NEW ZEALAND DATA SHEET

CELOL

1. Product Name

CELOL, 200 mg film coated tablets.

2. Qualitative and Quantitative Composition

Each CELOL tablet contains 200 mg of celiprolol hydrochloride.

CELOL tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

CELOL 200 mg tablets are yellow film coated, round, biconvex tablets. They are 9.5 mm in diameter, imprinted with “CL 200” on one side and “G” on the other.

4. Clinical Particulars

4.1 Therapeutic indications

CELOL is indicated for the management of mild to moderate hypertension and effort-induced angina pectoris.

4.2 Dose and method of administration

Dose

Hypertension

The usual dose is 200 mg once daily. The effect will be fully established after one to two weeks. The dose may be increased to two tablets (400 mg) once daily, if necessary, after a 2 to 4 week interval. The reduction in blood pressure may be progressive so, to achieve maximal therapeutic effects, several weeks of therapy may be required.

If treatment is to be discontinued, reduce the dosage gradually over a period of 1 to 2 weeks. In hypertensive patients, additional treatment with other anti-hypertensive agents is possible, in particular with diuretics. When a combination is initiated an increased monitoring of the blood pressure is recommended.

Angina Pectoris

The usual initial dose is 200 mg once daily. Dosage may be increased to 400 mg once daily after a 2 to 4 week interval until optimum clinical response is obtained.

If treatment is to be discontinued, reduce the dosage gradually over a period of one to two weeks.

Special populations

Elderly

The pharmacokinetics of celiprolol are not significantly different in the elderly.

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

Renal and hepatic impairment

Dosage may require adjustment (see section 4.4).

Paediatric

The safe and effective use of celiprolol in children has not been established. Therefore, treatment of children is not recommended.

Method of administration

CELOL should be taken orally once daily with a glass of water, preferably in the morning.
CELOL should be taken at least 30 minutes prior to a meal or 2 hours after a meal.

4.3 Contraindications

CELOL is contraindicated in cases of known hypersensitivity to celiprolol, to other beta-adrenergic blocking agents or to any of the excipients listed in section 6.1.

Celiprolol is also contraindicated in patients with:

- Acute episode of asthma
- Uncontrolled heart failure
- Cardiogenic shock
- Second or third degree heart block
- Sick sinus syndrome (including sino-atrial block)
- Severe bradycardia (<45-50 beats per minute)
- Severe renal impairment with creatinine clearance less than 15 mL per minute
- Untreated phaeochromocytoma
- Metabolic acidosis
- Hypotension
- Severe peripheral arterial circulatory disturbances.

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 should be used with the utmost caution under specialist supervision.

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

4.4 Special warnings and precautions for use

Withdrawal

In patients with coronary insufficiency, treatment should not be discontinued abruptly. 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. The dosage should gradually be reduced, i.e. over 1-2 weeks. If necessary, at the same time initiate replacement therapy in order to prevent exacerbation of angina pectoris.

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 bradycardia, the dosage should be reduced.

Cardiac failure

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

First degree heart block

Due to its negative effect on conduction time, celiprolol should only be given with caution in patients with first degree heart block.

Prinzmetal's angina

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

Peripheral circulatory disorders

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 orders may occur. Close monitoring of such patients is advisable.

General anaesthesia

Celiprolol therapy must be reported to the anaesthetist prior to general anaesthesia. If it is decided to withdraw celiprolol 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 celiprolol is continued, 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.

Impaired renal or hepatic function

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 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. 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.

Treated phaeochromocytoma

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.

Diabetes mellitus and thyrotoxicosis

Although celiprolol does not interfere with the metabolism of carbohydrates, celiprolol, as other beta blockers, may mask the symptoms of thyrotoxicosis or hypoglycaemia (in particular, tachycardia) (see section 4.5 and section 4.8).

Allergic reaction

In patients with a history of anaphylactic reactions induced by other medication, beta blockers may increase both the sensitivity to allergens and the seriousness of the reactions.

Psoriasis

Beta blockers have been reported to exacerbate psoriasis, and patients with a history of psoriasis should take celiprolol only after careful consideration.

Drug-screening tests

Celiprolol may induce 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 medicines 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.

Calcium antagonists

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 medicines is not recommended and should only be initiated with ECG monitoring. Patients with pre-existing conduction abnormalities should not be given the two medicines together.

Floctafenine

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

Clonidine

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

Monoamine oxidase inhibitors (exceptions MAO-B inhibitors)

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.

Digitalis

Digitalis glycosides, in association with beta-adrenoceptor blocking drugs, may increase A-V conduction time.

Associations to be used with caution

Anti-arrhythmic agents

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), since these agents may potentiate the negative effects on A-V conduction and myocardial contractility. Clinical and ECG monitoring must be performed.

Diltiazem

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

Insulin and oral antidiabetics

Beta blockers may intensify the blood sugar lowering effects of insulin and oral antidiabetic medicines, 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).

Anaesthetic agents

Celiprolol therapy 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).

Associations to be taken into account

Dihydropyridine calcium antagonists

Concomitant therapy with dihydropyridine calcium channel antagonists, such as nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with a 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 agents

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

Tricyclic antidepressants, barbiturates and phenothiazines

Concomitant use of other antihypertensive agents, or of tricyclic antidepressants, barbiturates or phenothiazines may potentiate the orthostatic hypotensive effects of beta blockers.

Sympathomimetic agents

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

Mefloquine

Concomitant therapy with mefloquine may cause bradycardia.

