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

NEBICARD T

1. Generic Name

Nebivolol Hydrochloride and Telmisartan Tablets

2. Qualitative and quantitative Composition

Each uncoated bilayered tablet contains:

Nebivolol Hydrochloride I.P.

Equivalent to Nebivolol ……. 5 mg

Telmisartan I.P……..…….. 40 mg

Colour: Ferric Oxide Red USP-NF

The excipients are Lactose, Maize Starch, Hydroxy Propyl Methyl cellulose, Croscarmellose Sodium, Ferric Oxide Red, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, Sodium Hydroxide, Tween-80, Colloidal Silicon Dioxide, Magnesium stearate, Polyplasdone XL-10, Sodium Lauryl Sulphate.

3. Dosage form and strength

Dosage form: Tablet

Strength: Nebivolol Hydrochloride 5 mg and Telmisartan 40 mg Tablets

4. Clinical particulars

4.1 Therapeutic indication

NEBICARD T is indicated in the treatment of Essential Hypertension.

4.2 Posology and method of administration

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.

Telmisartan:

Treatment of essential hypertension:

The usually effective dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, the dose of telmisartan can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Special populations

Renal impairment

Limited reported experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg is recommended in these patients.

No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

Telmisartan is contraindicated in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg once daily.

Elderly

No dose adjustment is necessary for elderly patients.

Paediatric population

The safety and efficacy of Telmisartan in children and adolescents aged below 18 years have not been established.

Method of administration

One tablet of Nebicard T daily, preferably at the same time of the day.

Tablets may be taken with meals or without meal.

4.3 Contraindications

- 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.

- Biliary obstructive disorders
- The concomitant use of telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2).

In addition, as with other beta-blocking agents, nebivolol 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

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. 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.

<u>Beta-adrenergic antagonists should be used with caution:</u>

- Peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), as aggravation of these disorders may occur upon use of beta blockers;
- First degree heart block, because of the negative effect of beta-blockers on conduction time;
- Prinzmetal's angina due to unopposed alpha-receptor mediated coronary artery vasoconstriction: beta-adrenergic antagonists may increase the number and duration of anginal attacks.
- Concomitant treatment with calcium channel antagonists of the verapamil and diltiazem type, with Class I antiarrhythmic drugs, and with centrally acting antihypertensive drugs.

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.

Other

Caution should be exercised when treating patients with a history of psoriasis with beta-adrenergic antagonists as they may increase the sensitivity to allergens and the severity of anaphylactic reactions.

The initiation of Chronic Heart Failure treatment with nebivolol necessitates regular monitoring. Treatment discontinuation should not be done abruptly unless clearly indicated.

Telmisartan:

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Hepatic impairment:

Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation

When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

• Diabetes mellitus, renal impairment, age (> 70 years)

• Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

• Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischaemia, rhabdomyolysis, extend trauma).

Close-monitoring of serum potassium in at risk patients is recommended.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Other

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

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:

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 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.

Telmisartan:

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia (see section 4.4). The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium

supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use

Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic use)

Reduction of the antihypertensive effect.

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

Nebicard:

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.

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy.

There are no adequate data from the use of Telmisartan in pregnant women. Studies in animals have shown reproductive toxicity.

Epidemiological reported evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor antagonists, similar risks may exist for this class of medicinal products. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.
Exposure to angiotensin II receptor antagonists therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).
Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

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.

Because no information is available regarding the use of Telmisartan during breast-feeding, Telmisartan is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

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 Nebicard T 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 and CHF 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.

Telmisartan:

Summary of the safety profile

Serious adverse reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4% vs 43.9%) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from reported controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated summary of adverse reactions

Adverse reactions have been ranked under headings of frequency using the following convention:

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)

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Upper respiratory tract infection including pharyngitis and sinusitis, urinary tract infection including cystitis

Rare: Sepsis including fatal outcome1Blood and the lymphatic system disorders

Uncommon: Anaemia

Rare: Eosinophilia, thrombocytopenia

Immune system disorders

Rare: Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders

Uncommon: Hyperkalaemia

Rare: Hypoglycaemia (in diabetic patients)

Psychiatric disorders

Uncommon: Depression, insomnia

Rare: Anxiety

Nervous system disorders

Uncommon: Syncope

Rare: Somnolence

Eye disorders

Rare: Visual disturbance

Ear and labyrinth disorders

Uncommon: Vertigo

Cardiac disorders

Uncommon: Bradycardia

Rare: Tachycardia

Vascular disorders

Uncommon: Hypotension2, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough

Very rare: Interstitial lung disease3

Gastrointestinal disorders

Uncommon: Abdominal pain, diarrhoea, dyspepsia , flatulence, vomiting

Rare: Stomach discomfort, dry mouth, dysgeusia

Hepato-biliary disorders

Rare: Hepatic function abnormal/liver disorder4

Skin and subcutaneous tissue disorders

Uncommon: Hyperhidrosis, pruritus, rash

Rare: Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Muscoloskeletal and connective tissue disorders

Uncommon: Myalgia, back pain (e.g. sciatica), muscle spasms

Rare: Arthralgia, pain in extremity, tendon pain (tendonitis like symptoms)

Renal and urinary disorders

Uncommon: Renal impairment including acute renal failure

General disorders and administration site conditions

Uncommon: Chest pain, asthenia (weakness)

Rare: Influenza-like illness

Investigations

Uncommon: Blood creatinine increased

Rare: Blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased, haemoglobin decreased.

