Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hypoloc Plus 5 mg / 25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Hypoloc Plus contains 5 mg of nebivolol (as nebivolol hydrochloride: 2.5 mg of SRRR-nebivolol or d-nebivolol and 2.5 mg of RSSS-nebivolol or l-nebivolol), and 25 mg of hydrochlorothiazide).
Excipient with known effect: each tablet contains 116.75 mg of lactose (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Almost violet, round, slight biconvex film-coated tablets with "5/25" embossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.
Hypoloc Plus 5 mg/25 mg fixed dose combination is indicated in patients whose blood pressure is adequately controlled on nebivolol 5 mg and hydrochlorothiazide 25 mg given concurrently.

4.2 Posology and method of administration

Posology

Adults

Hypoloc Plus 5 mg/25 mg is indicated in patients whose blood pressure is demonstrated to be adequately controlled on nebivolol 5 mg and hydrochlorothiazide 25 mg given concurrently.

The dose is one tablet (5 mg/25 mg) daily, preferably at the same time of the day.

Patients with renal insufficiency

Hypoloc Plus should not be given to patients with severe renal insufficiency (see also 4.3 and 4.4).

Patients with hepatic insufficiency

Data in patients with hepatic insufficiency or impaired liver function are limited. Therefore the use of Hypoloc Plus in these patients is contra-indicated.

Older people

In view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Paediatric population

The efficacy and safety of Hypoloc Plus in children and adolescents aged below 18 years has not been established. No data are available. Therefore, use in children and adolescents is not recommended.

Method of administration

Oral use.

Tablets may be taken with meals.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- Liver insufficiency or liver function impairment.
- Anuria, severe renal insufficiency (creatinine clearance < 30 ml/min.).
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy.
- Sick sinus syndrome, including sino-atrial block.
- Second and third degree atrioventricular block (without a pacemaker).
- Bradycardia (heart rate < 60 bpm prior to start therapy).
- Hypotension (systolic blood pressure < 90 mmHg).
- Severe peripheral circulatory disturbances.
- History of bronchospasm and bronchial asthma.
- Untreated phaeochromocytoma.
- Metabolic acidosis.
- Refractory hypokalaemia, hypercalcaemia, hyponatraemia and symptomatic hyperuricaemia

4.4 Special warnings and precautions for use

All warnings related to each monocomponent, as listed below, should apply also to the fixed combination of Hypoloc Plus. See also section 4.8.

Nebivolol
The following warnings and precautions apply to beta-adrenergic antagonists in general.

- *Anaesthesia*: Continuation of beta-blockade reduces the risk of arrhythmias during induction and intubation. If beta-blockade is interrupted in preparation for surgery, the beta-adrenergic antagonist should be discontinued at least 24 hours beforehand. Caution should be observed with certain anaesthetics that cause myocardial depression. The patient can be protected against vagal reactions by intravenous administration of atropine.

- *Cardiovascular*: In general, beta-adrenergic antagonists should not be used in patients with untreated congestive heart failure (CHF), unless their condition has been stabilised. In patients with ischaemic heart disease, treatment with a beta-adrenergic antagonist should be discontinued gradually, i.e. over 1-2 weeks. If necessary replacement therapy should be initiated at the same time, to prevent exacerbation of angina pectoris. Beta-adrenergic antagonists may induce bradycardia: if the pulse rate drops below 50-55 bpm at rest and/or the patient experiences symptoms that are suggestive of bradycardia, the dosage should be reduced. Beta-adrenergic antagonists should be used with caution:in patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur;in patients with first degreeatrioventricular block, because of the negative effect of beta-blockers on conduction time; in patients with Prinzmetal's angina due to unopposed alphareceptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.Combination of nebivolol with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs is generally not recommended, for details please refer to section 4.5.

- *Metabolic/Endocrinological*: Nebivolol does not affect glucose levels in diabetic patients. Care should be taken in diabetic patients however, as nebivolol may mask certain symptoms of hypoglycaemia (tachycardia, palpitations). Beta-adrenergic blocking agents may mask tachycardic symptoms in hyperthyroidism. Abrupt withdrawal may intensify symptoms.

