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

NEBICARD T 2.5 mg

WARNING: FETAL TOXICITY

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

1. Generic Name

Nebivolol Hydrochloride and Telmisartan Tablets (2.5 mg + 40 mg)

2. Qualitative and quantitative Composition:

Each uncoated bilayered tablet contains:

Nebivolol Hydrochloride I.P.

Eq. to Nebivolol ……. 2.5 mg

Telmisartan I.P. …… 40 mg

Excipients ……. q.s.

Colour: Sunset Yellow FCF

The List of Excipients used are Mannitol, Sodium Hydroxide, N. Methyl D. Glucemine Meglumine, Povidone, crospovidone, Magnesium Stearate, Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Sunset Yellow Lake, Pregelatinized Starch, Hydroxypropyl Methyl Cellulose, Polysorbate 80, Sodium Lauryl Sulphate and Colloidal Silicon Dioxide.

3. Dosage form and strength

Dosage form: Uncoated bilayered tablet

Strength: 2.5 mg + 40 mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the management of essential Hypertension.

4.2. Posology and method of administration

Posology

Nebivolol

Hypertension

The dose of Nebivolol must be individualized to the needs of the patient. For most patients, the recommended starting dose is 5 mg once daily, with or without food, as monotherapy or in combination with other agents. For patients requiring further reduction in blood pressure, the dose can be increased at 2-week intervals up to 40 mg. A more frequent dosing regimen is unlikely to be beneficial.

Renal Impairment

In patients with severe renal impairment (ClCr less than 30 mL/min) the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. Nebivolol has not been studied in patients receiving dialysis.

Hepatic Impairment

In patients with moderate hepatic impairment, the recommended initial dose is 2.5 mg once daily; titrate up slowly if needed. Nebivolol has not been studied in patients with severe hepatic impairment and therefore it is not recommended in that population.

Subpopulations

Geriatric Patients

It is not necessary to adjust the dose in the elderly.

CYP2D6 Polymorphism

No dose adjustments are necessary for patients who are CYP2D6 poor metabolizers. The clinical effect and safety profile observed in poor metabolizers were similar to those of extensive metabolizers.

Telmisartan

Hypertension

Dosage must be individualized. The usual starting dose of Telmisartan tablets is 40 mg orally once a day. Blood pressure response is dose-related over the range of 20 to 80 mg.

Most of the antihypertensive effect is apparent within 2 weeks and maximal reduction is generally attained after 4 weeks.

No initial dosage adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored. Telmisartan tablets may be administered with other antihypertensive agents.

Telmisartan tablets may be administered with or without food.

Cardiovascular Risk Reduction

The recommended dose of Telmisartan tablets is 80 mg once a day and can be administered with or without food. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality.

When initiating Telmisartan therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and if appropriate, adjustment of medications that lower blood pressure may be necessary.

Method of administration

These should be swallowed whole with water with or without food.

4.3. Contraindications

Nebivolol

Nebivolol is contraindicated in the following conditions:

- Severe bradycardia.
- Heart block greater than first degree.

- Patients with cardiogenic shock.
- Decompensated cardiac failure.
- Sick sinus syndrome (unless a permanent pacemaker is in place)
- Patients with severe hepatic impairment (Child-Pugh >B).
- Patients who are hypersensitive to any component of this product.

Telmisartan

Telmisartan is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or any other component of this product. Do not co-administer aliskiren with Telmisartan in patients with diabetes.

4.4. Special warnings and precautions for use

Nebivolol

Abrupt Cessation of Therapy

Do not abruptly discontinue Nebivolol therapy in patients with coronary artery disease. Severe exacerbation of angina, myocardial infarction and ventricular arrhythmias have been reported in patients with coronary artery disease following the abrupt discontinuation of therapy with β-blockers. Myocardial infarction and ventricular arrhythmias may occur with or without preceding exacerbation of the angina pectoris. Caution patients without overt coronary artery disease against interruption or abrupt discontinuation of therapy. As with other β-blockers, when discontinuation of Nebivolol is planned, carefully observe and advise patients to minimize physical activity. Taper Nebivolol over 1 to 2 weeks when possible. If the angina worsens or acute coronary insufficiency develops, re-start Nebivolol promptly, at least temporarily.

Angina and Acute Myocardial Infarction

Nebivolol was not studied in patients with angina pectoris or who had a recent MI.

Bronchospastic Diseases

In general, patients with bronchospastic diseases should not receive β-blockers.

