For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

NEBICARD-SM

1. Generic Name

Nebivolol and S-Amlodipine Tablets

2. Qualitative and quantitative Composition:

Each uncoated bilayered tablet contains:

Nebivolol Hydrochloride I.P. equivalent to

Nebivolol……5 mg

S-Amlodipine besylate I.P. equivalent to,

S-Amlodipine……..2.5 mg

Colour: Lake of Quinoline Yellow

The excipients used are Mannitol, croscarmellose sodium,Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Lake of quinoline yellow, starch, sodium starch glycolate

3. Dosage form and strength

Dosage form: Tablet

Strength: Nebivolol 5 mg and S-Amlodipine 2.5 mg

4. Clinical particulars

4.1 Therapeutic indication

Nebicard SM is indicated for the treatment of Hypertension.

4.2 Posology and method of administration

The NEBICARD SM must be taken as directed by the physician.

NEBIVOLOL

<u>Hypertension</u>

Adults

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

The blood pressure lowering effect becomes evident after 1-2 weeks of treatment. Occasionally, the optimal effect is reached only after 4 weeks.

Combination with other antihypertensive agents

Beta-blockers can be used alone or concomitantly with other antihypertensive agents. An additional antihypertensive effect has been observed only when Nebivolol 5 mg tablets are combined with hydrochlorothiazide 12.5-25 mg.

Patients with renal insufficiency

The recommended starting dose of Nebivolol is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg.

Patients with hepatic insufficiency

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

Elderly

In patients over 65 years, the recommended starting dose is 2.5 mg daily. If needed, the daily dose may be increased to 5 mg. However, in view of the limited experience in patients above 75 years, caution must be exercised and these patients monitored closely.

Paediatric hypertension population

Nebivolol is not recommended for use in children and adolescents under the age of 18 years due to a lack of data on safety and efficacy.

Method of administration

One tablet of NEBICARD-SM daily, preferably at the same time of the day. The tablets may be taken with meals.

4.3 Contraindications

NEBICARD SM is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients listed.
- Liver insufficiency or liver function impairment.
- Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring i.v. inotropic therapy.
- shock (including cardiogenic shock)

In addition, as with other beta-blocking agents, NEBICARD SM is contraindicated in:

• 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.

4.4 Special warnings and precautions for use

NEBICARD SM

*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.

Patients with renal insufficiency: Plasma concentration of nebivolol and its separate enantiomers along with the hydroxylated metabolites increase significantly in patients with renal disease. The pharmacokinetics of the racemic mixture (amlodipine) are not significantly affected by renal impairment. Published data on the pharmacokinetics of S-amlodipine in renal impairment are not

available. S-amlodipine is not dialyzed. The combination should be used with caution in patients with renal insufficiency.

Patients with hepatic insufficiency: Data on use of nebivolol in patients with hepatic insufficiency is limited. Nebivolol is contraindicated in such patients.

The half-life of S-amlodipine is prolonged in patients with hepatic insufficiency. The combination is contraindicated in patients with hepatic insufficiency.

Metabolic/Endocrinological: Nebivolol 5mg Tablets 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 aggravate symptoms.

Elderly: In view of the limited experience in elderly patients, caution must be exercised and these patients should be monitored closely.

Children: Safety and effectiveness of the combination is not established in children.

Pregnancy and Lactation

Use in pregnancy: Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death and in immature and premature delivery. In addition, adverse effects (hypoglycemia and bradycardia) may occur in the foetus and the neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, nebivolol should not be used during pregnancy.

Use of S-amlodipine in pregnancy is not established. The combination should not be used during pregnancy.

Use in lactation: Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Since it is not known whether nebivolol is excreted into human milk, the use of nebivolol when breast-feeding is contraindicated. Reported Animal studies have shown that nebivolol is excreted in breast milk.

Information on S-amlodipine is limited.

It is recommended that nursing be discontinued while this combination is administered. The combination may be used during lactation only when there is no safer alternative and the potential benefits outweigh the potential risks.

4.5 Drugs interactions

Nebivolol:

Pharmacodynamic interactions:

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.

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.

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). 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. 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).

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 considered *only after careful consideration:*

Digitalis glycosides: concomitant use may increase atrio-ventricular conduction time. Reported 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 hypothensive effect of the beta-blockers (additive effect).

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

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

Pharmacokinetic interactions:

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. Nebivolol does not affect the pharmacokinetics and pharmacodynamics of warfarin.

