Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Selectol Tablets 400mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of celiprolol hydrochloride.

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

A white film coated, heart shaped tablet embossed with 'Selectol' on one side and '400' on the reverse.

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.
Selectol should be taken 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 funcations 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 inpatients with a creatanine 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 to any of the excipients listed in section 6.1.
2. Second or third degree atrioventricular block.
3. Severe bradycardia (≤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 ßeta 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 weeeks. 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 ßeta-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 with caution in patients with obstructive respiratory disorders provided that adequate supervision is maintained. If increased airways resistance develops consideration must be given to discontinuation of the ß-blocker depending on the degree of airways resistance and the benefit derived from the ß-blockage.

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 Prinzmetals 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.

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 celiprol 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 hypoglycemia. (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.

Fingolimod
Concomitant use of fingolimod with beta blockers may potentiate byadycardia 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 hypoglycaemia, 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 β-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 cliprolol 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 ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 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 arrhytmia; 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 section 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; E-mail: 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 β-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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Celiprolol is a vasodilating ßeta-1 selective adrenoceptor antagonist with partial ßeta-2 agonist activity. The ßeta-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 dependant 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.

5.3 Preclinical safety data

Not relevant.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate
Opadry Y-1-7000 containing:
Hypromellose, titanium dioxide, polyethylene glycol
Opadry YS-1-7006
Hypromellose
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25ºC. Store in original package.

6.5 Nature and contents of container

1)Polypropylene tablet container with a white LDPE tamper evident closure.
Pack sizes: 28, 56, 70 and 100 tablets.
2)Al/PVDC 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

PA0540/126/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 October 1993

Date of last renewal: 11 October 2008

10 DATE OF REVISION OF THE TEXT

November 2018