SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Celiprolol hydrochloride 400 mg film coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg celiprolol hydrochloride.
Each tablet contains 3.6mg lactose.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White coloured, capsule shaped, biconvex film coated tablets, debossed with '400' on one side of the breakline and a deep breakline on the other side.
The tablet can be divided into equal doses.

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.
In hypertensive patients, additional treatment with other anti-hypertensive agents according to clinical guidelines is possible, in particular with diuretics. When a combination is initiated an increased monitoring of the blood pressure is recommended
Elderly:

The pharmacokinetics of celiprolol is not significantly different in the elderly people however a close monitoring of elderly patients should be exercised, as renal and hepatic functions may be decreased in this population
Dosage in renal impairment: The dosage of celiprolol should be reduced by half in patients with creatinine clearance values of 15-40 ml/minute. , heart rate should be monitored and treatment should be reconsidered in case of bradycardia (less than 50-55 beats per minute at rest).
Celiprolol is not recommended for patients with creatinine clearance less than 15 ml/minute. 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, please see section 4.4.
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

Hypersensitivity to celiprolol hydrochloride or to any of the excipients listed in section 6.1.

Celiprolol is also contraindicated in patients with:

- Second or third degree heart block;
- Severe bradycardia (< 45-50 beats per minute);
- Sick sinus syndrome (including Sinoartrial block);
- Untreated phaeochromocytoma (celiprolol may only be administered once the alpha receptors have been blocked);
- Metabolic acidosis;
- Hypotension (systolic blood pressure less than 100 mmHg);
- Severe peripheral arterial circulatory disturbances
- Uncontrolled heart failure;
- Cardiogenic shock;
- Severe renal impairment with creatinine clearance less than 15ml per minute; and
- Acute episode of asthma, Severe bronchial asthma and severe chronic obstructive pulmonary disease.
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome

Celiprolol should not be prescribed for patients being treatment with theophylline.

4.4 Special warnings and precautions for use

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 chronic obstructive airways disease, and in patients with a history of bronchospasm or bronchiol asthma, unless there are compelling clinical reasons for their use. Where such reasons exist, celiprolol may be used but with the utmost caution under specialist supervision. The label will carry the following warning: If you have a history of asthma or wheezing, please ask your doctor before taking this medicine

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. Celiprolol is not recommended for patients with creatinine clearance less than 15 ml per minute. Patients with hepatic impairment should also be carefully monitored after commencing therapy and a reduced dosage should be considered.
The initial treatment of severe malignant hypertension should be so designed as to avoid reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

In patients with coronary insufficiency, treatment should not be discontinued abruptly.
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, therapy should be gradually reduced over 1-2 weeks, at the same time, if necessary, initiating replacement therapy to prevent exacerbation of angina pectoris.

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. Continuation of beta blockade reduces the risk of arrhythmias during induction and intubation, although reflex tachycardia may be attenuated and the risk of hypotension may be increased (see “Interactions”). In the event of continuation of celiprolol treatment, special care should be exercised when using anaesthetic agents such as ether, cyclopropane or trichloroethylene (sees section 4.5 Interaction with other medicinal products and other forms of interaction). The patient may be protected against vagal reactions by the intravenous administration of atropine.

Celiprolol should only be used with caution in patients with well controlled congestive cardiac failure (patients treated with digitalis and/or diuretics) or

with a history of asthma under strict medical surveillance. Evidence of decompensation should be regarded as a signal to discontinue therapy.

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. Close monitoring is advisable.
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.

Due to its negative effect on conduction time, Celiprolol should be used with caution in patients with first degree AV block.

Beta blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal's angina, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. The use of beta-1 selective adrenoceptor blocking drugs such as celiprolol may be considered in these patients, but the utmost care should be exercised.

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.
Celiprolol should be used with caution in patients with treated phaeochromocytoma and must not be administered until after alpha-blockade has been established. Close monitoring is advisable.

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.

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 (such as tachycardia) 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 thyrotoxicosis (trachycardia and tremor) may be masked.

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

Celiprolol may give a positive reaction when drug-screening tests are conducted in competitive sport since beta-blockers may be restricted in certain sports. Competitors should check with the appropriate sports authorities.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations not recommended

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

Calcium Channel antagonists such as 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. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other. Patients with pre-existing conduction abnormalities should not be given the two medicinal products together.

In case of shock or hypotension due to floctafenine, beta-blockers may reduce the effectiveness of drugs used to compensate these symptoms.
Digitalis glycosides, in association with beta-adrenoceptor blocking drugs, may increase A-V conduction time.
Fingolimod: Concomitant use of fingolimod and beta blockers may potentiate bradycardia effects and is not recommended. Where such co-administration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.
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.
There is a theoretical risk that concurrent administration of monoamine oxidase inhibitors and high doses of beta-adrenoceptor blockers, even if they are cardio selective, can produce hypotension and is therefore not recommended.
Interactions with organic anion-transporting polypeptides (OATPs) inhibitors
Celiprolol is a substrate of the intestinal update transporters OPTPs, specifically OATP1A2 and OATP2B1. OATPs inhibitors may result in a decrease in celiprolol absorption.Citrus juices have been shown to decrease the absorption of celiprolol from the gastrointestinal tract through inhibition of OATP2B1 update transporter activity, resulting in approximately 90% decrease in AUC and C_{max}. Patients should be advised to avoid such beverages.

