Celiprolol
Core Safety Profile

Formulations: 200 mg and 400 mg tablets (Note: not all are registered in all countries)

4.2 Posology and method of administration

- General

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 (see section 5.2).

Adults
The usual initial dose is 200 mg once daily.
This dose may be increased after a few weeks to 400 mg and subsequently to 600 mg according to the therapeutic response.
If the 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.

- Pediatric Population

The safety and efficacy in children has not been established.

- 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.
P-RMS assessment and conclusion: Preferred wording by QRD template.

- Special Populations

Patients with hepatic impairment

Limited data is available in patients with hepatic impairment (see section 5.2). Patients with renal impairment
Celiprolol may be used in patients with mild to moderate degrees of reduced renal function.
For patients with a creatinine clearance 15- 40 ml per 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 in patients with a creatinine clearance less than 15 ml/min.

If 100 mg dosage is available should be used the following wording:
Celiprolol may be used in patients with mild to moderate degrees of reduced renal function.
For patients with a creatinine clearance 15-40 mL per minute, dose should be reduced to 100 mg once daily and heart rate should be monitored
Celiprolol is not recommended in patients with a creatinine clearance less than 15 mL/min.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

- Acute episodes of asthma
- Decompensated heart failure
- Cardiogenic shock
- Second or third degree atrioventricular block
- Sick sinus syndrome
- Severe bradycardia (< ~~45~~ 50 beats per minute)
- Hypotension (systolic blood pressure less than 100 mmHg)
- Untreated pheochromocytoma
- Late stages of peripheral arterial occlusive disease and Raynaud's syndrome

4.4 Special warnings and precautions for use

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. 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.

Cardiac failure: in patients with well-controlled cardiac insufficiency, celiprolol requires strict medical surveillance. Symptoms of cardiac decompensation should be regarded as a signal to discontinue therapy.

First degree heart block: celiprolol should 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.

Peripheral circulatory disorders: due to its vasodilating activity, celiprolol may be used in patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication). Nevertheless, close monitoring of such patients is advisable.

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

Asthma and bronchospastic diseases: due to its beta-1 selective blocking and beta-2 agonist properties, celiprolol may be used with caution in controlled asthmatics and in patients with compensated chronic obstructive pulmonary disease.

General Anaesthesia: celiprolol therapy must be reported to the anesthetist prior to general anesthesia. If it is decided to withdraw celiprolol before surgery, 48 hours should be allowed to elapse between the last dose and anesthesia. In the event celiprolol is continued, special care should be exercised when using anesthetic agents such as ether, cyclopropane or trichloroethylene.

Impaired Renal Function: (see section 4.2)

Treated pheochromocytoma: Celiprolol must not be administered until after alpha-blockade has been established. Close blood pressure monitoring should be exercised.

Diabetes mellitus: although celiprolol does not interfere with the metabolism of carbohydrates, latent diabetes mellitus may become manifest or an already existing worsern (see sections 4.5 and 4.8). In addition as with other beta-blockers, celiprolol, as other beta-blockers, may mask the symptoms of hypoglycemia (such as tachycardia).

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

Allergic reactions have been observed with celiprolol which may increase both the sensitivity towards allergens and the seriousness of anaphylactic reactions induced by other drugs.

Drug-screening tests: celiprolol which may induce a positive reaction when drug-screening tests are conducted and patients should be informed about such a possibility.

4.5 Interaction with other medicinal products and other forms of interaction

- ~~Associations~~ Concomitant use not recommended:

Non-dihydropyridine calcium channel blockers (e.g verapamil and to lesser extent diltiazem): calcium channel blockers and celiprolol both slow atrioventricular conduction and depress myocardial contractility through different mechanisms. Therefore, clinical signs and electrocardiogram should be carefully monitored during the treatment with this combination particularly when initiating therapy.

Digitalis glycosides: Association with beta-blockers may increase atrio-ventricular conduction time.

Floctafenine: In case of shock or hypotension due to floctafenine, beta-blockers make the drugs used for compensating these symptoms less effective.

Monoamineoxidase inhibitors (exception MOA-B inhibitors): co-administration of beta-blockers with MAOI is not recommended due to possible hypotension.

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

~~Theophylline: Beta-1 selective beta-blockers may diminish the bronchodilatory effect of theophylline.~~

Interactions with organic anion-transporting polypeptides (OATPs) inhibitors
Celiprolol is a substrate of the intestinal uptake transporters OATPs, 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 uptake transporter activity, resulting in approximately 90% decrease in AUC and Cmax. Patients should be advised to avoid such beverages.

