SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Celectol 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Celiprolol Hydrochloride 200 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White film-coated biconvex heart shaped tablets engraved with 200 and a breakline on one face and the Celectol logo on the other face.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The management of mild to moderate hypertension.

4.2 Posology and method of administration

Posology

Adults
The initial dose is 200 mg orally taken once daily with a glass of water. Celectol should preferably be taken first thing in the morning, 30 minutes before food or 2 hours after a meal. If response is inadequate, the dose may be increased to 400 mg once daily according to the therapeutic response.

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

Elderly
Dosage as for adults. However close monitoring of elderly patients should be exercised, as renal and hepatic functions may be decreased in this population.

Paediatric population
Not recommended.

Renal impairment

Dosage may require adjustment (see section 4.4). For patients with a creatinine clearance 15 – 40 ml per minute, heart rate should be monitored and treatment must be reconsidered in case of bradycardia (less than 50 – 55 beats per minute at rest) (see section 4.3). Celiprolol is not recommended in patients with a creatinine clearance less than 15 ml per minute (see section 4.3).

Method of administration
Oral administration.

4.3 Contraindications

As with other beta-adrenoceptor antagonists, celiprolol should not be used in cases of:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Cardiogenic shock, uncontrolled heart failure, sick-sinus syndrome, (including sino-atrial block), second or third degree heart block or severe bradycardia (≤ 50 beats per minute).
- Severe renal impairment with creatinine clearance less than 15 ml per minute.
- Acute episodes of asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Hypotension (systolic blood pressure less than 100 mmHg).
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome.

Celectol film-coated tablets should not be prescribed for patients being treated with theophylline.

4.4 Special warnings and precautions for use

Asthma and bronchospastic diseases
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 chronic obstructive airways disease, and in patients with a history of bronchospasm or bronchial 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: *Do not take this medicine if you have wheezing or asthma.*

Impaired renal and hepatic function
Celectol 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. Celectol 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.

Withdrawal
In patients with coronary insufficiency, treatment should not be discontinued abruptly.

Sudden withdrawal of beta-blockers 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 effects due to abrupt cessation of Celectol have been seen 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.

General anaesthesia
Celectol therapy must be reported to the anaesthetist 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. 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 section 4.5). In the event of continuation of Celectol treatment special care should be exercised when using anaesthetic agents such as ether, cyclopropane or trichloroethylene. The patient may be protected against vagal reactions by the intravenous administration of atropine.

Cardiac failure
Celectol should only be used with caution in patients with well-controlled congestive cardiac failure under strict medical surveillance. Evidence of decompensation should be regarded as a signal to discontinue therapy.

Peripheral circulatory disorders
In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication) excluding patients in the late stage (see section 4.3), beta-blockers should be used with great caution as aggravation of these disorders may occur. Close monitoring is advisable.

Bradycardia
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 the bradycardia, the dosage should be reduced.

First degree heart block
Due to its negative effect on conduction time, celiprolol should only be given with caution to 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, due to unopposed alpha-receptor mediated coronary artery vasoconstriction. The use of beta-1 selective adrenoceptor blockers such as celiprolol may be considered in these patients, but the utmost care should be exercised.

Treated pheochromocytoma
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.

Anaphylactic and allergic reactions
In patients with a history of anaphylactic reactions, beta-blockers may increase the sensitivity to allergens and the seriousness of the reactions.

Patients with psoriasis or a history of psoriasis should only be given beta-blockers after careful consideration, as psoriasis may be aggravated.

Diabetes mellitus
Although celiprolol does not interfere with the metabolism of carbohydrates, latent diabetes mellitus may become manifest or already existing diabetes mellitus may worsen (see sections 4.5 and 4.8). In addition, celiprolol as other beta-blockers may mask the symptoms of hypoglycaemia (in particular tachycardia) (see section 4.5).

Thyrotoxicosis
In patients with hyperthyroidism, the clinical signs of thyrotoxicosis (tachycardia and tremor) may be masked.

Drug screening tests
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.

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Associations not recommended
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.

Non-dihydropyridine calcium channel blockers
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 drugs is not recommended and should only be initiated with both clinical signs and ECG monitored carefully. Patients with pre-existing conduction abnormalities should not be given the two drugs together.

Floctafenine
In case of shock or hypotension due to floctafenine, beta-blockers may reduce the effectiveness of drugs used to compensate these symptoms.

Digitalis glycosides
Association with beta-blockers may increase A-V conduction time.

Fingolimod
Concomitant use of fingolimod with beta-blockers may potentiate bradycardic 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.

Clonidine
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are co-administered, the beta-blockers should be withdrawn several days before discontinuing clonidine.

Monoamine oxidase inhibitors (exception MAO-B inhibitors)

There is a theoretical risk that concurrent administration of monoamine oxidase inhibitors and high doses of beta-blockers, even if they are cardio-selective, can produce hypotension. Co-administration of beta-blockers with MAOIs is not recommended.

Interactions with organic anion-transporting polypeptide (OATP) inhibitors
Celiprolol is a substrate of the intestinal uptake transporters OATPs, specifically OATP1A2 and OATP2B1. OATP 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 uptake transporter activity, resulting in approximately 90% decrease in AUC and C_{max}. Patients should be advised to avoid such beverages.

Associations to be used with caution

Class I antiarrhythmic agents
Care should be taken in prescribing beta-blockers with Class I antiarrhythmic agents (e.g. disopyramide, quinidine) and amiodarone, since these agents may potentiate the negative effects on A-V conduction and myocardial contractility. Clinical and ECG monitoring must be performed.