Description of selected adverse reactions

Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

Interstitial lung disease

Reported Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

Hepatic function abnormal / liver disorder

Most reported cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Reporting of suspected adverse reactions

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

Nebivolol

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.

Telmisartan:

There is limited information available with regard to overdose in humans.

Symptoms: The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia, dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdose. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

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.

Telmisartan:

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse events.

5.2 Pharmacodynamic properties

Nebivolol

Pharmacotherapeutic group: Beta blocking agent, selective.

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 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.

Telmisartan:

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Clinical efficacy and safety

Treatment of essential hypertension

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in reported placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect reported data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

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.

Telmisartan:

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. Cmax and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 l.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Populations

Paediatric population

The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age related differences. Although the reported study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for Cmax.

Gender

Differences in plasma concentrations were observed, with Cmax and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment

Pharmacokinetic reported studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

6. Nonclinical properties

6.1 Animal toxicology or Pharmacology

Nebivolol:

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

Telmisartan:

In reported preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral sodium chloride solution supplementation.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

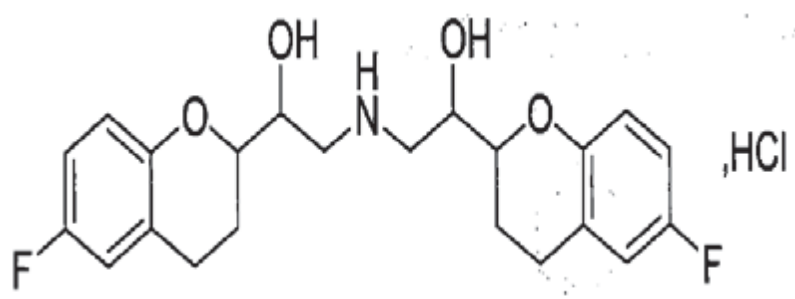
No clear reported evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed.

There was no reported evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

7. Description

Nebivolol Hydrochloride:

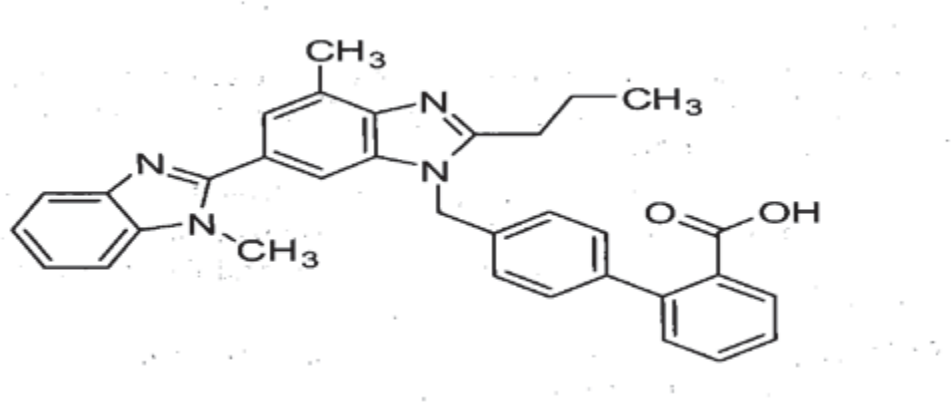
Nebivolol Hydrochloride is a beta 1 receptor blocker that works specifically on the heart to slow down the heart rate. Nebivolol Hydrochloride is chemically (1RS, 1 'RS)-1, 1 '-[(2RS,2'SR)-bis (6-flurochroman-2-yl)]-2,2'- iminodiethanol hydrochloride. Its empirical formula is $C_{22}H_{25}F_2NO_4$,HCl and its structural formula is:



Nebivolol Hydrochloride is a white to off-white powder with a molecular weight of 441.9. It is sparingly soluble in dimethyl form amide and slightly soluble in methanol**.**

Telmisartan

Telmisartan is 4'-{[4-mrthy-6-(1-methy-1H-benzimidazol-2-yl)-2-propyl-1Hbenzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid having molecular formula of $C_{33}H_{30}N_4O_2$ and molecular weight is 514.6. The chemical structure is:



Telmisartan is a white to off-white crystalline powder, Sparingly soluble in methylene chloride; slightly soluble in methanol; practically insoluble in water.

NEBICARD-T

White and Brown coloured, round, flat faced, beveled edge, bilayered, uncoated tablets, scored on one side, plain on other side.

The excipients are Lactose, Maize Starch, Hydroxy Propyl Methyl cellulose, Croscarmellose Sodium, Ferric Oxide Red, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, Sodium Hydroxide, Tween-80, Colloidal Silicon Dioxide, Magnesium stearate, Polyplasdone XL-10, Sodium Lauryl Sulphate.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Available in Blister strip pack of 10 tablets.