Anesthesia and Major Surgery

Because beta-blocker withdrawal has been associated with an increased risk of MI and chest pain, patients already on beta-blockers should generally continue treatment throughout the perioperative period. If Nebivolol is to be continued perioperatively, monitor patients closely when anesthetic agents which depress myocardial function, such as ether, cyclopropane, and trichloroethylene, are used. If β-blocking therapy is withdrawn prior to major surgery, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

The β-blocking effects of Nebivolol can be reversed by β-agonists, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Additionally, difficulty in restarting and maintaining the heartbeat has been reported with β-blockers.

Hypoglycemia

Beta-blockers may prevent early warning signs of hypoglycemia, such as tachycardia, and increase the risk for severe or prolonged hypoglycemia at any time during treatment, especially in patients with diabetes mellitus or children and patients who are fasting (i.e., surgery, not eating regularly, or are vomiting). If severe hypoglycemia occurs, patients should be instructed to seek emergency treatment.

Thyrotoxicosis

β-blockers may mask clinical signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of β-blockers may be followed by an exacerbation of the symptoms of hyperthyroidism or may precipitate a thyroid storm.

Peripheral Vascular Disease

β-blockers can precipitate or aggravate symptoms of arterial insufficiency in patients with peripheral vascular disease.

Non-dihydropyridine Calcium Channel Blockers

Because of significant negative inotropic and chronotropic effects in patients treated with β-blockers and calcium channel blockers of the verapamil and diltiazem type, monitor the ECG and blood pressure in patients treated concomitantly with these agents.

Use with CYP2D6 Inhibitors

Nebivolol exposure increases with inhibition of CYP2D6. The dose of Nebivolol may need to be reduced.

Impaired Renal Function

Renal clearance of nebivolol is decreased in patients with severe renal impairment. Nebivolol has not been studied in patients receiving dialysis.

Impaired Hepatic Function

Metabolism of nebivolol is decreased in patients with moderate hepatic impairment. Nebivolol has not been studied in patients with severe hepatic impairment.

Risk of Anaphylactic Reactions

While taking β-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.

Pheochromocytoma

In patients with known or suspected pheochromocytoma, initiate an α-blocker prior to the use of any β-blocker.

Telmisartan

Fetal Toxicity

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.

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible.

Hypotension

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after

initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hyperkalemia

Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.

Impaired Hepatic Function

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Initiate telmisartan at low doses and titrate slowly in these patients.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported with Telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis but anticipate an effect similar to that seen with ACE inhibitors.

Dual Blockade of the Renin-Angiotensin-Aldosterone System (RAS)

Dual blockade of the RAS with angiotensin-receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The ONTARGET trial enrolled 25,620 patients ≥55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of Telmisartan and ramipril did not obtain any additional benefit compared to monotherapy but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone.

In most patients no benefit has been associated with using two RAS inhibitors concomitantly. In general, avoid combined use of RAS inhibitors. Closely monitor blood pressure, renal function, and electrolytes in patients on Telmisartan and other agents that affect the RAS.

Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid concomitant use of aliskiren with Telmisartan in patients with renal impairment (GFR < 60 mL/min/1.73 m^2).

4.5. Drugs interactions

Nebivolol

CYP2D6 Inhibitors

Use caution when Nebivolol is co-administered with CYP2D6 inhibitors (quinidine, propafenone, fluoxetine, paroxetine, etc.).

Hypotensive Agents

Do not use Nebivolol with other β-blockers. Closely monitor patients receiving catecholamine-depleting drugs, such as reserpine or guanethidine, because the added β-blocking action of Nebivolol may produce excessive reduction of sympathetic activity. In patients who are receiving Nebivolol and clonidine, discontinue Nebivolol for several days before the gradual tapering of clonidine.

Digitalis Glycosides

Both digitalis glycosides and β-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

Calcium Channel Blockers

Nebivolol can exacerbate the effects of myocardial depressants or inhibitors of AV conduction, such as certain calcium antagonists (particularly of the phenylalkylamine [verapamil] and benzothiazepine [diltiazem] classes), or antiarrhythmic agents, such as disopyramide.

Telmisartan

Aliskiren

Do not co-administer aliskiren with Telmisartan in patients with diabetes. Avoid use of aliskiren with Telmisartan in patients with renal impairment (GFR< 60 mL/min).

Digoxin

When Telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. Therefore, monitor digoxin levels when initiating, adjusting, and discontinuing telmisartan for the purpose of keeping the digoxin level within the therapeutic range.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists including Telmisartan. Therefore, monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.

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

Nebivolol

Pregnancy

Risk Summary

Available data regarding use of Nebivolol in pregnant women are insufficient to determine whether there are drug-associated risks of adverse developmental outcomes. There are risks to the mother and fetus associated with poorly controlled hypertension in pregnancy. The use of beta blockers during the third trimester of pregnancy may increase the risk of hypotension, bradycardia, hypoglycemia, and respiratory depression in the neonate. Oral administration of nebivolol to pregnant rats during organogenesis resulted in embryofetal and perinatal lethality at doses approximately equivalent to the maximum recommended human dose (MRHD).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Neonates of women with hypertension, who are treated with beta-blockers during the third trimester of pregnancy, may be at increased risk for hypotension, bradycardia, hypoglycemia, and respiratory depression. Observe newborns for symptoms of hypotension, bradycardia, hypoglycemia and respiratory depression and manage accordingly.