S-AMLODIPINE:

S-amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal antiinflammatory drugs, antibiotics, and oral hypoglycemic agents.

Co administration of S-amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of cimetidine did not alter the pharmacokinetics of S-amlodipine.

In healthy volunteers, co administration of S-amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of S-amlodipine is not likely to result in the need for modification of an established warfarin regimen.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

NEBICARD SM:

Pregnancy

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 new born 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.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death and in immature and premature delivery. In addition, adverse effects (hypoglycemia and bradycardia) may occur in the foetus and the neonate. There is an increased risk of cardiac and pulmonary complications in the neonate in the postnatal period. Therefore, nebivolol should not be used during pregnancy.

Use of S-amlodipine in pregnancy is not established. The combination should not be used during pregnancy

Breast-feeding

In reported 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. Therefore, breastfeeding is not recommended during administration of nebivolol.

Most beta-blockers, particularly lipophilic compounds like nebivolol and its active metabolites, pass into breast milk although to a variable extent. Since it is not known whether nebivolol is excreted into human milk, the use of nebivolol when breast-feeding is contraindicated. Animal studies have shown that nebivolol is excreted in breast milk.

Information on S-amlodipine is limited.

It is recommended that nursing be discontinued while this combination is administered. The combination may be used during lactation only when there is no safer alternative and the potential benefits outweigh the potential risks.

4.7 Effects on ability to drive and use machines

No reported studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that nebivolol does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

4.8 Undesirable effects

Nebivolol:

Adverse events are listed separately for hypertension because of differences in the background diseases.

Hypertension

The adverse reactions reported, 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.

AMLODIPINE:

S-amlodipine:
S-amlodipine is generally well tolerated.
The most commonly observed side effects are headache, edema, fatigue, flushing and dizziness.
Less common side effects include nausea, abdominal pain, somnolence and palpitations.
Rare side effects include muscle cramps, frequency of micturition or nocturia, coughing, breathlessness, epistaxis, impotence, nervousness and conjunctivitis.
No clinically significant pattern of laboratory test abnormalities related to S-amlodipine has been observed.
S-amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids. S-amlodipine has been used safely in patients with well-compensated congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, abnormal lipid profiles and diabetes mellitus.

Reporting of suspected adverse reactions:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting
By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

No data are available on overdosage with 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.**S-AMLODIPINE:**

Symptoms:

Available data suggests that the gross over dosage could result in excessive peripheral vasodilatation with subsequent marked and probably prolonged hypotension.

Treatment:

Since absorption of S-amlodipine is slow, gastric lavage should be performed. Active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output should be given. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Since S-amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

5 Pharmacological properties

5.1 Mechanism of Action

NEBIVOLOL

The mechanism of action of the antihypertensive response of nebivolol has not been definitively established. Possible factors that may be involved include: (1) decreased heart rate, (2) decreased myocardial contractility,(3) diminution of tonic sympathetic outflow to the periphery from cerebral vasomotor centers, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Amlodipine

S Amlodipine Tablet belongs to a class of medicines known as calcium channel blockers. It is used to treat high blood pressure (hypertension) and prevent angina (heart-related chest pain).

5.2 Pharmacodynamic properties

NEBIVOLOL

Pharmacotherapeutic group: Beta blocking agent, selective.

ATC code: C07AB12

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 reported mortality–morbidity, placebo-controlled trial performed in 2128 patients ≥ 70 years (median age 75.2 years) with stable chronic heart failure with or without impaired left ventricular ejection fraction (mean LVEF: 36 ± 12.3%, with the following distribution: LVEF less than 35% in 56% of patients, LVEF between 35% and 45% in 25% of patients and LVEF greater than 45% in 19% of patients) followed for a mean time of 20 months, nebivolol, on top of standard therapy, significantly prolonged the time to occurrence of deaths or hospitalisations for cardiovascular reasons (primary end-point for efficacy) with a relative risk reduction of 14% (absolute reduction: 4.2%). This risk reduction developed after 6 months of treatment and was maintained for all treatment duration (median duration: 18 months). The effect of nebivolol was independent from age, gender, or left ventricular ejection fraction of the population on reported study. The benefit on all cause mortality did not reach statistical significance in comparison to placebo (absolute reduction: 2.3%).

A decrease in sudden death was observed in nebivolol treated patients (4.1% vs 6.6%, relative reduction of 38%).

