

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Selectol Tablets 200 mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg celiprolol hydrochloride.

For a full list of excipients, see 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated tablet

A white, film coated, heart shaped tablet with a distinctive heart-shaped logo on one side, '200' and a bisect line on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

#### Uses

Mild to moderate hypertension.

Management of angina pectoris.

### 4.2 Posology and method of administration

#### Posology

The route of administration is oral.

#### *Adults*

The usual dose is 200 mg once daily in the morning. In the case of an inadequate response the dose may be increased to 400 mg daily.

It is important to take Selectol one hour before or two hours after food with a glass of water. If the treatment is to be discontinued, reduce the dosage gradually over a period of 1-2 weeks.

#### *Hypertension*

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.

#### *Hepatic impairment*

Limited data is available in patients with hepatic impairment (see section 5.2)

#### *Renal impairment*

Celiprolol may be used in patients with mild to moderate degrees of reduced renal function. For patients with a creatinine clearance 15-40ml 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 15ml/min.

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.

#### *Paediatric population*

Not recommended.

### **4.3 Contraindications**

1. Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
2. Second or third degree atrioventricular block.
3. Severe bradycardia ( $\leq 50$  beats per minute).
4. Decompensated heart failure.
5. Cardiogenic shock.
6. Acute episodes of asthma.
7. Hypotension (systolic blood pressure less than 100 mmHg).
8. Untreated pheochromocytoma.
9. Sick sinus syndrome.
10. Late stages of peripheral arterial occlusive disease and Raynaud's syndrome.

#### 4.4 Special warnings and precautions for use

##### Coronary insufficiency

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 be gradually reduced, i.e. over 1-2 weeks. If necessary at the same time initiate replacement therapy in order to prevent exacerbation of angina pectoris.

##### Controlled congestive cardiac failure or history of asthma

The  $\beta$ -blocker should only be used with caution in patients with controlled congestive cardiac failure or with a history of asthma. Evidence of recrudescence of either condition should be regarded as a signal to discontinue therapy.

##### Obstructive respiratory disorders

Celiprolol may be used in patients with obstructive respiratory disorders provided that adequate supervision is maintained to permit any necessary adjustment of dosage of the bronchodilator employed.

##### Severe malignant hypertension

The initial treatment of severe malignant hypertension should be so designed as to avoid reduction in diastolic blood pressure with impairment of autoregulatory mechanisms.

##### Hepatic or renal insufficiency

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

##### 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 (Raynauds disease or syndrome, intermittent claudication). Nevertheless, close monitoring of such patients is advisable.

### Psoriasis

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 anaesthesia. If it is decided to withdraw celiprolol before surgery, 48 hours should be allowed to elapse between the last dose and anaesthesia. 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 dosage and method of administration.

### 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 already existing diabetes mellitus worsen (see sections 4.5 and 4.8). In addition, as with other beta-blockers, celiprolol as other beta blockers may mask the symptoms of hypoglycaemia (such as tachycardia).

### Thyrotoxicosis

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

### Allergic reactions

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.

Discontinuation of therapy should be gradual i.e. over 1-2 weeks.

#### 4.5 Interaction with other medicinal products and other forms of interactions

Blood pressure should be closely monitored in case of co-administration of celiprolol and 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.

##### **Concomitant use not recommended**

##### Non-dihydropyridine calcium channel blockers (e.g verapamil and to a 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.

##### Diltiazem

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

##### Digitalis glycosides

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

##### Fingloimod

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.

##### 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.

##### 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.

### **Combinations to be used with caution**

#### Class I antiarrhythmic agents (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 hypoglycemia, such as tachycardia. In diabetics treated by sulfonylureas, efficacy of the treatment may be increased and drug adjustment may be required.

#### Anaesthetic drugs

Celiprolol therapy must be reported to the anaesthetist prior to general anaesthesia. (See also section 4.4 Anaesthesia) Celiprolol, as other  $\beta$  blockers, attenuates the reflex tachycardia and increases the risk of hypotension.

#### 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.

### **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, barbituates, phenothiazines):

Concomitant administration may potentiate the orthostatic hypotensive effect of beta-blockers.

Mefloquine

Risk of bradycardia.

Sympathomimetic agents

Sympathomimetic agents may counteract the effects of beta blockers.