Data

Animal Data

Nebivolol was shown to increase embryo-fetal and perinatal lethality in rats at approximately 1.2 times the MRHD or 40 mg/day on a mg/m2 basis. Decreased pup body weights occurred at 1.25 and 2.5 mg/kg in rats, when exposed during the perinatal period (late gestation, parturition and lactation). At 5 mg/kg and higher doses (1.2 times the MRHD), prolonged gestation, dystocia and reduced maternal care were produced with corresponding increases in late fetal deaths and stillbirths and decreased birth weight, live litter size and pup survival. These events occurred only when nebivolol was given during the perinatal period (late gestation, parturition and lactation). Insufficient numbers of pups survived at 5 mg/kg to evaluate the offspring for reproductive performance.

In studies in which pregnant rats were given nebivolol during organogenesis, reduced fetal body weights were observed at maternally toxic doses of 20 and 40 mg/kg/day (5 and 10 times the MRHD), and small reversible delays in sternal and thoracic ossification associated with the reduced fetal body weights and a small increase in resorption occurred at 40 mg/kg/day (10 times the MRHD).

No adverse effects on embryo-fetal viability, sex, weight or morphology were observed in studies in which nebivolol was given to pregnant rabbits at doses as high as 20 mg/kg/day (10 times the MRHD).

Lactation

Risk Summary

There is no information regarding the presence of nebivolol in human milk, the effects on the breastfed infant, or the effects on milk production. Nebivolol is present in rat milk. Because of the potential for β-blockers to produce serious adverse reactions in nursing infants, especially bradycardia, Nebivolol is not recommended during nursing.

Data

In lactating rats, maximum milk levels of unchanged nebivolol were observed at 4 hours after single and repeat doses of 2.5 mg/kg/day. The daily dose (mg/kg body weight) ingested by a rat pup is 0.3% of the dam dose for unchanged nebivolol.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies in ages newborn to 18 years old have not been conducted because of incomplete characterization of developmental toxicity and possible adverse effects on long-term fertility.

Juvenile Animal Toxicity Data

Daily oral doses of nebivolol to juvenile rats from post-natal day 14 to post-natal day 27 showed sudden unexplained death at exposures equal to those in human poor metabolizers given a single dose of 10 mg. No mortality was seen at half the adult human exposure.

In surviving rats, cardiomyopathy was seen at exposures greater than or equal to the human exposure. Male rat pups exposed to twice the human exposure showed decreases in total sperm count as well as decreases in the total and percentage of motile sperm.

Geriatric Use

Of the 2800 patients in the U.S. sponsored placebo-controlled clinical hypertension studies, 478 patients were 65 years of age or older. No overall differences in efficacy or in the incidence of adverse events were observed between older and younger patients.

Heart Failure

In a placebo-controlled trial of 2128 patients (1067 Nebivolol, 1061 placebo) over 70 years of age with chronic heart failure receiving a maximum dose of 10 mg per day for a median of 20 months, no worsening of heart failure was reported with nebivolol compared to placebo. However, if heart failure worsens consider discontinuation of Nebivolol.

Telmisartan

Pregnancy

Risk Summary

Telmisartan can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Studies in rats and rabbits with telmisartan showed fetotoxicity only at maternally toxic doses. When pregnancy is detected, discontinue Telmisartan as soon as possible.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, and post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Pregnant women with hypertension should be carefully monitored and managed accordingly.

Fetal/Neonatal adverse reactions

Use of drugs that act on the RAS in the second and third trimesters of pregnancy can result in the following: oligohydramnios, reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death. In the unusual case that there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system for a particular patient, apprise the mother of the potential risk to the fetus.

In patients taking Telmisartan during pregnancy, perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. If oligohydramnios is observed, discontinue Telmisartan, unless it is considered lifesaving for the mother. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of in utero exposure to Telmisartan for hypotension, oliguria, and hyperkalemia. If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Data

Animal Data

No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. The no-observed-effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Lactation

Risk Summary

There is no information regarding the presence of telmisartan in human milk, the effects on the breastfed infant, or the effects on milk production. Telmisartan is present in the milk of lactating rats. Because of the potential for serious adverse reactions in the breastfed infant including

hypotension, hyperkalemia and renal impairment, advise a nursing woman not to breastfeed during treatment with Telmisartan.