In reported vitro and in vivo experiments in animals showed that Nebivolol has no intrinsic sympathicomimetic activity.

In reported 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 nebivolol has a detrimental effect on erectile function.

S-AMLODIPINE

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects.

S-amlodipine is a long-acting calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile process of cardiac muscle and vascular smooth muscle are dependent upon movement of extra cellular calcium ions into these cells through specific ion channels. By inhibiting calcium ion influx this product dilates vascular smooth muscle, thereby decreasing the blood pressure. The mechanism of beneficial action in angina pectoris with this product is not yet determined completely, but it is clear that this product can abate myocardial ischaemia through the following actions:

1. Dilatation of peripheral small arteries, decreasing peripheral resistance and thus causing a reduction of energy consumption and oxygen requirement of cardiac muscle.

2. Dilatation of the coronary arteries and the coronary small arteries at normal and ischaemic areas. It is capable of increasing the oxygen supply to the cardiac muscle of patients with coronary artery spasm**.**

Rationale of Nebivolol + S-amlodipine combination

The combination contains nebivolol (beta-blocker) and S-amlodipine (calcium channel blocker) which interact by complementary hemodynamic mechanisms. The calcium channel antagonist causes vasodilatation and reduces the alpha-adrenergic reflex vasoconstriction induced by the beta-blocker. The beta-blocker, at least in part, acts through a reduction in cardiac output. The calcium channel antagonist causes arteriolar dilatation, which leads to reflex tachycardia as one of the side effects. The increase in heart rate increases the oxygen requirement of the heart, which may have a deleterious effect in patients with angina pectoris. Beta-blockers attenuate the tachycardia and sympathetic nervous system stimulation that occurs with calcium channel blockers. Thus the combination is rational from the point of view of safety as well as efficacy.

5.3 Pharmacokinetic properties

Nebivolol:

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.

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. 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.

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.

Plasma concentrations are dose-proportional between 1 and 30 mg. The pharmacokinetics of nebivolol are not affected by age.

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.

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.

S-AMLODIPINE

Absorption

S-amlodipine: After oral administration of S-amlodipine besylate tablet, the blood-drug concentration reaches peak value within 6-12 hours. The absolute bioavailability has been estimated to be in between 64-80% and the apparent distribution volume is approximately 21 L/kg.

Distribution

The blood-drug concentration comes up to homeostasis after successive administration with once a day for 7-8 days. Approximately 93% of the circulating drug is bound to plasma proteins.

Metabolism

S-amlodipine: S-amlodipine besylate is extensively converted to inactive metabolites via hepatic metabolism *Elimination*

S-amlodipine: S-amlodipine is excreted in urine, 10% is excreted as the parent compound, and 60% excreted in the form of metabolites. The terminal elimination half-life for S-amlodipine is 35-50 hours. The average final elimination half-life period of (S)-amlodipine is 49.6 hours while for (R)-amlodipine it is 34.9 hours

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

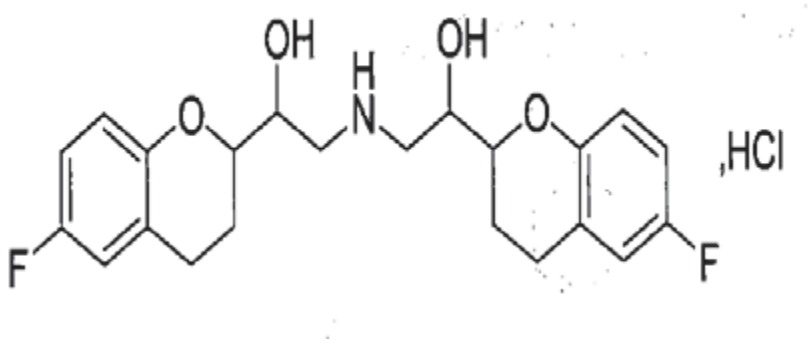
NEBICARD SM

Preclinical reported data reveal no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

7 Description

Nebivolol:

