

IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0408/058/001

Case No: 2085471

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

Ranbaxy Ireland Limited

Spafield, Cork Road, Cashel, Co. Tipperary, Ireland

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

Celiprolol Hydrochloride, 200 Milligram

the particulars of which are set out in 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 **06/08/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Celiprolol hydrochloride 200mg film coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg celiprolol hydrochloride.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow coloured, capsule shaped, biconvex film coated tablets, debossed with '200' on one side of the breakline and a deep breakline on the other side.

The tablet can be broken into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Celiprolol is indicated for the treatment of hypertension.

4.2 Posology and method of administration

Adults: The initial dose is 200 mg 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 response is inadequate, the dose may be increased to 400 mg once daily, after 2 to 4 weeks of treatment with 200mg once daily. It may take several weeks of treatment for the anti-hypertensive effect of celiprolol to be fully established. There is no limit for the duration of treatment. This depends on the nature and severity of the disease. Treatment with celiprolol should not be discontinued abruptly, but should be discontinued gradually (i.e. over a period of 7-10 days), as discontinuing treatment abruptly may lead to an acute worsening of the patient's condition.

Elderly: 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.

Dosage in hepatic impairment: Patients with hepatic impairment should also be carefully monitored after commencing therapy and a reduced dosage should be considered.

Children: Not recommended.

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 50 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 arterial occlusive disease (stage III and IV according to Fontaine);
- Overt heart failure;
- Cardiogenic shock;
- Severe renal impairment with creatinine clearance less than 15ml per minute; and
- Severe bronchial asthma and severe chronic obstructive pulmonary disease.

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 to 40ml 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 cardiac 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 some 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 ischemic heart disease may result in the appearance of anginal attacks of increased frequency or severity or deterioration in cardiac state. Although no adverse effects 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 hypoglycaemic 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 β -blockers (e.g. celiprolol) the symptoms of 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 exanthema. 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*).

4.5 Interaction with other medicinal products and other forms of interaction

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. If the two medicinal products are co-administered, the beta-adrenoceptor blocking medicinal product should be withdrawn several days before discontinuing clonidine.

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

Combinations to be used with caution

Care should be taken in prescribing beta-adrenoceptor blockers 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.

Certain antiarrhythmic medicinal products (disopyramide, quinidine, amiodarone, sotalol) may produce torsade de pointes. Therefore, ECG monitoring is necessary. In case of torsade de pointes administering of antiarrhythmic agents is not 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 not 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.

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 vasodilators, 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.

4.6 Pregnancy and lactation

Pregnancy

The safety of celiprolol product 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

It has been shown that driving ability is unlikely to be impaired in patients taking Celiprolol.

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 disorders

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 phenomenon, 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 (0.1-1%) 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 (0.1-1%) 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.

Respiratory: bronchospasm may occur in patients with bronchial asthma or with a history of bronchial complaints.

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 a total dose of 2 mg. Inadequate response requires intravenous administration of a bolus dose of glucagons 10 mg. If required this may be repeated or followed by an intravenous infusion of glucagons 1-10 mg/hr, depending on response. If no response, or glucagons is unavailable, a slow intravenous infusion of isoprenaline 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. Bioavailability of orally administered celiprolol ranges from 30 to 70% depending upon 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 0.86 $\mu\text{mol/L}$, celiprolol is about 25% bound to human plasma proteins. After once daily administration, celiprolol is only slightly metabolised before excretion in the bile and urine in almost equal quantities.

It has been shown that the bioavailability 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

Microcrystalline cellulose
Mannitol
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

Film coating material:

Hypromellose
Titanium dioxide (E171)
Macrogol 400
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Store in the original container

6.5 Nature and contents of container

Blister strips comprising of white opaque PVC film with a backing of aluminium foil coated with heat seal lacquer.
Pack of 10, 20, 28, 30, 50, 56 and 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Ranbaxy Ireland Ltd
Spafield, Cork Road
Cashel
Co Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 0408/058/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 December 2003

Date of last renewal: 26 June 2007

10 DATE OF REVISION OF THE TEXT

October 2007