
NEBICARD T

WARNING: FETAL TOXICITY

- When pregnancy is detected, discontinue the product as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and death to developing fetus.

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 Mannitol, Hydroxy Propyl Methyl cellulose, Croscarmellose Sodium, Ferric Oxide Red, Microcrystalline Cellulose, , Polysorbate 80 (Tween-80), Colloidal Silicon Dioxide, Magnesium stearate.

3. Dosage form and strength

Dosage form: Uncoated bilayered tablet

Strength: 5mg/40mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated in the treatment of Essential Hypertension.

4.2. Posology and method of administration

Posology

Nebivolol

Hypertension

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.

Beta-adrenergic antagonists should be used with caution:

- 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 dehydration, 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 β -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 tone (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 neбиволol 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 neбиволol have not shown any clinical evidence of an interaction. Nebivolol does not influence the kinetics of digoxin.

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

Antipsychotics, antidepressants (tricyclics, barbiturates and phenothiazines): concomitant use

may enhance the hypotensive effect of the beta-blockers (additive effect).

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

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

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 nifedipine 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. spironolactone, 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 AUC_{0-24} and C_{max} 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.

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 ($\geq 1/10,000$ 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ 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 outcome

Blood 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: Hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, cough

Very rare: Interstitial lung disease

Gastrointestinal disorders

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

Rare: Stomach discomfort, dry mouth, dysgeusia

Hepato-biliary disorders

Rare: Hepatic function abnormal/liver disorder

Skin and subcutaneous tissue disorders

Uncommon: Hyperhidrosis, pruritus, rash

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

Musculoskeletal 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 adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com or at email: pv@torrentpharma.com or call on 1800-120-3001.

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. 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

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 enantiomer (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: $36 \pm 12.3\%$, 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

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 R_{SSS}-enantiomer are slightly higher than for the S_{RRR}-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 S_{RRR}-nebivolol and 97.9% for R_{SSS}-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 ($AUC_{0-\infty}$) 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. C_{\max} 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 ($V_{d_{ss}}$) 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 (C_{\max}) 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 (Cl_{tot}) 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 C_{\max} .

Gender

Differences in plasma concentrations were observed, with C_{\max} 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.

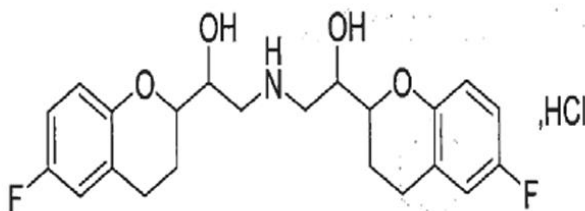
No clear reported evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the offsprings such as lower body weight and delayed eye opening was observed.

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

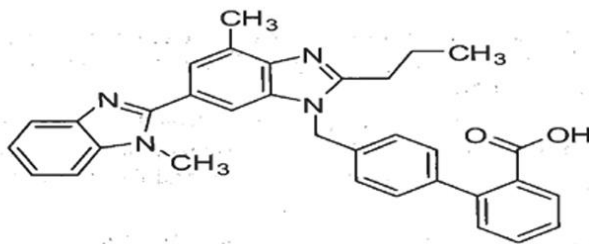
Nebivolol Hydrochloride is a beta 1 receptor blocker that works specifically on the heart to slow down the heart rate. Nebivolol Hydrochloride is chemically (1*RS*, 1'*RS*)-1, 1' - [(2*RS*, 2'*SR*)-bis (6- fluorchroman-2-yl)]-2, 2'- iminodiethanol hydrochloride. Its empirical formula is C₂₂H₂₅F₂NO₄.HCl 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 formamide and slightly soluble in methanol.

Telmisartan

Telmisartan is 4'-{[4-methyl -6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid having molecular formula of C₃₃H₃₀N₄O₂ and molecular weight is 514.6. The chemical structure is:



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

NEBICARD-T

White and Brick red colored , round, flat face beveled edge, bilayered, uncoated tablets, scored on one side and plain on other side.

The excipients are Mannitol , Hydroxy Propyl Methyl cellulose, Croscarmellose Sodium, Ferric Oxide Red, Microcrystalline Cellulose, , Polysorbate 80 (Tween-80), Colloidal Silicon Dioxide, Magnesium stearate.

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-T is available in 10 Blister strips of 15 tablets each.

8.4. Storage and handling instructions

Store below 30°C, Protect from light and moisture.

Keep all medicine out of reach of children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Torrent Pharmaceuticals Limited,

32 No. Middle Camp NH-10,
East District, Gangtok, Sikkim-737 135.

11. Details of permission or licence number with date

M/563/2010 dated on 07.06.2022

12. Date of revision

JUN 2026

MARKETED BY

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IN/NEBICARD T 5+40mg/JUN 2026/03/PI