

# CELOL

## *Celiprolol hydrochloride 200 mg tablets*

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### Presentation

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CELOL is available as a tablet containing 200 mg of celiprolol hydrochloride. Each tablet is a yellow film coated, round, biconvex tablet, 9.5 mm diameter, imprinted "CL 200" on one side and "G" on the other.

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### Uses

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#### *Actions*

##### **Cardioselectivity**

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 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.

##### **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.

#### ***Pharmacokinetics***

##### **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%.

## **Metabolism**

A <sup>14</sup>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 patients:***

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

### ***Impaired renal function:***

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.

### ***Impaired hepatic function:***

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

## **Indications**

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

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## **Dosage and Administration**

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Celiprolol should be taken once daily, preferably in the morning.

Celiprolol should be taken at least 30 minutes prior to a meal or 2 hours after a meal.

### ***Adults***

#### **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 patients**

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.

## **Children**

The safe and effective use of celiprolol in children has not been established.

## **Patients with hepatic impairment**

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

## **Patients with renal insufficiency**

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.

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## **Contraindications**

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Celiprolol is contraindicated in patients who are sensitive to celiprolol, to other beta-adrenergic blocking agents or to any of the excipients of this product. 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 pheochromocytoma
- 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.

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

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## **Warnings and Precautions**

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### ***Warnings***

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.

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.

## ***Precautions***

### **Cardiac failure**

Celiprolol should only be used with caution in patients with controlled congestive cardiac failure. 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-i 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 Interactions). 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 precaution in treated phaeochromocytoma and blood pressure levels should be closely monitored.

### **Diabetes mellitus**

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).

## 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 and patients should be informed about such a possibility.

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## Adverse Effects

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Occasional side effects which are usually mild and transient have occurred. These include headache, dizziness, fatigue, nausea, 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, asthmatic dyspnoea 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:** bradycardia, slowed A-V conduction, hypotension, cold and cyanotic extremities, cardiac failure and arrhythmias. In susceptible patients: precipitation of existing A-V block, exacerbation of intermittent claudication, Raynaud's disease or syndrome.

**CNS:** confusion, hallucinations, psychoses, nightmares.

**Neurological:** paraesthesia, asthenia.

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

**Gastro-intestinal:** vomiting, diarrhoea, gastralgia.

**Integumentary:** skin disorders (especially rash), dry eyes.

**Liver and biliary system:** increase in transaminase levels.

**Metabolism and nutrition:** apparent diabetes mellitus may worsen. Beta-adrenoceptor blockers may mask the symptoms of thyrotoxicosis or hypoglycaemia (in particular, tachycardia) (see Warnings and Precautions).

**Others:** disturbances of libido and potency, hot flushes. An increase in ANA (antinuclear antibodies) has been reported, although its clinical relevance is not clear.

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## Interactions

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### ***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.

### **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-A inhibitors and high doses of beta-adrenoceptor blockers, even if they are cardio selective, can produce hypertension.

### **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.

#### **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 (see Warnings and Precautions: General anaesthesia). Continuation of celiprolol, as with other beta-blockers, reduces the risk of arrhythmias during induction and intubation, but reflex tachycardia may be attenuated and the risk of hypotension may be increased. Anaesthetic agents causing myocardial depression (e.g. ether, cyclopropane, trichloroethylene) are best avoided.

### ***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 hypotensive effects of beta blockers and the risk of orthostatic hypotension.

## **Sympathomimetic agents**

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

## **Mefloquine**

Risk of 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.

## ***Use during Pregnancy and Lactation***

### **Pregnancy**

Category C.

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.

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: this residual effect is usually without clinical consequences, but there is a possibility of heart failure requiring hospitalisation in an intensive care unit (see Overdosage). Plasma volume should not be increased as risk of acute pulmonary oedema may exist. In addition, bradycardia, respiratory distress, and hypoglycaemia have been reported. For these reasons, careful monitoring of the neonate (heart rate – glycaemia) in a specialised unit is recommended for the first 3 to 5 days of life.

### **Lactation**

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.

## ***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. This should be considered when extra alertness is required e.g. when driving or operating machinery.

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## **Overdosage**

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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 include 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.

The effects of excessive beta blockade can be countered by the slow intravenous infusion of a beta-adrenoceptor stimulant such as isoprenaline, starting with a dose of approximately 5 micrograms per minute with close cardiac monitoring, or dobutamine, starting with a dose of 2.5 micrograms per kilogram per minute, until the required effect has been obtained. In severe overdosage, intravenous glucagon may be considered; an initial bolus dose of 10 mg may be repeated within one hour, if required, or followed by intravenous infusion of glucagon at a rate of 1-10 mg per hour, depending on response.

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## Pharmaceutical Precautions

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

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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Blister packs of 180 tablets (in platforms of 20).

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## Further Information

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### *Ingredients*

Each tablet contains the active ingredient celiprolol hydrochloride.

Each tablet also contains mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, Opadry Clear YS-1-7006 and Opadry Yellow 32K52903 (contains the colours titanium dioxide (E171), quinoline yellow aluminium lake (E104) and iron oxide yellow (E172)).

Lactose is a component of the Opadry Yellow film coat.

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## Name and Address

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## Date of Preparation

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9 September 2009