Sinus arrest may occur when beta blockers, including Selectol, are used in combination with other drugs known to induce sinus arrest (see Section 4.8, Undesirable effects).

#### **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 (see below section re case of cardiac decompensation on the neonate of mother treated with beta-blockers).

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, bradycardia, respiratory distress, and hypoglycaemia have been reported. For these reasons, careful monitoring of the neonate (heart rate – glycemia) 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.

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.

#### Breast-feeding

Beta-blockers are excreted in human breast milk. 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.

Therefore, breast feeding is not recommended during treatment with celiprolol.

### **4.7 Effects on ability to drive and use machines**

When driving vehicles or operating machinery, it should be taken into account that dizziness or fatigue may occasionally occur.

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

### **4.8 Undesirable effects**

*The following CIOMS frequency rating is used, when applicable:*

*Very common  $\geq 10\%$ ; Common  $\geq 1$  and  $< 10\%$ ; Uncommon  $\geq 0.1$  and  $< 1\%$ ; Rare  $\geq 0.01$  and  $< 0.1\%$ ; Very rare  $< 0.01\%$ , Unknown (cannot be estimated from available data).*

#### Skin and subcutaneous tissue disorders

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

#### Musculoskeletal and connective tissue disorders

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

#### Nervous System disorders

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



### Eye disorders

- Not known: xerophthalmias, impaired vision.

### Psychiatric disorders

- Common: depression
- Uncommon: Insomnia
- Not known: libido decrease, hallucination, nightmare

### Gastro-intestinal disorders

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

### Metabolism and nutrition disorders

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

### Cardiac disorders

- Uncommon: palpitations
- Not known: bradycardia; cardiac failure and arrhythmias; sinus arrest in predisposed patients (e.g., elderly patients or patients with pre-existing bradycardia, sinus node dysfunction or atrioventricular 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 and interstitial pneumonitis

### Reproductive System and breast disorders

- Common: erectile dysfunction

### Investigations

- Common: antinuclear antibody
- 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: [www.hpra.ie](http://www.hpra.ie); E-mail: [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

## **4.9 Overdose**

### Symptoms

Bradycardia, hypotension, bronchospasm, acute cardiac failure and sinus arrest 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 patients 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.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Celiprolol is a vasodilating beta-1 selective adrenoceptor antagonist with partial beta-2 agonist activity. The beta-2 agonist activity is thought to account for its mild vasodilating and positive inotropic properties. It lowers the blood pressure in hypertensive patients at rest and 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, Selectol attenuates chronotropic and inotropic responses to sympathetic stimulation. However, at rest minimal impairment of cardiac function is seen.

## **5.2 Pharmacokinetic properties**

The plasma half-life is approximately 5 hours although pharmacodynamic effects are pre-set for 24 hours.

Excretion is both urinary and through the gut. Metabolism is minimal.

Simultaneous ingestion of food reduces bioavailability.

## **5.3 Preclinical safety data**

Not relevant.

# **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Mannitol (E421)  
Microcrystalline Cellulose  
Croscarmellose Sodium  
Magnesium Stearate

### Film coating

Opadry Y – IR – 7000 containing:

Hypromellose  
Polyethylene glycol  
Titanium dioxide

Opadry YS-1-7006 (clear) containing:

Hypromellose  
Polyethylene glycol

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

Do not store above 25°C. Store in original package.

## **6.5 Nature and contents of container**

- 1) Polypropylene tablet container with a white LDPE tamper closure.  
Pack sizes: 28, 56, 70 and 100 tablets.
- 2) Al/PVC strips, in an outer box.  
Pack sizes: 3, 4, 5, 7, 10 and 28 tablets.
- 3) HDPE tablet container with a white LDPE child resistant cap.  
Pack sizes: 28, 56, 70 and 100 tablets.

Not all pack sizes are marketed.

## **6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Sanofi-Aventis Ireland Ltd. T/A SANOFI  
Citywest Business Campus  
Dublin 24  
Ireland

## **8 MARKETING AUTHORISATION NUMBER**

PA0540/126/001

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 01 February 1989

Date of last renewal: 11 October 2008

## **10 DATE OF REVISION OF THE TEXT**

November 2018