- *Respiratory*: In patients with chronic obstructive pulmonary disorders, beta-adrenergic antagonists should be used with caution as airway constriction may be aggravated.

- O*ther*: Patients with a history of psoriasis should take beta-adrenergic antagonists only after careful consideration. Beta-adrenergic antagonists may increase the sensitivity to allergens and the severity of anaphylactic reactions.

Hydrochlorothiazide

- *Renal impairment*: Full benefit from thiazide diuretics can be derived only if the kidney function is not altered. In patients with renal disease, thiazides may increase azotaemia. Cumulative effects of this active substance may develop in patients with impaired renal function. If progressive renal impairment becomes evident, as indicated by a rising non-protein nitrogen, careful reappraisal of therapy is necessary, with consideration given to discontinuing diuretic therapy.

- *Metabolic and endocrine effects*: Thiazide therapy may impair glucose tolerance. Dosage adjustments of insulin or oral hypoglycaemic agents may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. Thiazide therapy may precipitate hyperuricaemia and/or gout in certain patients.

- *Electrolyte imbalance*: As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting. The risk of hypokalaemia is greatest in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or ACTH (see section 4.5). Patients with long QT syndrome, either congenital or iatrogenic, are particularly at high risk in case of hypokalaemia. Hypokalaemia increases the cardiotoxicity of digitalis glycosides and the risk of cardiac arrhythmia. More frequent plasma potassium monitoring is indicated in patients at risk of hypokalaemia, starting within the week after initiation of therapy. Dilutional hyponatraemia may occur in oedematous patients in hot weather. Chloride deficit is generally mild and usually does not require treatment. Thiazides may decrease urinary calcium excretion and may cause an intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. A marked hypercalcaemia may be the evidence of a hidden hyperparathyroidism. Thiazides should be discontinued before carrying out test for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

- *Lupus erythematosus*: Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

- *Anti-doping test*: Hydrochlorothiazide contained in this medication could produce a positive analytic result in an anti-doping test.

- *Other*: Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Photosensitivity reactions have been reported with thiazide diuretics in rare cases (see section 4.8). If photosensitivity reactions occur during treatment, it is recommended to stop the treatment. If a re-administration of treatment is deemed necessary, it is recommended to protect exposed areas from the sun or artificial UVA-light.

- *Protein bound iodine*: Thiazides may decrease serum protein bound iodine levels without signs of thyroid disturbance.

- *Non-melanoma skin cancer:* An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC. Patients taking HCTZ should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

- *Acute Respiratory Toxicity* Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, Hypoloc should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Nebivolol/Hydrochlorothiazide Combination

In addition to the warnings related to the monocomponents, the followings specifically apply to Hypoloc Plus:

- *Choroidal effusion, acute myopia and secondary angle-closure glaucoma:*Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

- *Galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption*: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malapsorption should not take this medicinal product.

- This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially' sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic interactions:

Nebivolol
The following interactions apply to beta-adrenergic antagonists in general.

- Combinations not recommended
Class I antiarrhythmics (quinidine, hydroquinidine, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine, propafenone): effect on atrio-ventricular conduction time may be potentiated and negative inotropic effect increased (see section 4.4).

Calcium channel antagonists of verapamil/diltiazem type: negative influence on contractility and atrio-ventricular conduction. Intravenous administration of verapamil in patients with ß-blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).

Centrally-acting antihypertensives (clonidine, guanfacin, moxonidine, methyldopa, rilmenidine): concomitant use of centrally acting antihypertensive drugs may worsen heart failure by a decrease in the central sympathetic tonus (reduction of heart rate and cardiac output, vasodilation) (see section 4.4). Abrupt withdrawal, particularly if prior to beta-blocker discontinuation, may increase risk of “rebound hypertension”.

- Combinations to be used with caution
*Class III antiarrhythmic drugs (Amiodarone):*effect on atrio-ventricular conduction time may be potentiated.

Anaesthetics - volatile halogenated: concomitant use of beta-adrenergic antagonists and anaesthetics may attenuate reflex tachycardia and increase the risk of hypotension (see section 4.4). As a general rule, avoid sudden withdrawal of beta-blocker treatment.The anaesthesiologist should be informed when the patient is receiving Hypoloc Plus.