Grapefruit and orange juice

The bioavailability of celiprolol is significantly decreased by grapefruit juice and orange juice. Although the clinical relevance of this interaction has not been fully assessed, studies have suggested that the effects of celiprolol on blood pressure and heart rate are not affected. Nevertheless, the marked reduction in celiprolol bioavailability in the presence of grapefruit or orange juice suggests this interaction may be of clinical significance in some patients.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of celiprolol 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 blockers in general have been associated with reduced placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. Celiprolol should 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 foetus and neonate. Therefore, close monitoring of the neonate is recommended for the first 3 to 5 days of life.

Breast-feeding

Beta-blockers are excreted in human breast milk. It is not known to which extent celiprolol is excreted. The risks of hypoglycaemia and bradycardia occurring in the nursing infant have not been evaluated. Therefore, breast-feeding is not recommended during treatment with celiprolol.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

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) (see section 4.4).

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. Depression and hypersensitivity pneumonitis have been reported rarely.

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

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

Cardiovascular disorders

Bradycardia, slowed A-V conduction, hypotension, cold and cyanotic extremities, cardiac failure. In susceptible patients: precipitation of existing A-V block, exacerbation of intermittent claudication, Raynaud's disease or syndrome.

Psychiatric disorders

Confusion, hallucinations, psychoses, nightmares.

Nervous system disorders

Paraesthesia.

Respiratory, thoracic and mediastinal disorders

Bronchospasm may occur in patients with bronchial asthma or with a history of bronchial complaints. Dyspnoea and interstitial pneumonitis have also been rarely reported.

Gastrointestinal disorders

Vomiting, diarrhoea, nausea and gastralgia.

Skin and subcutaneous tissue disorders

Skin disorders (cutaneous effects including psoriasiform rash), antinuclear antibodies have been observed, exceptional and reversible lupus syndrome.

Reproductive system and breast disorders

Libido decrease, male impotency.

Eye disorders

Visual disturbances have been reported including xerophthalmias, dry eyes.

Hepatobiliary disorders

Increase in transaminase levels.

Metabolism and nutrition disorders

hypoglycaemia, hyperglycemia.

Investigations

An increase in ANA (antinuclear antibodies) has been reported, although its clinical relevance is not clear.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

No data are available regarding celiprolol overdose in humans.

The most common symptoms to be expected following overdosage with beta-adrenoceptor blocking agents 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 - 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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective

ATC code: C07A B08

Mechanism of action

CELOL (celiprolol) is a vasoactive beta-1 selective adrenoceptor antagonist with partial beta-2 agonist activity. 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.

Clinical efficacy and safety

Haemodynamic effects

The haemodynamic profile of celiprolol is significantly different from that of propranolol and atenolol. Celiprolol decreases total peripheral vascular resistance but the renal blood flow does not change.

Metabolic effects

On lipids

Celiprolol does not exhibit deleterious effect on lipid profile: it tends to reduce plasma cholesterol, triglycerides LDL-C levels and increased HDL-C levels. All these changes appeared to increase with the duration of treatment.

On glucides

Celiprolol does not modify the plasma levels of insulin and glucose in Insulin Dependent and in Non-Insulin Dependent Diabetics**.**

5.2 Pharmacokinetic properties

Absorption

Absorption of an oral dose is rapid and consistent but incomplete (55% for 200 mg dose and 74% for 400 mg dose) from the gastrointestinal tract. The bioavailability of celiprolol has been shown to be markedly affected by food and one should avoid administration of celiprolol with food. Co-administration of chlorthalidone, hydrochlorothiazide and theophylline also reduces the bioavailability of celiprolol. Following oral dosing, maximal blood concentrations are reached between 2 and 3 hours.

Distribution

The distribution volume is 4.5L/kg. Celiprolol is hydrophilic and does not cross the blood-brain barrier. The binding to plasma proteins is about 25 - 30%.

Biotransformation

A $_{14}$C labelled dose was completely recovered within 48 hours. The first-pass effect in the liver is insignificant. Celiprolol is metabolized to a minor extent (1 - 3%).

Elimination

After 24 hours, 95% of the dose is eliminated unchanged, 12 - 18% by renal excretion and the remainder in the faeces. Although the plasma elimination half-life is approximately 5 - 6 hours, the pharmacodynamic effects are present for at least 24 hours after once daily administration.

Elderly population

The pharmacokinetic parameters, maximal blood concentration, bioavailability, and plasma elimination half-life are comparable with a younger population.

Renal impairment

The urinary excretion of celiprolol in patients with renal insufficiency is decreased in comparison with the excretion observed in healthy population. Close monitoring of blood pressure and heart rate is required in case of moderate or severe renal insufficiency.

Hepatic impairment

The bioavailability and the elimination half-life are not modified in the cirrhotic patient.

6. Pharmaceutical Particulars

6.1 List of excipients

Each CELOL tablet also contains

- Mannitol
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate
- Lactose monohydrate
- Hypromellose
- Macrogol 400
- Macrogol 6000
- Titanium dioxide (E171)
- Quinoline yellow aluminium lake (E104)
- Triacetin
- Iron oxide yellow (E172)

CELOL is gluten free.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a dry place below 30°C.
Protect from light.

6.5 Nature and contents of container

Al/PVC/PVDC blister packs of 180 tablets (in platforms of 20).

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

28 October 1999

10. Date of Revision of the Text

05 November 2018

Summary table of changes

Section	Summary of new information
4.2	Amended readability by cross-referencing to section 4.4.
4.2	Specified method of administration.
4.4	Cross-referencing to section 4.5 and section 4.8.
4.5	Addition of floctafenine and diltiazem. Amendment of clonidine. Cross-referencing to section 4.4 for anaesthetic agents.
4.8	Cross-referencing to section 4.4. Adjustments to SOC.