Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nebkliq 5 mg/5 mg film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of Nebkliq 5 mg/5 mg film-coated tablets contains 5 mg of nebivolol (as 5.45 mg of nebivolol hydrochloride) and 5 mg of amlodipine (as 6.94 mg of amlodipine besilate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Nebkliq 5 mg/5 mg film-coated tablets:
Yellow, oval, film-coated tablets with one-sided break-mark (length c.a. 12 mm, width c.a. 6 mm).

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension as substitution therapy in adult patients adequately controlled with nebivolol and amlodipine given concurrently at the same dose level as in the combination, but with separate tablets.

4.2 Posology and method of administration

Posology

The recommended dose is one tablet per day as a single dose, preferably at the same time of the day. The fixed dose combination is not suitable for initial therapy. If a change of posology is required, titration should be done with the individual components.

Special populations

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

Renal impairment
Dose adjustment should be done with the individual components before switching to the fixed combination in case of mild to moderate renal impairment. Changes in plasma concentrations of amlodipine are not related to the degree of renal impairment. Amlodipine is not dialysable (see section 4.4).

Hepatic impairment
Nebkliq is contraindicated in patients with hepatic insufficiency or impaired liver function.

Paediatric population
The safety and efficacy of Nebkliq in children and adolescents aged below 18 years have 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 or without meals.

4.3 Contraindications

Hypersensitivity to the active substances, dihydropyridine derivatives or to any of the excipients listed in section 6.1.

- Liver insufficiency or liver function impairment
- Acute heart failure
- Shock (including cardiogenic shock)
- Episodes of heart failure decompensation (also after acute myocardial infarction) requiring i.v. inotropic therapy
- Sick sinus syndrome, including sino-atrial block
- Second- and third-degree heart block (without a pacemaker)
- History of bronchospasm and bronchial asthma
- Untreated phaeochromocytoma
- Metabolic acidosis
- Bradycardia (heart rate < 60 bpm prior to start therapy)
- Hypotension (systolic blood pressure < 90 mmHg)
- Severe peripheral circulatory disturbances
- Obstruction of the outflow tract of the left ventricle (e.g. high grade aortic stenosis)

4.4 Special warnings and precautions for use

Special warnings and precautions related to each monocomponent, as listed below, apply to the fixed combination {TM}.

Nebivolol

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 (see section 4.5). 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;
- with first degree heart block, because of the negative effect of beta-blockers on conduction time;
- with Prinzmetal's angina due to unopposed alpha-receptor 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-blockers could further increase the risk of severe hypoglycaemia when used concurrently with sulfonylureas. Diabetic patients should be advised to carefully monitor blood glucose levels. (see Section 4.5).
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.

Other
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.

Amlodipine

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
Due to the amlodipine component of {TM}, as with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Heart failure
Patients with heart failure should be treated with caution. In a long-term, placebo controlled study of amlodipine in patients with severe heart failure (NYHA III and IV), the reported incidence of pulmonary oedema was higher in the amlodipine group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Other
As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Renal failure
Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No clinical study evaluating drug interactions has been performed using {TM}. Interactions that have been identified in studies with individual components of {TM} (nebivolol or amlodipine) may occur with {TM}. Based on the known characteristics of nebivolol and amlodipine, no clinically relevant pharmacokinetic interaction is expected between the individual components in {TM}.

Pharmacokinetic interactions

Effects of other medicinal products on {TM}
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 nebivolol 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.

CYP3A4 inhibitors:
Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these PK variations may be more pronounced in the elderly. There is an increased risk of hypotension. Close observation of patients is recommended and dose adjustment may thus be required.

CYP3A4 inducers:
Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Effects of {TM} on other medicinal products
Nebivolol does not affect the pharmacokinetics of warfarin.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Simvastatin: Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Tacrolimus: There is a risk of increased tacrolimus blood levels when co-administered with amlodipine. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors: mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine: In a prospective study in renal transplant patients, an average 40% increase in trough cyclosporine levels was observed when used concomitantly with amlodipine. The co-administration of {TM} with cyclosporine may increase exposure to cyclosporine. Monitor trough cyclosporine levels during concomitant use and cyclosporine dose reductions should be made as necessary.

Pharmacodynamic interactions
The blood pressure lowering effects of amlodipine and nebivolol add to the blood pressure-lowering effects of other antihypertensive agents.