Insulin and oral antidiabetic drugs: although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia).

Baclofen (antispastic agent), amifostine (antineoplastic adjunct): concomitant use with antihypertensives is likely to increase the fall in blood pressure, therefore the dosage of the antihypertensive medication should be adjusted accordingly.

- Combinations to be taken in account
Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. Clinical trials with nebivolol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

Calcium antagonists of the dihydropyridine type (amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine, nitrendipine): concomitant use may increase the risk of hypotension, and an increase in the risk of a further deterioration of the ventricular pump function in patients with heart failure cannot be excluded.

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use may enhance the hypotensive effect of the beta-blockers (additive effect).

Non steroidal anti-inflammatory drugs (NSAID): no effect on the blood pressure lowering effect of nebivolol.

Sympathomimetic agents: concomitant use may counteract the effect of beta-adrenergic antagonists. Beta-adrenergic agents may lead to unopposed alpha-adrenergic activity of sympathomimetic agents with both alpha- and beta-adrenergic effects (risk of hypertension, severe bradycardia and heart block).

Hydrochlorothiazide
Potential interactions related to hydrochlorothiazide:

- Concomitant use not recommended

Lithium: The renal clearance of lithium is reduced by thiazides and consequently the risk of lithium toxicity may be increased when used in concomitance with hydrochlorothiazide. Therefore the use of Hypoloc Plus in combination with lithium is not recommended. If the use of such combination proves necessary, careful monitoring of serum lithium levels is recommended.

Medicinal products affecting potassium levels: The potassium-depleting effect of hydrochlorothiazide (see section 4.4) may be potentiated by the coadministration of other medicinal products associated with potassium loss and hypokalaemia (eg other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium or salicylic acid derivatives). Such concomitant use is therefore not recommended.

- Concomitant use requiring caution

Non steroidal anti-inflammatory drugs (NSAID): NSAIDs (ie acetylsalicylic acid (> 3 g/day), COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of thiazide diuretics.

Calcium salts: Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when Hypoloc Plus is administered with medicinal products affected by serum potassium disturbances (eg digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrythmics (eg quinidine, hydroquinidine, disopyramide).
- Class III antiarrythmics (eg amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (eg thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (eg bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).

Non-depolarizing skeletal muscle relaxants (eg tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide.

Antidiabetic medicinal products (oral agents and insulin): The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic medicinal product may be required (see section 4.4).

Metformin: Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Beta-blockers and diazoxide: The hyperglycaemic effect of beta-blockers other than nebivolol and diazoxide may be enhanced by thiazides.

Pressor amines (eg noradrenaline): The effect of pressor amines may be decreased.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol): Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Amantadine: Thiazides may increase the risk of adverse effects caused by amantadine.

Salicylates: In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Cyclosporine: Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Iodinated contrast media: In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be rehydrated before the administration.

Potential interactions related to both Nebivolol and Hydrochlorothiazide:

- Concomitant use to be taken into account
*Other anti-hypertensive drugs:*there may be additive hypotensive effects or potentiation during concomitant treatment with other anti-hypertensive drugs.
Antipsychotics, tricyclic antidepressants, barbiturates, narcotic drugs and alcohol: concomitant administration of Hypoloc Plus with these medicines may enhance the hypotensive effect and/or lead to postural hypothension.

Pharmacokinetic interactions:

Nebivolol
As nebivolol metabolism involves the CYP2D6 isoenzyme, co-administration with substances inhibiting this enzyme, especially paroxetine, fluoxetine, thioridazine and quinidine may lead to increased plasma levels of nebivolol associated with an increased risk of excessive bradycardia and adverse events.
Co-administration of cimetidine increased the plasma levels of nebivolol, without changing the clinical effect.
Co-administration of ranitidine did not affect the pharmacokinetics of nebivolol. Provided Hypoloc Plus is taken with the meal, and an antacid between meals, the two treatments can be co-prescribed.
Combining nebivolol with nicardipine slightly increased the plasma levels of both drugs, without changing the clinical effect.
Co-administration of alcohol, furosemide or hydrochlorothiazide did not affect the pharmacokinetics of nebivolol. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

Hydrochlorothiazide
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins (e.g *cholestyramine and colestipol resins)*.
Cytotoxic agents: With concurrent use of hydrochlorothiazide and cytotoxic agents (*eg cyclophosphamide, fluorouracil, methotrexate*) increased bone marrow toxicity (in particular granulocytopenia) has to be expected..

