IRISH MEDICINES BOARD ACTS 1995 AND 2006

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

(S.I. No.540 of 2007)

PA0577/052/001
Case No: 2052531

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

McDermott Laboratories Ltd t/a Gerard Laboratories

35/36 Baldoyle Industrial Estate, **Grange Road**, **Dublin 13**, **Ireland**

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

Seliprol 200 mg 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 **08/10/2008**.

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

Seliprol 200 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 200 mg tablet contains celiprolol hydrochloride 200 mg.
Each 200 mg tablet contains lactose monohydrate in the film coating material Opadry Yellow 32K52903.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow film-coated, round biconvex tablets, 9.5 mm diameter, imprinted ‘CL breakline 200’ on one side and ‘G’ on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Celiprolol hydrochloride is indicated for the management of mild to moderate hypertension and for prophylaxis of angina pectoris.

4.2 Posology and method of administration

Tablets for oral administration.

Adults

Hypertension

The initial dose is 200mg orally, taken once daily with a glass of water. Celiprolol should be taken on rising, one hour before meals, or 2 hours after meals. If the response is inadequate, the dose may be increased to 2 x 200mg tablets in one single administration of 400mg or one 400mg tablet once daily, after 2 to 4 weeks of treatment with 200mg once daily. Treatment with celiprolol should not be discontinued abruptly, but should be discontinued gradually (i.e. over a period of 15 days), as discontinuing treatment abruptly may lead to an acute worsening of the patient’s condition.

Angina Pectoris

The initial dose is 200mg orally, taken once daily with a glass of water. Celiprolol should be taken on rising, one hour before meals, or 2 hours after meals. If the response is inadequate, the dose may be increased to 2x 200mg in one single administration of 400mg, or one 400mg tablet once daily, after 2 to 4 weeks of treatment with 200mg once daily. Treatment with celiprolol should be discontinued gradually (i.e. over a period of 15 days), as discontinuing treatment abruptly may lead to an acute worsening of the patient’s condition, especially in the case of pre-existing ischaemic cardiac disease.

Elderly patients
Dosage as for adults.

Dosage in renal impairment
The dosage of celiprolol should be reduced by half in patients with creatinine clearance values of 15-40 ml/minute. Celiprolol is not recommended for patients with creatinine clearance less than 15 ml/minute.

Children
Celiprolol is not indicated for use in children.

4.3 Contraindications

Celiprolol is contraindicated in patients who are hypersensitive to celiprolol, to other β-adrenergic blocking agents or to any of the excipients of this product. Celiprolol is also contraindicated in patients with:

- Second or third degree heart block;
- Severe bradycardia (pulse rate at rest lower than 45 beats per minute before beginning of treatment);
- Sick sinus syndrome;
- Sinoatrial block
- Untreated phaeochromocytoma (celiprolol may only be administered once the alpha receptors have been blocked);
- Metabolic acidosis;
- Hypotension;
- Late stages of peripheral aterial occlusive disease (stage III and IV according to Fontaine);
- Uncontrolled Heart Failure;
- Cardiogenic shock;
- Severe renal impairment with creatinine clearance less than 15ml per minute;
- Severe bronchial asthma, or acute asthmatic attack and severe chronic obstructive pulmonary disease;
- Right cardiac failure secondary to pulmonary hypertension

Celiprolol should not be prescribed for patients being treated with theophylline. Verapamil and beta-blockers both slow A-V conduction and depress myocardial contractility through different mechanisms. When changing from verapamil to celiprolol and vice-versa, a period between stopping one and starting the other is recommended. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

The pharmacokinetics are not significantly different in the elderly, however these patients should be regularly monitored and due regard made for decreased renal and liver function in this age group. Celiprolol may be used in patients with mild to moderate degrees of reduced renal function as celiprolol is cleared by both renal and non-renal excretory pathways. A reduction in dosage by half may be appropriate in patients with creatinine clearances in the range of 15-40 ml per minute. However, careful surveillance of such patients is recommended until steady state blood levels are achieved which typically would be within one week. Patients with hepatic impairment should also be carefully monitored after commencing therapy.

Celiprolol should only be used with caution in patients with controlled congestive cardiac failure (patients treated with digitalis and/or diuretics). Evidence of decompensation should be regarded as a signal to discontinue therapy.

Although cardio selective beta blockers may have less effect on lung function than non-selective beta blockers, as with all beta blockers, these should be avoided in patients with reversible obstructive airways disease unless there are compelling clinical reasons for use (see Section 4.3 Contraindications).