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

- Concomitant use 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 beta-blocker treatment may lead to profound hypotension and atrio-ventricular block (see section 4.4).*Centrally-acting antihypertensives (clonidine, guanfacine, 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".
- Concomitant use requiring 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 nebivolol. *Insulin and oral antidiabetic drugs*: although nebivolol does not affect glucose level, concomitant use may mask certain symptoms of hypoglycaemia (palpitations, tachycardia). The concomitant use of beta-blockers with sulfonylureas could increase the risk of severe hypoglycaemia. (see Section 4.4). *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.
- Concomitant use to be taken into 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). Nebivolol does not affect the pharmacodynamics of warfarin. Dantrolene (infusion): In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no available data from the use of Nebkliq in pregnant women.
Animal studies are insufficient with respect to reproductive toxicity of Nebkliq (see section 5.3).
Nebkliq is not recommended during pregnancy.

Nebivolol

Beta-adrenoceptor blockers have 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, $beta_1$-selective adrenoceptor blockers, like nebivolol, 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.

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Breast-feeding
Nebkliq is not recommended during lactation.

Nebivolol

Animal studies have shown that nebivolol is excreted in breast milk. It is not known whether this drug is excreted in human milk. Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. A risk to the newborns/infants cannot be excluded. Therefore, mothers receiving nebivolol should not breastfeed.

Amlodipine

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3 – 7%, with a maximum of 15%. The effect of amlodipine on infants is unknown.

Fertility
There are no clinical data on fertility with the use of Nebkliq.

Nebivolol

Nebivolol had no effect on rat fertility except at doses several-fold higher than the human maximum recommended dose when adverse effects on male and female reproductive organs in rats and mice were observed (see section 5.3). The effect of nebivolol on human fertility is unknown.

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects of Nebkliq on the ability to drive and use machines have been performed. Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

Summary of safety profile
Adverse reactions from the individual components nebivolol and amlodipine in clinical trials, post-authorisation safety studies and spontaneous reporting are summarised in the below table.

Tabulated list of adverse reactions
The following terminologies have been used in order to classify the occurrence of undesirable effects:
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)

Table 1: Overview of adverse reactions with the single components of Nebkliq

MedDRA System Organ Class	**Adverse reactions**	**Frequency**	
		Nebivolol	**Amlodipine**
Blood and lymphatic system disorders	Leukopenia	-	Very rare
	Thrombocytopenia	-	Very rare
Immune system disorders			
	Drug hypersensitivity	Not known	Very rare
Metabolism and nutrition disorders	Hyperglycaemia	-	Very rare
Psychiatric disorders	Confusion	-	Rare
	Depression	Uncommon	Uncommon
	Insomnia	-	Uncommon
	Mood changes (including anxiety)	-	Uncommon
	Nightmares	Uncommon	-
Nervous system disorders	Dizziness	Common	Common
	Dysgeusia	-	Uncommon
	Headache	Common	Common (especially at the beginning of treatment)
	Hypertonia	-	Very rare
	Hypoaesthesia	-	Uncommon
	Paraesthesia	Common	Uncommon

	Peripheral neuropathy	-	Very rare
	Somnolence	-	Common
	Syncope	Very rare	Uncommon
	Tremor	-	Uncommon
	Extrapyramidal disorder	-	Not known
Eye disorders	Impaired vision	Uncommon	-
	Visual disturbance (including diplopia)	-	Common
Ear and labyrinth disorders	Tinnitus	-	Uncommon
Cardiac disorders	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)	-	Uncommon
	Bradycardia	Uncommon	-
	Heart Failure	Uncommon	-
	Myocardial infarction	-	Very rare
	Palpitations	-	Common
	slowed AV conduction / AV-block	Uncommon	-
Vascular disorders	Hypotension	Uncommon	Uncommon
	Flushing	-	Common
	(increase of) intermittent claudication	Uncommon	-
	Vasculitis	-	Very rare
Respiratory, thoracic and mediastinal disorders	Bronchospasm	Uncommon	-
	Cough	-	Uncommon
	Dyspnoea	Common	Common
	Rhinitis	-	Uncommon
Gastrointestinal disorders	Abdominal pain	-	Common
	Altered bowel habits (including diarrhoea and constipation)	-	Common
	Constipation	Common	-
	Diarrhoea	Common	-
	Dry mouth	-	Uncommon
	Dyspepsia	Uncommon	Common
	Flatulence	Uncommon	-
	Gastritis	-	Very rare
	Gingival hyperplasia	-	Very rare
	Nausea	Common	Common
	Pancreatitis	-	Very rare
	Vomiting	Uncommon	Uncommon
Hepatobiliary disorders	Hepatic enzymes increased	-	Very rare (mostly consistent with cholestasis)
	Hepatitis	-	Very rare
	Jaundice	-	Very rare
Skin and subcutaneous tissue disorders	Alopecia	-	Uncommon
	Angioedema	Not known	Very rare
	Erythema multiforme	-	Very rare
	Exanthema	-	Uncommon
	Exfoliative dermatitis	-	Very rare
	Hyperhidrosis	-	Uncommon
	Photosensitivity	-	Very rare
	Pruritus	Uncommon	Uncommon
	Psoriasis aggravated	Very rare	-
	Purpura	-	Uncommon
	Rash	Uncommon	Uncommon
	Skin discoloration	-	Uncommon
	Stevens-Johnson syndrome	-	Very rare