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Hypoloc Plus in pregnant women. Animal studies on the two individual components are insufficient with respect to the effects of the combination of nebivolol and hydrochlorothiazide on reproduction (see section 5.3).
Nebivolol
Insufficient data exist on the use of nebivolol in human pregnancy to determine its potential harmfulness. However, Nebivolol has pharmacological effects that may cause harmful effects on pregnancy and/or the foetus/newborn. In general, beta-adrenoceptor blockers reduce placental perfusion, which has been associated with growth retardation, intrauterine death, abortion or early labour. Adverse effects (e.g. hypoglycaemia and bradycardia) may occur in the foetus and newborn infant. If treatment with beta-adrenoceptor blockers is necessary, beta1-selective adrenoceptor blockers are preferable.
Nebivolol should not be used during pregnancy unless clearly necessary. If treatment with nebivolol is considered necessary, the uteroplacental blood flow and the foetal growth should be monitored. In case of harmful effects on pregnancy or the foetus alternative treatment should be considered. The newborn infant must be closely monitored. Symptoms of hypoglycaemia and bradycardia are generally to be expected within the first 3 days.
Hydrochlorothiazide
There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.
Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Breast-feeding

It is unknown whether nebivolol is excreted into human breast milk. Animal studies have shown that nebivolol is excreted into breast milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Hypoloc Plus during breast feeding is not recommended. If Hypoloc Plus is used during breast feeding, doses should be kept as low as possible.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed . However, when driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur when taking antihypertensive therapy.

4.8 Undesirable effects

Adverse events are listed separately for each single active substance.

Nebivolol

The adverse reactions reported following administration of nebivolol alone, which are in most of the cases of mild to moderate intensity, are tabulated below, classified by system organ class and ordered by frequency:

SYSTEM ORGAN CLASS	Common (≥1/100 to < 1/10)	Uncommon (≥1/1,000 to ≤1/100)	Very Rare (≤1/10,000)	Not Known
Immune system disorders				Angioneurotic oedema, hypersensitivity
Psychiatric disorders		nightmares; depression		
Nervous system disorders	headache, dizziness, paraesthesia		syncope	
Eye disorders		impaired vision		
Cardiac disorders		bradycardia, heart failure, slowed AV conduction/AV-block		
Vascular disorders		hypotension, (increase of) intermittent claudication		
Respiratory, thoracic and mediastinal disorders	dyspnoea	bronchospasm		
Gastrointestinal disorders	constipation, nausea, diarrhoea	dyspepsia, flatulence, vomiting		
Skin and subcutaneous tissue disorders		pruritus, rash erythematous	psoriasis aggravated	urticaria
Reproductive system and breast disorders		impotence		
General disorders and administration site conditions	tiredness, oedema			

The following adverse reactions have also been reported with some beta-adrenergic antagonists: hallucinations, psychoses, confusion, cold/cyanotic extremities, Raynaud phenomenon, dry eyes, and oculo-mucocutaneous toxicity of the practolol-type.