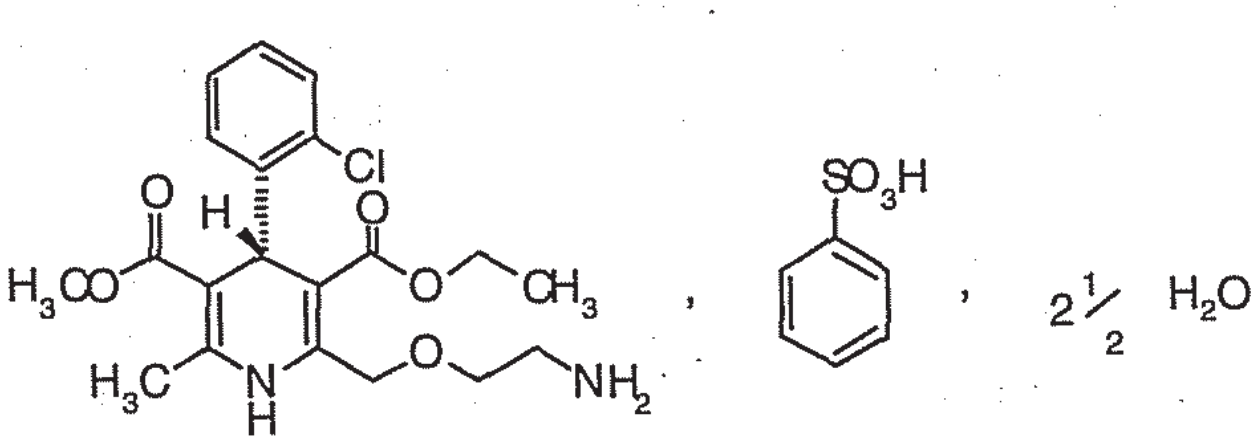
Nebivolol Hydrochloride is (1RS, 1'RS)-1, 1'-[(2RS,2'SR)-bis(6-flurochroman-2-yl)]-2,2' iminodiethanol hydrochloride having molecular formula of $C_{22}H_{25}F_2NO_4$, HCL and molecular weight is 441.9 the chemical structure is:



Nebivolol Hydrochloride is a white to off white Powder, Sparingly soluble in dimethyl-formamide; slightly soluble in methanol.

;

S-Amlodipine Besy late is (S)-2-[(2-aminoethoxy)Ii1ethyl]-4-(2-chloropheny 1)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid 3-ethy15-methyl ester hemipentahydrate.. having molecular formula of $C_{26}H_{31}ClN_2O_8S$. 2 1/2. and molecular weight is 612.1. the chemical structure is:



S-Amlodipine Besylate is a white to pale yellow powder. Freely soluble in methanol and methylene dichloride, sparingly soluble in isopropyl alcohol, slightly soluble in water.

NEBICARD-SM tablets are uncoated bilayered flat circular beveled edge tablets with white colour on one side and light yellow colour on other side of tablets.

The excipients used are Mannitol, croscarmellose sodium, Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Lake of quinoline yellow, starch, sodium starch Glycolate.**8 Pharmaceutical particulars**

8.1 Incompatibilities

Not Applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

NEBICARD-SM is packed in blister strips of 10 tablets

8.4 Storage and handing instructions

STORE AT A TEMPERATURE NOT EXCEEDING 25°C.

PROTECTED FROM LIGHT AND MOISTURE

Keep out of the reach of children.

9 Patient Counselling Information

Package leaflet: Information for the user

NEBICARD SM
Nebivolol And S-Amlodipine Tablets

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

What is in this leaflet

9.1. What NEBICARD SM and what they are used for
9.2. What you need to know before you take NEBICARD SM
9.3 How to take NEBICARD SM
9.4. Possible side effects
9.5. How to store NEBICARD SM Tablets
9.6. Contents of the pack and other information

9.1 What is NEBICARD SM and what it is used for

NEBICARD SM contains combination of Nebivolol and S-Amlodipine Tablets).

Nebicard SM is used in the treatment of essential hypertension.

9.2 What you need to know before you take NEBICARD SM

Do not take NEBICARD SM

- If you are allergic to Nebicard SM or any of the other ingredients of this medicine.
- If you have one or more of the following disorders:
- Low blood pressure
- serious circulation problems in the arms or legs
- Very slow heartbeat (less than 60 beats per minute)
- Certain other serious heart rhythm problems (e.g. 2nd and 3rd degree atrioventricular block, heart conduction disorders).
- Heart failure, which has just occurred or which has recently become worse, or you are receiving treatment for circulatory shock due to acute heart failure by intravenous drip feed to help your heart work.
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- Asthma or wheezing (now or in the past).
- untreated phaeochromocytoma, a tumour located on top of the kidneys (in the adrenal glands)
- Liver function disorder
- a metabolic disorder (metabolic acidosis), for example, diabetic ketoacidosis
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).