Celiprolol should be used with caution in patients with first degree AV block and in patients with Prinzmetal´s angina.

Celiprolol may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to bradycardia, the dosage should be reduced. Treatment with celiprolol should be stopped if the heart rate decreases to less than 45 beats per min.

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. Although no adverse events due to abrupt cessation of celiprolol have been studied in clinical trials, gradual discontinuation of therapy is recommended.

In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta blockers should be used with great caution as aggravation of these disorders may occur.

Beta-blockers should be used with caution in patients with apparent or latent diabetes mellitus because severe hypoglycemic conditions are possible or symptoms of hypoglycaemia can be masked (regular monitoring of blood glucose status is necessary) (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Under treatment with ß-blockers (e.g. celiprolol) the symptoms of a thyrotoxicosis may be masked.

Beta blockers may in individual cases cause psoriasis, aggravate the symptoms of the pre-existing disease, or lead to psoriasis-like exanthem. Patients with a history of psoriasis should take celiprolol only after careful consideration.

Beta-blockers may increase sensitivity to allergens and severity of anaphylactic reactions. Patients who have a history of severe hypersensitivity and patients undergoing desensitisation treatment may suffer severe anaphylactic reactions.

Celiprolol therapy must be reported to the anaesthetist prior to general anaesthesia. If it is decided to withdraw the medicinal product before surgery, 48 hours should be allowed to elapse between the last dose and anaesthesia. In the event of continuation of celiprolol treatment, special care should be exercised when using anaesthetic agents such as ether, cyclopropane or trichloroethylene (see Section 4.5 Interaction with other medicinal products and other forms of interaction).

Celiprolol should be used with caution in patients suffering from asthma or bronchospastic disease. Although celiprolol is relatively cardio-selective and exerts mild β2 receptor agonism it should not be used in patients suffering from asthma or nocturnal wheeze. In case of crisis salbutamol could be used. Beta selective adrenoreceptor antagonist is contraindicated in the case of acute asthma attack.

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

Combinations not recommended

Verapamil (and to a lesser extent diltiazem) and beta-blockers both slow A-V conduction and depress myocardial contractility through different mechanisms. When changing from verapamil to celiprolol and vice-versa, a period between stopping one and starting the other is recommended. Concomitant administration of both medicinal products is not recommended and should only be initiated with ECG monitoring. Patients with pre-existing conduction abnormalities should not be given the two medicinal products together.

Calcium antagonists of the verapamil- or diltiazem-type and antiarrhythmic agents (e.g. disopyramide, quinidine, amiodarone) should not be given intravenously during therapy with celiprolol because the co-administration may lead to profound hypotension and atrioventricular block (see Section 4.3 Contraindications).

Celiprolol should not be prescribed for patients being treated with theophylline (see Section 4.3 Contraindications).

Beta blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine and other central antihypertensive drugs (alpha-methyldopa, guanfacine, moxonidine, rilmenidine). If the two medicinal products are co-administered, the beta-adrenoreceptor blocking medicinal product should be withdrawn several days before discontinuing the central antihypertensive drug..

The simultaneous administration of celiprolol with Monoamine oxidase inhibitors (except MAO-B inhibitors) may enhance the hypotensive effect of ß-blockers but also the risk of hypertensive crisis.

Combinations to be used with caution

Care should be taken in prescribing a beta-adrenoceptor blocking agent with class I antiarrhythmic agents (e.g., disopyramide, quinidine) and class III antiarrhythmic agents (e.g., amiodarone), because hypotension, bradycardia or other cardiac arrhythmias and/or heart failure may result.

Combination with propafenone may induce cardiac contractility, automatism and conduction disorders (due to removal of compensating sympathetic mechanisms) ECG and clinical monitoring recommended.

Certain antiarrhythmic medicinal products may produce torsade de pointes.

Medications inducing torsades de pointe (except sultopfride):
Class Ia antiarrhytmic agents (hydroquinidine, disopyramide),
Class III antiarrhythmic agents (dofetilide, ibutilide, sotalol),
Neuroleptic agents; phenotiazinic drugs (chlorpromazine, cyamemazine, levomepromazine, thioridazine, trifluoperazine), benzamide drugs (amisulpride, sulpride, tiapride), butyrophonone drugs (droperidol, haloperidol) and other neuroleptic drugs (pimozide),
Other drugs; bepridil, cisapride, diphemanil, IV spiramycin, IV erythromycin, halofantrine, mizolastine, moxifloxacin, pentamidine, IV vincamycin, astemizole, terfenadine.
Increased risk of ventricular rhythm disorders especially torsade de pointes. ECG and clinical monitoring recommended.