Hydrochlorothiazide
The adverse events that have been reported with the use of hydrochlorothiazide alone include the following:
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Frequency 'not known': Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma).
Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).
Blood and lymphatic system disorders: leukopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow failure.
Immune system disorders: anaphylactic reaction.
Metabolism and nutritional disorders: anorexia, dehydration, gout, diabetes mellitus, metabolic alkalosis, hyperuricaemia, electrolyte imbalance (including hyponatraemia, hypokalaemia, hypomagnesaemia, hypochloraemia, hypercalcaemia), hyperglycaemia, hyperamylasaemia.
Psychiatric disorders: apathy, confusional state, depression, nervousness, restlessness, sleep disorder.
Nervous system disorders: convulsions, depressed level of consciousness, coma, headache, dizziness, paraesthesia, paresis.
Eye disorders: Frequency 'not known': choroidal effusion, acute myopia, acute angle closure glaucoma. Xanthopsia, blurred vision, myopia (aggravated), lacrimation decreased.
Ear and labyrinth disorders: vertigo.
Cardiac disorders: cardiac arrhythmias, palpitations.
Vascular disorders: orthostatic hypotension, thrombosis, embolism, shock
Respiratory, thoracic and mediastinal disorders: respiratory distress, pneumonitis, interstitial lung disease, pulmonary oedema.
Frequency 'very rare': Acute respiratory distress syndrome (ARDS) (see section 4.4)
Gastrointestinal disorders: dry mouth, nausea, vomiting, stomach discomfort, diarrhoea, constipation, abdominal pain, ileus paralytic, flatulence, sialoadenitis, pancreatitis.
Hepato-biliary disorders: jaundice cholestatic, cholecystitis.
Skin and subcutaneous tissue disorders: pruritus, purpura, urticaria, photosensitivity reaction, rash, cutaneous lupus erythematosus, vasculitis necrotising, toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders: muscle spasms, myalgia.
Renal and urinary disorders: renal impairment, renal failure acute, nephritis interstitial, glycosuria.
Reproductive system and breast disorders: erectile dysfunction.
General disorders and administration site conditions: asthenia, pyrexia, fatigue, thirst.
Investigations: electrocardiogram change, blood cholesterol increased, blood triglycerides 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 the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

Symptoms
No data are available on overdosage with nebivolol. Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

Overdosage with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdosage with hydrochlorothiazide are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

Treatment
In case of overdosage or hypersensitivity, the patient should be kept under close supervision and be treated in an intensive care ward. Blood glucose levels should be checked. Serum electrolytes and creatinine should be monitored frequently. Absorption of any drug residues still present in the gastro-intestinal tract can be prevented by gastric lavage and the administration of activated charcoal and a laxative. Artificial respiration may be required. Bradycardia or extensive vagal reactions should be treated by administering atropine or methylatropine. Hypotension and shock should be treated with plasma/plasma substitutes and, if necessary, catecholamines. Electrolyte imbalances should be corrected. The beta-blocking

effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 microgram/minute, or dobutamine, starting with a dose of 2.5 microgram/minute, until the required effect has been obtained. In refractory cases isoprenaline can be combined with dopamine. If this does not produce the desired effect either, intravenous administration of glucagon 50-100 microgram/kg i.v. may be considered. If required, the injection should be repeated within one hour, to be followed -if required- by an i.v. infusion of glucagon 70 microgram/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta blocking agents, selective, and thiazides
ATC code: C07BB12

Hypoloc Plus is a combination of nebivolol, a selective beta-receptor antagonist, and hydrochlorothiazide, a thiazide diuretic. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) and RSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:
- It is a competitive and selective beta-receptor antagonist: this effect is attributed to the SRRR-enatiomer (d-enantiomer).
- It has mild vasodilating properties due to an interaction with the L-arginine/nitric oxide pathway.

Single and repeated doses of nebivolol reduce heart rate and blood pressure at rest and during exercise, both in normotensive subjects and in hypertensive patients. The antihypertensive effect is maintained during chronic treatment.
At therapeutic doses, nebivolol is devoid of alpha-adrenergic antagonism.
During acute and chronic treatment with nebivolol in hypertensive patients systemic vascular resistance is decreased. Despite heart rate reduction, reduction in cardiac output during rest and exercise may be limited due to an increase in stroke volume. The clinical relevance of these haemodynamic differences as compared to other beta1 receptor antagonists has not been fully established.
In hypertensive patients, nebivolol increases the NO-mediated vascular response to acetylcholine (ACh) which is reduced in patients with endothelial dysfunction.

In vitro and in vivo experiments in animals showed that nebivolol has no intrinsic sympathomimetic activity.
In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilising action.
In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. With hydrochlorothiazide, onset of diuresis occurs at about 2 hours and peak effect occurs at about 4 hours post-dose, whilst the action persists for approximately 6-12 hours.