	Toxic Epidermal Necrolysis	-	Not known
	Urticaria	Not known	Uncommon
Musculoskeletal and connective tissue disorders	Ankle swelling	-	Common
	Arthralgia	-	Uncommon
	Back pain	-	Uncommon
	Muscle cramp	-	Common
	Myalgia	-	Uncommon
Renal and urinary disorders	Micturition disorder	-	Uncommon
	Nocturia	-	Uncommon
	Increased urinary frequency	-	Uncommon
Reproductive system and breast disorders	Erectile dysfunction	Uncommon	Uncommon
	Gynecomastia	-	Uncommon
General disorders and administration site conditions	Asthenia	-	Common
	Chest pain	-	Uncommon
	Fatigue	Common	Common
	Malaise	-	Uncommon
	Oedema	Common	Very common
	Pain	-	Uncommon
Investigations	Weight decrease	-	Uncommon
	Weight increase	-	Uncommon

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.

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, website: www.hpra.ie.

4.9 Overdose

There is no information on overdose with Nebkliq in humans.

Nebivolol

Symptoms
Symptoms of overdosage with beta-blockers are: bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

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. 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. The beta-blocking effect can be counteracted by slow intravenous administration of isoprenaline hydrochloride, starting with a dose of approximately 5 µg/minute, or dobutamine, starting with a dose of 2.5 µg/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 µg/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 µg/kg/h. In extreme cases of treatment-resistant bradycardia, a pacemaker may be inserted.

Amlodipine

Symptoms

Amlodipine overdosage can be expected to lead to excessive peripheral vasodilatation with marked hypotension and possibly a reflex tachycardia. Marked and potentially prolonged systemic hypotension up to and including shock with fatal outcome has been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24-48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Treatment
If intake is recent, gastric lavage may be considered. In healthy subjects, the administration of activated charcoal immediately or up to 2 hours after ingestion of amlodipine has been shown to substantially reduce the absorption of amlodipine.

Clinically significant hypotension due to an overdose requires active support of the cardiovascular system, including close monitoring of heart and lung function, elevation of the extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents and calcium channel blockers, ATC code: C07FB12

Nebkliq is a combination of a selective beta-blocking agent, nebivolol (as nebivolol hydrochloride), and a calcium channel blocker, amlodipine (as amlodipine besilate). The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than each component alone.

Nebivolol / Amlodipine

Clinical efficacy and safety
An open-label, interventional, Phase IV study (MEIN/21/AmNe-Hyp/001; BOTTICELLI study) evaluated the efficacy and safety of the extemporaneous combination of nebivolol 5 mg and amlodipine 5 mg or 10 mg in hypertensive patients whose blood pressure was uncontrolled under monotherapy with a beta blocker or a calcium channel blocker. After 8 weeks of treatment, the extemporaneous combination provided a statistically significant mean reduction of -15.2 mmHg (± 8.32) and -24.2 mmHg (± 11.75) of sitting diastolic and systolic blood pressure, respectively, versus baseline (i.e. values measured after 4 weeks of monotherapy with either nebivolol 5 mg or amlodipine 5 mg). The extemporaneous combination of nebivolol 5 mg and amlodipine 5 mg or 10 mg once daily was safe and well-tolerated and in line with the well-known safety profile of the two monotherapies.