Warnings and precautions

Talk to your doctor or pharmacist before taking NEBICARD SM**.**

Nebicard SM:

- Abnormally slow heartbeat.
- a type of chest pain due to spontaneously occurring heart cramp called Prinzmetal angina
- Untreated chronic heart failure or recent heart attack..
- If you have severe kidney disease or if you are undergoing dialysis.
- If you are suffering from a narrowing of the kidney artery.
- If you have recently undergone kidney transplantation (received a new kidney).

- If you are treated after a heart attack or for heart failure, your doctor may check your kidney function.
- If you have severe heart disease other than heart failure or heart attack.
- 1st degree heart block (a kind of light heart conduction disorder that affects heart rhythm).
- Poor circulation in the arms or legs, e.g. Raynaud's disease or syndrome, cramp-like pains when walking.
- Prolonged breathing problems.
- Diabetes: This medicine has no effect on blood sugar, but it could conceal the warning signs of a low sugar level (e.g. palpitations, fast heartbeat).
- Overactive thyroid gland: This medicine may mask the signs of an abnormally fast heart rate due to this condition
- Allergy: This medicine may intensify your reaction to pollen or other substances you are allergic to.
- Psoriasis (a skin disease - scaly pink patches) or if you have ever had psoriasis.
- If you have to have surgery, always inform your anaesthetist that you are on Nebivolol before being anaesthetised.
- Severe increase in blood pressure (Hypertensive crisis).
- Liver disease
- You are elderly and your dose needs to be increased.

Children and adolescents*:*

Because of the lack of reported data on the use of the product in children and adolescents, Nebivolol is not recommended for use in them.

Amlodipine has not been studied in children under the age of 6 years. Amlodipine should only use for hypertension in children and adolescents from 6 years to 17 years of age.

For more information, talk to your doctor.

Pregnancy and breast-feeding:

NEBICARD SM should not be used during pregnancy, unless clearly necessary. It is not recommended for use while breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Other medicines and NEBICARD SM

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Nebivolol:

The following medicines may interact with nebivolol by decreasing or increasing its effects:

• Calcium channel blockers, used to treat high blood pressure or other heart problems, such as verapamil, diltiazem, amlodipine, felodipine, lacidipine, nifedipine, nicardipine, nimodipine and nitrendipine. It is particularly important that verapamil is not injected into a vein during treatment with nebivolol.

• Clonidine, guanfacine, moxonidine, methyldopa and rilmenidine, which are used to treat high blood pressure.

• Quinidine, hydroquinidine, amiodarone, cibenzoline, flecainide, disopyramide, lidocaine, mexiletine and propafenone, which are used to treat cardiac arrhythmias (irregular

heartbeat).

• Barbiturates and phenothiazine, which are used to treat anxiety and levomepromazine for schizophrenia.

• Amitriptyline, trazodone, paroxetine, fluoxetine and thioridiazine, which are used to treat depression.

• Asthma medications, medications for blocked nose (e.g. pseudoephedrine) or for certain eye disorders such as glaucoma (increased pressure in the eye) or dilation of the pupil.

• Medicines for diabetes (insulin and medicines for oral use).

• Anaesthetics. Always inform your anaesthetist that you are on nebivolol before being

anaesthetised.

• Antacids (e.g. cimetidine), which are used to treat excessive stomach acid. If you are being treated for excessive stomach acid, you should take nebivolol during a meal, and the antacid drug between meals.

• Dextromethorphan (found in cough medicines).

• Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen and diclofenac, which are used to treat certain types of pain and inflammation.

• Baclofen (a muscle relaxant).

• Amifostine (used to treat some infections), chloroquine (used to treat malaria) and terbinafine (for fungal infections).

• Bupropion for smoking cessation.

S-AMLODIPINE:

S-amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal antiinflammatory drugs, antibiotics, and oral hypoglycemic agents.

Co administration of S-amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of cimetidine did not alter the pharmacokinetics of S-amlodipine.

In healthy volunteers, co administration of S-amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of S-amlodipine is not likely to result in the need for modification of an established warfarin regimen.

Driving and using machines

No reported studies on the effects on the ability to drive and use machines have been performed. Pharmacodynamic studies have shown that NEBICARD SM does not affect psychomotor function. When driving vehicles or operating machines it should be taken into account that dizziness and fatigue may occasionally occur.