The simultaneous administration of nifedipine can cause a severe decrease of the blood pressure.

The simultaneous administration of celiprolol and reserpine, alpha-methyldopa, guanfacine, clonidine or digitalis glycosides can cause an excessive reduction in the heart rate or an increase in the atrioventricular conduction time.

Celiprolol can enhance the effect of antihypertensive medications that are given simultaneously.

The simultaneous administration of celiprolol with insulin or oral antidiabetic agents may intensify the blood glucose lowering effect. Beta-adrenergic blockade may mask symptoms of hypoglycaemia (tachycardia) (see Section 4.4 Special warnings and special precautions for use). Therefore, it is recommended that the blood glucose values be regularly monitored.

The co-administration of anaesthetic drugs with celiprolol attenuates the reflex tachycardia and increases the risk of hypotension. Therefore, before administering anaesthetic agents, the anaesthesiologist should be informed. An anaesthetic drug with a minimal negative inotropic effect should preferably be used (see Section 4.4 Special warnings and special precautions for use).

Simultaneous administration of celiprolol and adrenaline, noradrenaline or other sympathomimetic agents (e.g. those contained in cough medicine or nose and eye drops) may cause an increase of blood pressure.

Simultaneous administration of vasodilatators, tricyclic antidepressants, barbiturates, phenothiazines and other antidepressants as well as alcohol can increase the hypotensive effect of celiprolol.

It has been shown that the bioavailability of celiprolol is impaired when it is given with food. Co-administration of chlorthalidone and hydrochlorothiazide also reduces the bioavailability of celiprolol.

Care should be taken when administering NSAIDs including selective COXII inhibitors and acetylsaliciylic acid (aspirin) ≥ 3g daily.

Simultaneous administration of urologic alpha blocking agents (alfuzosine, doxazosine, prazosine, tamsulosine, terazosine). May increase the risk of hypotensive effect and consequently of orthostatic hypotension.

4.6 Pregnancy and lactation

Pregnancy
The safety of celiprolol for use in human pregnancy has not been established.
Celiprolol passes the placenta in humans. Some β-adrenoceptor blocking agents can cause intrauterine growth retardations. For this reason celiprolol should be administered during pregnancy only after serious risk-benefit-assessment by the treating physician.

Treatment close to the calculated birth date can cause bradycardia, hypotension, hypoglycaemia and neonate asphyxia in a newborn infant. For this reason the therapy with celiprolol should be discontinued 48-72 hours before the calculated delivery date. If this is not feasible, the neonates must be carefully monitored for 48-72 hours after birth.

Lactation
During lactation, celiprolol should only be used following serious risk-benefit-assessment by the treating physician. There is no data available regarding excretion of celiprolol into mother's milk. As other β-adrenergic blocking agents are excreted into mother's milk, excretion of celiprolol into breast milk is possible and the suckling infant should be watched for signs of β-adrenoreceptor blockade.

4.7 Effects on ability to drive and use machines

Driving ability is unlikely to be impaired in all patients taking celiprolol, however in some cases celiprolol may have a minor or moderate influence on the patient's ability to react. This should be considered when extra alertness is required e.g when driving or operating machinery.

4.8 Undesirable effects

Occasional adverse reactions, which are usually mild and transient, have occurred. The following undesirable effects have been observed during treatment with celiprolol and other beta blockers with the following frequencies: Very common (>10%), common (1-10%), uncommon (0.1-1%), rare (0.01-0.1%), very rare (<0.01%) including isolated reports.

Immune system disorders
Rarely (0.01-0.1%) An increase in antinuclear antibodies (ANA) has been seen, its clinical relevance is not clear.

Metabolism and nutrition disorders
Latent diabetes mellitus may come to light, and apparent diabetes mellitus may worsen. Beta-blockers may mask the symptoms of hypoglycaemia or thyrotoxicosis (in particular tachycardia and tremor).

Psychiatric disorders
Rarely (0.01-0.1%) depression has been reported.
Very rare (<0.01%) hallucinations, psychoses

Nervous system disorders
Commonly (1-10%) headache and dizziness, somnolence, nightmares and insomnia (sleep disturbances), tremor and sensation of coldness in the extremities have been reported.
Rarely (0.01-0.1%) paraesthesia
Very rare (<0.01%) confusion

Eye disorders
Very rare (<0.01%) impaired vision, dry eyes with reduced lacrimation (to be considered if the patient uses contact lenses).