Nebivolol

Nebivolol is a racemate of two enantiomers, SRRR-nebivolol (or d-nebivolol) andRSSS-nebivolol (or l-nebivolol). It combines two pharmacological activities:
It is a competitive and highly selective beta-receptor antagonist: this effect is attributed to the SRRR-enantiomer (d-enantiomer).
It has 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.
Available preclinical and clinical evidence in hypertensive patients has not shown that nebivololhas a detrimental effect on erectile function.

Amlodipine

The amlodipine component of Nebkliq is a calcium channel blocker that inhibits the transmembrane influx of calcium ions through the potential-dependent L-type channels into the heart and smooth muscle. Experimental data indicate that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. Amlodipine is relatively vessel-selective, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. The antihypertensive effect of amlodipine derives from a direct relaxant effect on arterial smooth muscle, which leads to a lowering of peripheral resistance and hence of blood pressure.

In hypertensive patients, amlodipine causes a dose-dependent, long-lasting reduction in arterial blood pressure. There has been no evidence of first-dose hypotension, of tachyphylaxis during long-term treatment, or of rebound hypertension after abrupt cessation of therapy.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces an effective reduction in blood pressure in the supine, sitting and standing positions. Chronic use of amlodipine is not associated with significant changes in heart rate or plasma catecholamine levels. In hypertensive patients with normal renal function, therapeutic doses of amlodipine reduce renal vascular resistance and increase glomerular filtration rate and effective renal plasma flow, without changing filtration fraction or proteinuria.

5.2 Pharmacokinetic properties

One bioequivalence study in healthy volunteers was carried out to compare Nebkliq 5 mg/5 mg and 5 mg/10 mg film-coated tablets versus the two single agents given as extemporaneous combination, demonstrating bioequivalence in terms of AUC and Cmax parameters.

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 nebivolol should always be adjusted to the individual requirements of the patient: poor metabolisers therefore may require lower doses.
After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%.
The absorption of amlodipine is unaffected by the concomitant intake of food.

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.
The volume of distribution is approximately 21 l/kg for amlodipine. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

Biotransformation
Nebivolol is extensively metabolised, partly to active hydroxy-metabolites. Nebivolol 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.
Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

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.
The terminal plasma elimination half-life is about 35-50 hours for amlodipine and is consistent with once daily dosing.

Linearity
Plasma concentrations of nebivolol are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol are not affected by age. Amlodipine shows linear dose-related pharmacokinetic characteristics and, at steady-state, there are relatively small fluctuations in plasma concentrations across a dosage interval.

Special populations
Pharmacokinetics in the elderly:
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half life in elderly people.

Pharmacokinetics in renal dysfunction:
Changes in amlodipine plasma concentration are not correlated with the degree of renal impairment. In these patients, amlodipine may be administered at the normal dosage. Amlodipine is not dialysable.

Pharmacokinetics in hepatic dysfunction:
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.

5.3 Preclinical safety data

No animal studies on the combination nebivolol / amlodipine have been performed.

Nebivolol

Non-clinical data reveal no special hazard for humans based on conventional studies of genotoxicity, carcinogenic potential, toxicity to reproduction and development. Adverse effects on the reproductive function were only recorded at high doses, exceeding by several fold the maximum recommended human dose (see Section 4.6).

Amlodipine

Reproductive toxicology
Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility
There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis
There is no evidence for a genotoxic and carcinogenic effect of amlodipine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

- Cellulose microcrystalline, type 101
- Croscarmellose sodium
- Maize starch
- Hypromellose, type 2910
- Polysorbate 80
- Silica colloidal anhydrous
- Magnesium stearate

Film Coating:
OPADRY® 02B220019 Yellow, for Nebkliq 5 mg/5 mg, composed of:

- Hypromellose
- Titanium dioxide (E171)
- Macrogol 400
- Yellow iron oxide (E172)

OPADRY® Y-1-7000 White, for Nebkliq 5 mg/10 mg, composed of:

- Hypromellose
- Titanium dioxide
- Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Tablets are provided in blisters (PVC/PVDC-Al blister).
Pack sizes of 14, 28, 30, 56, 84, 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: 13th December 2024

10 DATE OF REVISION OF THE TEXT

May 2025