Precautions for use

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 product torsade de pointes. Therefore, ECG monitoring is necessary. In case of torsade de pointes administering of antiarrhythmic agents is not recommended.

Beta blockers may intensify the blood sugar lowering effects of insulin and oral antidiabetic drugs, and the dosage of antidiabetics may therefore require adjustment. In addition, beta-adrenoceptor blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia (in particular, tachycardia).

Therapy with beta-adrenoceptor blockers must be reported to the anaesthetist prior to general anaesthesia as they may attenuate the reflex tachycardia and increase the risk of hypotension (see section 4.4 “Special warnings and special precautions for use”). 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).
Interactions with inhibitors/inducers of P-glycoprotein:
Concomitant use with drugs that inhibit P-gp (e.g. verapamil, erythromycin, clarithromycin, ciclosporin, quinidine, ketoconazole and itraconazole) are likely to result in increased plasma concentrations of celiprolol. Co-administration of celiprolol 100mg and the P-gp-inhibitor itraconazole 200mg resulted in an 80& increase in celiprolol AUC. A dose-reduction of celiprolol could be considered when concomitantly used with drugs that inhibit P-gp.
Concomitant use with drugs that induce P-gp (e.g. rifampicin and St. John's wort) could result in decreased plasma concentrations of celiprolol. Co-administration of celiprolol 200mg and rifampicin 600mg o.d. for 5 consecutive days resulted in a 40% decrease of celiprolol AUC. A more pronounced effect after longer treatment with rifampicin cannot be ruled out. A dosage adjustment of celiprolol might be necessary when treatment with a P-gp inducing drug is initiated or discontinued.

Take into account

Concomitant therapy with dihydropyridine calcium channel antagonists, such as nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent or uncontrolled cardiac insufficiency. Blood pressure should be closely monitored in case of co-administration of celiprolol and dihydropyridine derivatives especially when therapy is initiated.

The simultaneous administration of celiprolol and resperine, 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.

Simultaneous administration of celiprolol and adrenaline, noradrenaline or other sympathomimetic agents (e.g. those contained in cough medicine or nose and eye drops) may counteract the effects of beta blockers

Simultaneous administration of vasodilators, tricyclic antidepressants, barbiturates, phenothiazines and other antidepressants as well as alcohol may increase the orthostatic hypotensive effect of celiprolol.

Drugs inhibiting prostaglandin synthetase, such as ibuprofen or indomethacin, may decrease the hypotensive effects of beta-adrenoceptor blocking drugs.
Concomitant therapy with mefloquine may cause bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of celiprolol product for use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and post-natal development.

However, beta-adrenoceptor blocking drugs in general have been associated with reduced placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. Celiprolol should therefore not be used during pregnancy unless there is no safer alternative.

In the newborn of treated mothers, beta-blocking activity persists for several days after birth and this may result in an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period (See section 4.9 Overdose).
In general beta blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. Plasma volume should not be increased as risk of acute pulmonary oedema may exist. In addition, adverse effects (especially hypoglycaemia, bradycardia and respiratory distress) may occur in foetus and neonate. Therefore close monitoring of the neonate is recommended for the first 3 to 5 days of life. When given within 48 hours of delivery of an obstetric patient, hypotension and bradycardia may be seen in the infant.

Lactation
Most beta blockers will pass into breast milk, although to variable extents. There is insufficient information on the excretion of celiprolol in human milk. The risk of hypoglycaemia and bradycardia occurring in the nursing infant have not been evaluated. A risk to the newborns/infants cannot be excluded. The use of Celiprolol is therefore not recommended in breast-feeding mothers.

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. However, it should be taken into account that occasional dizziness or fatigue may occur as well as the potential for tremor, headaches or impaired vision. If affected, patients should be advised not to drive or operate machines.

4.8 Undesirable effects

Beta-adrenoceptor blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia (in particular, tachycardia).

Occasional side effects, which are usually mild and transient have occurred. These include headache, hot flushes, asthenia, dizziness, fatigue, somnolence and insomnia (sleep disturbances). Additional side effects associated with beta-2 agonist activity, tremor and palpitations, have been reported. These effects usually do not require withdrawal of therapy.

Bronchospasm, skin rashes and/or visual disturbances have been reported in association with the use of beta blockers. Celiprolol should be discontinued if these effects occur.

The following undesirable effects have been observed during treatment with celiprolol and other beta-blockers with the following frequencies.
The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000), Not known (cannot be estimated from available data).

Metabolism and nutrition disorders

Not known: Hypoglycaemia, Hyperglycaemia

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

Common: depression has been reported.