Ear and labyrinth disorder
Rarely (0.01-0.1%) tinnitus

Cardiac disorders
Commonly (1-10%) palpitations, bradycardia, significant decrease in blood pressure including when standing up from a lying position (orthostatic dysregulation), have been reported.
Rarely (0.01-0.1%) AV-conduction disorders, increased cardiac insufficiency with peripheral oedema and/or exertional dyspnoea, Raynaud´s phenomen, increase of symptoms in patients with peripheral circulatory disturbances (with existing intermittent claudication, in patients suffering from Raynaud´s syndrome)

Respiratory disorders
Rarely (0.01-0.1%) hypersensitivity pneumonitis, bronchospasm, asthmatic dyspnoea especially in patients with bronchial asthma or a history of asthmatic complaints

Gastrointestinal disorders
Commonly (1-10 %) nausea, vomiting, abdominal pain and abdominal discomfort can occur.
Rarely (0.01-0.1%) diarrhoea, constipation

Skin and subcutaneous tissue disorders
Rarely (0.01-0.1%) allergic skin reactions (e.g. itching, flush, rash, pruritus, urticaria, purpura)
Very rarely (< 0.01%) Betablockers can cause psoriasis in isolated cases, worsen the symptoms of this disease or lead to the formation of psoriasiform exanthemes

Musculoskeletal disorders
Commonly (1-10%) muscle cramps
Rarely (0.01-0.1%) muscle weakness

Reproductive system disorders
Rarely (0.01-0.1%) impotence

General disorders and administration site conditions
Commonly (1-10%) fatigue

Decrease in libido, nervousness, cardiac failure and arrhythmias have also been reported.

4.9 Overdose

No data are available regarding overdose in humans. In the event of excessive bradycardia, intravenous atropine sulphate should be administered without delay to total dose of 0.25-2mg. Inadequate response requires intravenous administration of a bolus dose of glucagon 10mg. If required this may be repeated or followed by an intravenous infusion of glucagon 1-10 mg/hr, depending on the response. If no response, or glucagons is unavailable, a slow intravenous infusion of isoprenaline (5mcg/min) with close cardiac monitoring is suggested. Cardiac pacing should be considered in refractory bradycardia and heart block. Hypotension should be treated with intravenous catecholamines including dopamine and dobutamine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Betablocking agents, selective.
ATC Code: C07A B08
Mode of Action

Celiprolol is a vasoactive, beta-1 selective adrenoceptor antagonist with partial beta-2 agonist activity indicated in mild to moderate hypertension. The beta-2 agonist activity is thought to account for its mild vasodilating properties. It lowers blood pressure in hypertensive patients at rest and on 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, celiprolol attenuates chronotropic and inotropic responses to sympathetic stimulation. However, at rest, minimal impairment of cardiac function is seen.
Celiprolol therapy has not been shown to adversely affect plasma lipid profiles.

5.2 Pharmacokinetic properties

Celiprolol is a hydrophilic compound that is incompletely absorbed from the gastrointestinal tract. Celiprolol hydrochloride is hydrophilic and crosses the blood-brain barrier only to a negligible extent.

Biovailability of orally administered celiprolol ranges from 30-74% depending on the dose administered. Plasma half-life is approximately 5-6 hours and pharmacodynamic effects are present for at least 24 hours. At plasma concentrations of 0.11 to 0.86μmol/L, celiprolol is only slightly metabolised (1-3%) before excretion in the bile (50%) and urine (15-25%). It has been shown that the bioavailablity of celiprolol is impaired when it is given with food. Co-administration of chlorthalidone, hydrochlorothiazide and theophylline also reduces the bioavailability of celiprolol.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Mannitol (e421)
Croscarmellose sodium
Magnesium stearate

Film coat
Clear film coat opadry ys-1-7006:
Hypromellose (e464),
Macrogol
Yellow film coat opadry 32k52903:
Lactose monohydrate
Titanium dioxide (e171
Hypromellose
Iron oxide yellow (e172)
Quinoline yellow lake (e104
Glycerol triacetate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Celiprolol hydrochloride tablets 200 mg are available either:

in cartoned PVC/PVdC/Aluminium foil blister packs of 5, 7, 10, 14, 15, 20, 21, 28, 30, 50, 56, 60, 84, 90 and 100 tablets;

in polypropylene (PP) bottles fitted with low density polyethylene (LDPE) caps (30 and 100 tablets).

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

McDermott Laboratories Ltd T/A Gerard Laboratories
Grange Road
Baldoyle
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 577/52/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th September 2003

Date of last authorisation: 23rd April 2006

10 DATE OF REVISION OF THE TEXT

August 2008