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were
matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Concomitant administration of nebivolol and hydrochlorothiazide has no effect on the bioavailability of either active substance. The combination tablet is bioequivalent to the concomitant administration of the separate components.

Nebivolol

Absorption
Both nebivolol enantiomers are rapidly absorbed after oral administration. The absorption of nebivolol is not affected by food; nebivolol can be given with or without meals.
The oral bioavailability of nebivolol averages 12% in fast metabolisers and is virtually complete in slow metabolisers. At steady state and at the same dose level, the peak plasma concentration of unchanged nebivolol is about 23 times higher in poor metabolisers than in extensive metabolisers. When unchanged drug plus active metabolites are considered, the difference in peak plasma concentrations is 1.3 to 1.4 fold. Because of the variation in rates of metabolism, the dose of Nebilet should always be adjusted to the individual requirements of the patient: poor metabolisers therefore may require lower doses.
Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol is not affected by age.

Distribution
In plasma, both nebivolol enantiomers are predominantly bound to albumin. Plasma protein binding is 98.1% for SRRR-nebivolol and 97.9% for RSSS-nebivolol.

Bio-*transformation*
Nebivolol is extensively metabolised, partly to active hydroxy-metabolites. Nebivol is metabolised via alicyclic and aromatic hydroxylation, N-dealkylation and glucuronidation; in addition, glucuronides of the hydroxy-metabolites are formed. The metabolism of nebivolol by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism.

Elimination
In fast metabolisers, elimination half-lives of the nebivolol enantiomers average 10 hours. In slow metabolisers, they are 3-5 times longer. In fast metabolisers, plasma levels of the RSSS-enantiomer are slightly higher than for the SRRR-enantiomer. In slow metabolisers, this difference is larger. In fast metabolisers, elimination half-lives of the hydroxymetabolites of both enantiomers average 24 hours, and are about twice as long in slow metabolisers.
Steady-state plasma levels in most subjects (fast metabolisers) are reached within 24 hours for nebivolol and within a few days for the hydroxy-metabolites.
One week after administration, 38% of the dose is excreted in the urine and 48% in the faeces. Urinary excretion of unchanged nebivolol is less than 0.5% of the dose.

Hydrochlorothiazide

Absorption
Hydrochlorothiazide is well absorbed (65 to 75 %) following oral administration. Plasma concentrations are linearly related to the administered dose. The absorption of Hydrochlorothiazide is dependent on intestinal transit time, being increased when the intestinal transit time is slow, for example when given with food. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours and peak plasma levels were observed within 1 and 5 h after dosing.

Distribution
Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0.83 – 1.14 1/kg.
Hydrochlorothiazide crosses the placental but not the blood-brain barrier.

Biotransformation
Hydrochlorothiazide metabolism is very poor. Almost all of hydrochlorothiazide is excreted in the urine unchanged.

Elimination
Hydrochlorothiazide is eliminated primarily by the renal pathway. More than 95 % of hydrochlorothiazide appears unchanged in the urine within 3-6 hours after an oral dose.
In patients with renal disease, plasma concentrations of Hydrochlorothiazide are increased and elimination half-life is prolonged.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans of a combination of nebivolol and hydrochlorothiazide. This is based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential of the individual components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Polysorbate 80 (E433)
Hypromellose (E464)
Lactose monohydrate
Maize starch
Croscarmellose sodium (E468)
Cellulose microcrystalline (E460(i))
Silica colloidal anhydrous (E551)
Magnesium stearate (E470b)

Coating

Hypromellose (E464)
Cellulose microcrystalline (E460(i))
Macrogol 40 stearate Type I (E431)
Titanium dioxide (E171)
Carmines (Carminic acid aluminium lake, E120)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage precautions.

6.5 Nature and contents of container

Tablets are provided in blisters (PP/COC/PP/Aluminium).
Pack sizes of 7, 14, 28, 30, 56, 90 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Menarini International Operations Luxembourg S.A.
1, Avenue de la Gare
1611 Luxembourg
Luxembourg

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 6th March 2009
Date of last renewal: 30th November 2012

10 DATE OF REVISION OF THE TEXT

January 2022