8.4 Storage and handing instructions

Store below 30ºC. Protected from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

NEBICARD T

Nebivolol Hydrochloride and Telmisartan 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

9.1 What is NEBICARD T and what it is used for

NEBICARD T contains combination of Nebivolol Hydrochloride and Telmisartan Tablets.

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.

Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The

functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse events.
Nebicard T is used in the treatment of essential hypertension.

9.2 What you need to know before you take NEBICARD T

Do not take NEBICARD T

- if you are allergic to Nebicard 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.
- 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 such as such as cholestasis or biliary obstruction (problems with the drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- a metabolic disorder (metabolic acidosis), for example, diabetic ketoacidosis
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.
- if you are more than 3 months pregnant.

Warnings and precautions

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

Nebicard:

- Abnormally slow heartbeat
- A type of chest pain due to spontaneously occurring heart cramp called Prinzmetal angina
- Untreated chronic heart failure
- If you have severe kidney disease or if you are undergoing dialysis.
- If you are suffering from a narrowing of the kidney artery or kidney transplant.
- 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
- Liver disease
- Elevated potassium levels in your blood

- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- 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 NEBICARD T before being anaesthetised.

Children and adolescents*:*

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

Other medicines and NEBICARD

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

Nebivolol:

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

Telmisartan:

Your doctor may need to change the dose of these other medicines or take other precautions. In some cases you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with Telmisartan

- Lithium containing medicines to treat some types of depression.

- Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors (angiotensin-converting enzyme inhibitors, to treat high blood pressure), angiotensin II receptor antagonists (to treat high blood pressure), NSAIDs (non steroidal anti-inammatory medicines, e.g. aspirin or ibuprofen), heparin (a medicine for thinning the blood), immunosuppressives (e.g. ciclosporin or tacrolimus), and the antibiotic trimethoprim.

- Diuretics ('water tablets'), especially if taken in high doses together with Telmisartan, may lead to excessive loss of body water and low blood pressure (hypotension).

- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings “Do not take Telmisartan” and “Warnings and precautions”).

- Digoxin.

The effect of Telmisartan may be reduced when you take NSAIDs (non steroidal anti-inammatory drugs, e.g. aspirin or ibuprofen) or corticosteroids. Telmisartan may increase the blood pressure lowering e-ect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine). Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking Telmisartan.

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 T 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 T

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

Nebicard T can be taken with or without food unless you take antacids. The tablet should be swallowed with a glass of water or other liquid. Try to take the tablet at the same time. each day The tablets should be swallowed with some water or other non-alcoholic drink.

If you take more NEBICARD T than you should:

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

If you forget to take NEBICARD T

If you forget to take a dose of NEBICARD T, 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 T

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 Nebicard 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 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).

Side effects in children and adolescents are similar to those seen in adults**.**

Telmisartan:

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

Some side e-ects can be serious and need immediate medical attention:

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inammatory response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated they could be fatal.

Possible side effects of telmisartan:

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

Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

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

Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inamed sinuses, common cold), deciency in red blood cells (anaemia), high potassium levels, diculty falling

asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), slow heart rate (bradycardia), low blood pressure (hypotension) in users treated for high blood pressure, dizziness on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhoea, discomfort in the abdomen, bloating, vomiting, itching, increased sweating, drug rash, back pain,

muscle cramps, muscle pain (myalgia), kidney impairment including acute kidney failure, pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

Rare side effects (may affect up to 1 in 1,000 people):

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic reaction (e.g. rash, itching, diculty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heartbeat (tachycardia), dry mouth, upset stomach, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side e-ect), rapid swelling of the skin and mucosa which can also lead to death (angioedema also with fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flu-like-illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood.

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

Progressive scarring of lung tissue (interstitial lung disease)**.

* The event may have happened by chance or could be related to a way that telmisartan works that is currently not known.

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 T

Store below 30ºC. Protected from light and moisture.

9.6 Contents of the pack and other information

The active substance in NEBICARD T are Nebivolol Hydrochloride and Telmisartan Tablets.

The excipients are Lactose, Maize Starch, Hydroxy Propyl Methyl cellulose, Croscarmellose Sodium, Ferric Oxide Red, Microcrystalline Cellulose, Sodium Starch Glycollate, Isopropyl Alcohol, Sodium Hydroxide, Tween-80, Colloidal Silicon Dioxide, Magnesium stearate, Polyplasdone XL-10, Sodium Lauryl Sulphate.

Available in Blister strip pack of 10 tablets.

10. Details of manufacturer

Manufactured in India by:

Windlas Biotech Pvt. Limited (Plant-2).

Khasra No.: 141-143 & 145, Mohabewala Industrial Area,

Dehradun-248 110, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No.: 34//UA/2013 issued on 05.08.2021

12. Date of revision

FEB 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ NEBICARD T 5+40mg/FEB 2022/02/PI