An increased risk of depression has been reported when beta-blockers are co-administered with diltiazem (see section 4.8).

Insulin and oral antidiabetic drugs
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-blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia (in particular, tachycardia).

Anaesthetic drugs
Therapy with beta-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).

Interactions with inhibitors/inducers of P-glycoprotein
Celiprolol is a substrate for the P-glycoprotein (P-gp) efflux transporter. Concomitant uses 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. 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. A dosage adjustment of celiprolol might be necessary when treatment with a P-gp inducing drug is initiated or discontinued.

Associations to be taken into account

Dihydropyridine derivatives
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.

Prostaglandin synthetase inhibiting drugs
Drugs inhibiting prostaglandin synthetase, such as ibuprofen or indomethacin, may decrease the hypotensive effects of beta-blockers.

Sympathomimetic agents
Sympathomimetic agents, such as adrenaline, may counteract the effects of beta-blockers.

Medicinal products with blood pressure lowering effect (e.g. tricyclic antidepressants, barbituates, phenothiazines)
Concomitant administration may potentiate the anti-hypertensive effect of beta-blockers and the risk of orthostatic hypotension.

Mefloquine
Concomitant therapy with mefloquine may cause bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of this medicinal 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 fetus, the course of gestation and peri- and post-natal development.

However, beta-blockers in general have been associated with reduced placental perfusion, which may result in intrauterine fetal 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. In addition, adverse effects (especially hypoglycaemia, bradycardia and respiratory distress) may occur in fetus and neonate. Therefore close monitoring of the neonate is recommended for the first 3 – 5 days of life.

Breast-feeding
Most beta-blockers will pass into breast milk, although to variable extents. The use of Celectol 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 Celectol. 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

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10);

uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

The following undesirable effects, listed by body system, are generally attributable to the pharmacological activity of beta-blockers:

Metabolism and nutrition disorders:
Not known: hypoglycaemia, hyperglycemia (see sections 4.4 and 4.5)

Psychiatric disorders:
Common: depression
Uncommon: insomnia
Not known: libido decrease, hallucination, nightmare
Confusion and psychoses have also been reported.

Nervous system disorders:
Common: tremor, paraesthesia, headache, asthenia, somnolence, dizziness

Eye disorders:
Not known: xerophthalamias, impaired vision

Cardiac disorders:
Uncommon: palpitations
Not known: bradycardia, syncope, cardiac failure and arrhythmias (including slowed A-V conduction and in susceptible patients there may be precipitation of existing A-V block).

Vascular disorders:
Common: hot flush, aggravation of peripheral vascular disorders such as intermittent claudication, or Raynaud's phenomenon (see sections 4.3 and 4.4)
Uncommon: hypotension, peripheral coldness

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea
Not known: bronchospasm (in patients with bronchial asthma or with a history of bronchial complaints) and interstitial pneumonitis

Gastrointestinal disorders:
Common: vomiting, nausea, abdominal pain, dry mouth
Not known: diarrhoea

Skin and subcutaneous tissue disorders:
Common: hyperhidrosis, erythema, rash, pruritus
Not known: dermatitis psoriasiform, aggravation of psoriasis, alopecia

Musculoskeletal and connective tissue disorders:
Uncommon: muscle spasms
Not known: systemic lupus erythematosus, arthralgia

Reproductive system and breast disorders:

Common: erectile dysfunction

Investigations:
Common: increase in antinuclear antibodies (ANAs)
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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No data are available regarding celiprolol overdose in humans.

The most common symptoms to be expected following overdose with a beta-blocker 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 gastrointestinal tract. Haemodialysis or haemoperfusion may be considered.

Bradycardia or extensive vagal reactions should be treated with intravenous atropine, 1 – 2 mg. 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 – 10 mg IV in adults (50 – 150 micrograms/kg in a child) should be followed by an infusion of 1 – 5 mg/hour (50 micrograms/kg/hour), titrated to clinical response. Note vials normally contain 1 mg = 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 occasions. 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 occasionally 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.

5.1 Pharmacodynamic properties

Celiprolol is a vasoactive beta-l 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 dependant 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.

Celectol therapy has not been shown to adversely effect plasma lipid profiles.

5.2 Pharmacokinetic properties

Celiprolol is a hydrophilic compound that is incompletely absorbed from the gastrointestinal tract. Plasma half-life is approximately 5 - 6 hours and pharmacodynamic effects are present for at least 24 hours. 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

There are no preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6.1 List of excipients

Mannitol BP
Microcrystalline Cellulose BP
Croscarmellose Sodium NF
Magnesium Stearate BP

Film coating:
Opadry YS-1R-7006 (clear) contains hypromellose (E464) and polyethylene glycol (E1521).
Opadry Y-1-7000 (white) contains titanium dioxide (E171), hypromellose (E464) and polyethylene glycol (E1521).

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25 °C.

6.5 Nature and contents of container

Container	Pack size
1. Securitainers.	100
2. HDPE (High Density Polyethylene Bottles).	100
3. Blister packs 250µ clear rigid UPVC with 20µ hard temper aluminium foil	56, 28, 10, 7, 5, 4 or 3
4. Blister packs 250µ opaque rigid UPVC with 20µ hard temper aluminium foil.	56, 28, 10, 7, 5, 4 or 3

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Ltd.
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Crane Mead
Ware, Hertfordshire
SG12 9PY
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0027

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