported to the anesthetist prior to general anesthesia. (See also section 6. Anesthesia) Celiprolol, as other β blockers, attenuates the reflex tachycardia and increases the risk of hypotension.

Associations to be taken into account:

Prostaglandin synthetase inhibiting drugs; may decrease the hypotensive effects of beta-blockers.

Tricyclic antidepressants and phenothiazines: concomitant administration may increase the anti-hypertensive effect of beta blockers and the risk of orthostatic hypotension.

Mefloquine: risk of bradycardia.

4.6 Pregnancy and lactation

No teratogenic effects have been shown in animal studies, but safety during human pregnancy has not been established. Celiprolol should not be used during pregnancy unless there is no safer alternative.

When given within 48 hours of delivery of an obstetric patient, hypotension and bradycardia may be seen in the infant.

The extent to which the drug is excreted in breast milk has not been established. It should not be given to mothers who are breastfeeding their babies.
For treatment information on neonate, please refer to section 4.9.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machinery, it should be taken into account that dizziness or fatigue may occasionally occur.
Patients should be warned about potential for tremor, headaches and impaired vision. They should be advised not to drive or operate machines if such symptoms occur.

4.8 Undesirable effects

A variety of adverse effects observed with other bea-adrenergic blocking agents should be considered as potential adverse effects of celiprolol, although less likely to occur: asthenia, dizziness, nightmares, sleep disturbances, Raynaud's disease.

The most frequent adverse events reported are the following ones:
Skin and appendages: cutaneous effects including psoriasiform rashes.

Collagen disorders: antinuclear antibodies have been observed: Exceptional and reversible lupus syndrome.

Peripheral and central nervous system: tremor, paresthesia.

Vision disorders: xerophthalmias, impaired vision.

Psychiatric disorders: depression, libido decrease

Gastro-intestinal system: diarrhoea and vomiting, nausea, gastralgia

Liver and biliary system: increases in transaminases.

Metabolism and nutrition: hypoglycaemia, hyperglycaemia.

Cardiovascular system: bradycardia, palpitations, hypotension, cold extremities, cardiac failure and arrhythmias.

Respiratory system: bronchospasm, asthmatic dyspnoea and interstitial pneumonitis have been rarely reported.

Reproductive system, male: impotence
Body as a whole: headaches, hot flushes.

4.9 Overdose

Symptoms:

Bradycardia, hypotension, bronchospasm and acute cardiac failure have been reported with beta-blocker overdosage.

Treatment:

As no specific antidote is available for overdosage by β-blockers, treatment should be symptomatic, supportive and the patients should be kept under close surveillance.

In the case of bradycardia or severe hypotension, the following should be administered:

• Atropine, 1 to 2 mg I.V.

• Glucagon at the dose of 1mg repeatable

• Followed, if necessary by isoprenaline 25mcg in slow intravenous or dobutamine 2.5 to 10 mcg/kg/min in intravenous perfusion.

In the case of conduction disturbances, cardiac pacing should be considered.

In the case of cardiac decompensation in the neonate of mother treated with beta-blockers:

• Glucagons, 0.3 mg/kg

• Hospitalization in an intensive care unit,

• Isoprenaline: treatment is generally needed at a high dosage, therefore patients monitoring in a specialized care unit is recommended.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Celiprolol is a vasodilating beta-1 selective adrenoceptor antagonist with partial beta-2 agonist activity. The beta-2 agonist activity is thought to account for its mild vasodilating and positive inotropic properties. It lowers the blood pressure in hypertensive patients at rest and exercise. The effects on heart rate and cardiac output are dependent on the pre-existing background level of sympathetic tone.

Under conditions of stress such as exercise, Selectol attenuates chronotropic and inotropic responses to sympathetic stimulation. However, at rest minimal impairment of cardiac function is seen.

5.2 Pharmacokinetic properties

The plasma half-life is approximately 5 hours although pharmacodynamic effects are pre-set for 24 hours.
Excretion is both urinary and through the gut. Metabolism is minimal.

Stimultaneous ingestion of food reduces bioavailability.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate

Film Coating:
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25ºC.
Store in the original package.

6.5 Nature and contents of container

Blister packs of 28 tablets contained in an outer cardboard carton.

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

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 MARKETING AUTHORISATION NUMBER

PPA 0465/121/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 February 2004
Date of last authorisation: 06 February 2009

10 DATE OF REVISION OF THE TEXT

February 2010