Uncommon: insomnia

Very rare: psychoses

Not known: hallucinations, nightmare, libido decrease

Nervous system disorders

Common: headache and dizziness, somnolence, nightmares and insomnia (sleep disturbances), tremor and sensation of coldness in the extremities have been reported, paraesthesia, asthenia.

Very rare: confusion

Not known: syncope

Eye disorders

Not known: impaired vision, visual disturbances have been reported including xerophthalamias; dry eyes (to be considered if the patient uses contact lenses).

Ear and labyrinth disorders

Rare: tinnitus

Cardiac disorders

Common: significant decrease in blood pressure including when standing up from a lying position (orthostatic hypotension), have been reported.

Uncommon: palpitations

Rare: slowed AV-conduction, increased cardiac insufficiency with peripheral oedema and/or exertional dyspnoea. Heart failure, cold and cyanotic extremities. In susceptible patients: precipitation of existing A-V block.

Not known: bradycardia, cardiac failure

Vascular disorders

Common: Hot flush, In susceptible patients: exacerbation of intermittent claudication Raynaud's disease or syndrome have been reported.

Uncommon: Cold extremities, hypotension

Respiratory,thoracic and mediastinal system disorders

Uncommon: Dyspnoea

Rare: hypersensitivity pneumonitis, asthmatic dyspnoea especially in patients with bronchial asthma or a history of asthmatic complaints.

Not known: Interstitial pneumonitis, bronchospasm

Gastrointestinal disorders

Common: nausea, vomiting, abdominal pain and abdominal discomfort can occur, dry mouth

Rare: constipation.

Not known: diarrhoea.

Hepatobiliary disorders

Not known: Increase in transaminases

Skin and subcutaneous tissue disorders

Common: rash, pruritus, hyperhidrosis, erythema

Rare: allergic skin reactions (e.g. itching, flush, rash, pruritus, urticaria, purpura).

Very rare: Beta blockers can cause psoriasis in isolated cases, worsen the symptoms of this disease or lead to the formation of psoriasiform exanthemes.

Musculoskeletal and connective tissue disorders

Common: muscle cramps
Uncommon: arthralgia

Rare: muscle weakness

Not known: systemic lupus erythmatosus

Reproductive system and breast disorders

Common: erectile dysfunction

Rare: male impotence, libido decrease

General disorders and administration site conditions

Common: fatigue.

Investigations

Common: An increase in antinuclear antibodies (ANA) has been seen, its clinical relevance is not clear.

Antinuclear antibodies have been observed, exceptional and reversible lupus syndrome
Not known: hepatic transaminases increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

No data are available regarding overdose in humans.

The most common symptoms to be expected following overdosage with a beta-adrenoceptor blocking drug are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

General treatment should be symptomatic and supportive and be conducted under close supervision, with the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any drug still present in the gastro-intestinal tract.
Haemodialysis or haemoperfusion may be considered.

Bradycardia or extensive vagal reactions should be treated with intravenous atropine, 1-2mg. Cardiac pacing should be considered in refractory bradycardia and heart block. Hypotension should be treated with plasma or

plasma substitutes and, if necessary, intravenous catecholamines including dopamine and dobutamine.
Glucagon is the treatment of choice for severe hypotension, heart failure or cardiogenic shock. A bolus of 2-10mg IV in adults (50-150 micrograms/kg in a child) should be followed by an infusion of 1-5mg/hour (50 micrograms/kg/hour), titrated to clinical response. Note vials normally contain 1mg = 1 unit and other treatments may be more convenient to use. Some patients do not respond to glucagon and if vomiting occurs without any improvement in blood pressure, further glucagon is unlikely to be of benefit. Adverse effects of glucagon administration include vomiting, hyperglycaemia, hypokalaemia and hypocalcaemia.

If glucagon is not available or if there is severe bradycardia and hypotension, which is not improved by glucagon, use isoprenaline starting at an infusion rate of 5-10 micrograms/minute (0.02 micrograms/kg/min in children increasing to a maximum of 0.5 micrograms/kg/min) and increased as necessary depending on clinical response. Large doses (up to 800 micrograms/min) have been reported to be necessary on some occassions. Isoprenaline may be ineffective at improving blood pressure despite increasing heart rate.

In severe hypotension additional inotropic support may be necessary with a beta agonist such as dobutamine 2.5-40 micrograms/kg/min (adults and children). Other inotropes such as dopamine, adrenaline (epinephrine) or noradrenaline (norepinephrine) may occassionally be of benefit or consider the use of an intra-aortic balloon pump to sustain an adequate cardiac output. Management of cases of severe hypotension and cardiogenic shock should be discussed with your local poisons service in the UK NPIS 0844 892 0111.

In the case of cardiac decompensation in the neonate of mother treated with beta-blockers, the following should be administered:

• 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.

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 μmol/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
Lactose monohydrate

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 14894/0046

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27/06/2007

10 DATE OF REVISION OF THE TEXT

29/02/2024