9.3 How to take NEBICARD SM

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Nebivolol can be taken with or without food unless you take antacids. The tablet should be swallowed with a glass of water or other liquid.

Grapefruit juice and grapefruit should not be consumed by people who are taking NEBICARD SM. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of

the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of Amlodipine.

If you take more NEBICARD SM than you should:

If you had taken too many NEBICARD SM tablets contact your doctor or nearest hospital for advice.

If you forget to take NEBICARD SM

If you forget to take a dose of NEBICARD SM, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

If you stop taking NEBICARD SM

Do not stop the treatment unless your doctor tells you so. Contact your doctor or pharmacist before stopping.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Nebivolol:

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When Nebivolol is used for the treatment of raised blood pressure, the possible side effects are:

Common side effects (may affect up to 1 in 10 people):

- Headache
- Dizziness
- Tiredness
- An unusual itching or tingling feeling
- Diarrhoea
- Constipation
- Nausea
- Shortness of breath
- Swollen hands or feet.

Uncommon side effects (may affect up to 1 in 100 people):

- Slow heartbeat or other heart complaints
- Low blood pressure
- Cramp-like leg pains on walking
- Abnormal vision
- Impotence
- Feelings of depression
- Digestive difficulties (dyspepsia), gas in stomach or bowel, vomiting
- Skin rash, itchiness
- Breathlessness such as in asthma, due to sudden cramps in the muscles around the airways (bronchospasm)

- Nightmares.

Very rare side effects (may affect up to 1 in 10,000 people):

- fainting

- worsening of psoriasis (a skin disease - scaly pink patches).

The following side effects have been reported only in some isolated cases during Nebilet treatment:

- Whole-body allergic reactions, with generalised skin eruption (hypersensitivity reactions);

- Rapid-onset swelling, especially around the lips, eyes, or of the tongue with possible sudden difficulty breathing (angioedema);

- Kind of skin rash notable for pale red, raised, itchy bumps of allergic or non allergic causes (urticaria).

In a reported clinical study for chronic heart failure, the following side effects were seen:

Very common side effects (may affect more than 1 in 10 people):

- Slow heart beat

- Dizziness

Common side effects (may affect up to 1 in 10 people):

- worsening of heart failure

- Low blood pressure (such as feeling faint when getting up quickly)

- Inability to tolerate this medicine

- a kind of light heart conduction disorder that affects heart rhythm (1st degree AV-block)

- swelling of the lower limbs (such as swollen ankles).

S-Amlodipine:

Visit your doctor immediately if you experience any of the following effects after taking this medicine.

S-amlodipine is generally well tolerated.
The most commonly observed side effects are headache, edema, fatigue, flushing and dizziness.
Less common side effects include nausea, abdominal pain, somnolence and palpitations.
Rare side effects include muscle cramps, frequency of micturition or nocturia, coughing, breathlessness, epistaxis, impotence, nervousness and conjunctivitis.
No clinically significant pattern of laboratory test abnormalities related to S-amlodipine has been observed.
S-amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids. S-amlodipine has been used safely in patients with well-compensated congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, abnormal lipid profiles and diabetes mellitus.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of

contact of Torrent Pharma available at: https://torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store NEBICARD SM

STORE AT A TEMPERATURE NOT EXCEEDING 25^0C. PROTECTED

FROM LIGHT AND MOISTURE

KEEP OUT OF THE REACH OF CHILDREN

9.6 Contents of the pack and other information

The active substance in NEBICARD SM are Nebivolol and S-Amlodipine Tablets.

The excipients used are Mannitol, croscarmellose sodium,Hydroxy propyl methyl Cellulose, Polysorbate 80, Microcrystalline Cellulose, Magnesium Stearate, Colloidal Silicon Dioxide, Lake of quinoline yellow, starch, sodium starch glycolate

NEBICARD-SM is packed in blister strips of 10 tablets

10 Details of manufacturer

TORRENT PHARMACEUTICALS LTD.

32 No.Middle Camp, NH-10

East District, Gangtok, Sikkim-737 135.

OR

Ravenbhel Biotech

EPIP, SIDCO, Kartholi, Bari-Brahmana, Jammu-181133

11 Details of permission or licence number with date

M/563/2010 issued on 23.12.2016

OR

JK/01/11-12/192 issued on 10.07.2021

12. Date of revision

FEB 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/ NEBICARD SM/Feb-22/02/PI