- ~~Associations~~ Combinations to be used with caution:

Class I antiarrhythmic agents (e.g disopyramide, quinidine) and amiodarone: risk of disturbances in rhythm and atrioventricular conduction. Therefore, clinical and ECG monitoring must be performed.

Insulin and oral antidiabetic drugs: beta-adrenergic blockade may prevent the appearance of signs of hypoglycaemia, such as tachycardia. In diabetics treated by sulfonylureas, efficacy of the treatment may be increased and drug adjustment may be required.

Anesthetic drugs: celiprolol therapy must be reported to the anesthetist prior to general anesthesia (see section 4.4). Celiprolol, as other beta-blockers, attenuates the reflex tachycardia and increases the risk of hypotension.

Interactions with inhibitors/inducers of P-glycoprotein: Celiprolol is a substrate for the P-glycoprotein (P-gp) efflux transporter. Concomitant use with drugs that inhibit P-gp (e.g. verapamil, erythromycin, clarithromycin, ciclosporin, quinidine, ketokonazole and itraconazole) are likely to result in increased plasma concentrations of celiprolol. Co-administration of celiprolol 100 mg and the P-gp-inhibitor itraconazole 200 mg 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 200 mg and rifampicin 600 mg 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.

- Combinations to be taken into account:

Dihydropyridine derivatives such as nifedipine: the risk of hypotension may be increased. There is also a risk of cardiac failure 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 drugs (e.g. ibuprofen, indomethacin): may decrease the hypotensive effects of beta-blockers.

Medicinal products with blood pressure lowering effect (eg, tricyclic antidepressants, barbiturates, phenothiazines): concomitant administration may potentiate orthostatic hypotensive effect of beta-blockers

Mefloquine: risk of bradycardia.

Sympathomimetic agents may counteract the effects of beta blockers.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of celiprolol in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
As a precautionary measure, it is preferable to avoid the use of celiprolol during pregnancy.
Other beta-blocking agents decrease placental circulation which may cause foetal death and preterm delivery. The effect of celiprolol on placental blood supply is not known.

In neonates: 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 hospitalization in an intensive care unit. Plasma volume should not be increased as risk of acute

pulmonary oedema may exist. In addition, bradycardia, respiratory distress, and hypoglyceamia have been reported. For these reasons, careful monitoring of the neonate (heart rate - glycaemia) in a specialized unit is recommended for the first 3 to 5 days of life.

Breast feeding
Beta-blockers are excreted in human breast milk. There is insufficient information on the excretion of celiprolol in human milk.
The risks of hypoglycemia and bradycardia occurring in the nursing infant have not been evaluated. A risk to the newborns/infants cannot be excluded.
Therefore, breast-feeding is not recommended during treatment with celiprolol.

4.7 Effects on ability to drive and use machines

Patients should be warned about potential for dizziness, fatigue, tremor, headaches and impaired vision. They should be advised not to drive or operate machines if such symptoms occur.

4.8 Undesirable effects

The frequency classification of adverse effects is following: 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).

- Metabolism and nutrition disorders

Not known: hypoglycaemia, hyperglycaemia (see section 4.4 and 4.5)

- Psychiatric disorders

Common: depression,
Uncommon: insomnia
Not known: libido decreased, hallucination, nightmare

- Nervous system disorders

Common: tremor, paresthesia, headache, asthenia, somnolence, dizziness
Not known: syncope

- Eye disorders

Not known: xerophthalmias, impaired vision

- Cardiac disorders

Uncommon: palpitations,
Not known: bradycardia, cardiac failure and arrhythmias

- 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 and interstitial pneumonitis

- Gastrointestinal disorders

Common: vomiting, nausea, upper abdominal pain, dry mouth
Not known: diarrhea

- Skin and subcutaneous tissue disorders

Common: hyperhidrosis, erythema, rash, pruritus
Not known: dermatitis psoriasiform, aggravation of psoriasis

- Musculoskeletal and connective tissue disorders:

Uncommon: muscle spasms, arthralgia
Not known: systemic lupus erythematosus

- Reproductive system and breast disorders

Common: erectile dysfunction

- Investigations:

Common: antinuclear antibody
Not known: hepatic transaminases increased

4.9 Overdose

Symptoms:
Bradycardia, hypotension, bronchospasm and acute cardiac failure have been reported with beta-blocker overdosage.

Treatment:
As no specific antidote is available for overdosage by beta-blockers, treatment should be symptomatic, supportive and the patient should be kept under close surveillance. Administration of active charcoal may prevent absorption. Artificial ventilation may become necessary. When necessary, treatment should include glucagon, atropine, and isoprenaline or dobutamide.