Data

Telmisartan was present in the milk of lactating rats at concentrations 1.5 to 2 times those found in plasma from 4 to 8 hours after administration.

Pediatric Use

Safety and effectiveness in pediatric patients have not been.

Neonates with a history of in utero exposure to Telmisartan

If oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

Geriatric Use

Of the total number of patients receiving Telmisartan in hypertension clinical studies, 551 (19%) were 65 to 74 years of age and 130 (4%) were 75 years or older. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Of the total number of patients receiving Telmisartan in the cardiovascular risk reduction study (ONTARGET), the percentage of patients ≥65 to < 75 years of age was 42%; 15% of patients were ≥75 years old. No overall differences in effectiveness and safety were observed in these patients compared to younger patients and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Insufficiency

Monitor carefully and uptitrate slowly in patients with biliary obstructive disorders or hepatic insufficiency.

4.7. Effects on ability to drive and use machines

Nebivolol

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

Telmisartan

When driving vehicles or operating machinery it should taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan

4.8. Undesirable effects

Nebivolol

Hyperkalaemia

Clinical Studies Experience

Nebivolol has been evaluated for safety in patients with hypertension and in patients with heart failure. The observed adverse reaction profile was consistent with the pharmacology of the drug and the health status of the patients in the clinical trials. Adverse reactions reported for each of

these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

The data described below reflect worldwide clinical trial exposure to Nebivolol in 6545 patients, including 5038 patients treated for hypertension and the remaining 1507 subjects treated for other cardiovascular diseases. Doses ranged from 0.5 mg to 40 mg. Patients received Nebivolol for up to 24 months, with over 1900 patients treated for at least 6 months, and approximately 1300 patients for more than one year.

Hypertension: In placebo-controlled clinical trials comparing Nebivolol with placebo, discontinuation of therapy due to adverse reactions was reported in 2.8% of patients treated with nebivolol and 2.2% of patients given placebo. The most common adverse reactions that led to discontinuation of Nebivolol were headache (0.4%), nausea (0.2%) and bradycardia (0.2%).

The table below lists treatment-emergent adverse reactions that were reported in three 12-week, placebo-controlled monotherapy trials involving 1597 hypertensive patients treated with either 5 mg, 10 mg, or 20-40 mg of Nebivolol and 205 patients given placebo and for which the rate of occurrence was at least 1% of patients treated with nebivolol and greater than the rate for those treated with placebo in at least one dose group.

Table: Treatment-Emergent Adverse Reactions with an Incidence (over 6 weeks) ≥ 1% in Nebivolol-Treated Patients and at a Higher Frequency than Placebo-Treated Patients

System Organ Class – Preferred Term	Placebo (n = 205) (%)	Nebivolol 5 mg (n = 459) (%)	Nebivolol 10 mg (n = 461) (%)	Nebivolol 20-40 mg (n = 677) (%)
Cardiac Disorders				
Bradycardia	0	0	0	1
Gastrointestinal Disorders				
Diarrhea	2	2	2	3
Nausea	0	1	3	2
General Disorders				
Fatigue	1	2	2	5
Chest pain	0	0	1	1
Peripheral edema	0	1	1	1
Nervous System Disorders				
Headache	6	9	6	7
Dizziness	2	2	3	4
Psychiatric Disorders				
Insomnia	0	0	0	1
Respiratory Disorders				
Dyspnea	0	0	1	1
Skin and subcutaneous Tissue Disorders				
Rash	0	0	1	1

Listed below are other reported adverse reactions with an incidence of at least 1% in the more than 4300 patients treated with Nebivolol in controlled or open-label trials except for those already appearing in Table 1, terms too general to be informative, minor symptoms, or adverse reactions unlikely to be attributable to drug because they are common in the population. These

adverse reactions were in most cases observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: asthenia.

Gastrointestinal System Disorders: abdominal pain

Metabolic and Nutritional Disorders: hypercholesterolemia

Nervous System Disorders: paraesthesia.

Laboratory Abnormalities

In controlled monotherapy trials of hypertensive patients, Nebivolol was associated with an increase in BUN, uric acid, triglycerides and a decrease in HDL cholesterol and platelet count.

Postmarketing Experience

The following adverse reactions have been identified from spontaneous reports of Nebivolol received worldwide and have not been listed elsewhere. These adverse reactions have been chosen for inclusion due to a combination of seriousness, frequency of reporting or potential causal connection to Nebivolol. Adverse reactions common in the population have generally been omitted. Because these adverse reactions were reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency or establish a causal relationship to Nebivolol exposure: abnormal hepatic function (including increased AST, ALT and bilirubin), acute pulmonary edema, acute renal failure, atrioventricular block (both second and third degree), bronchospasm, erectile dysfunction, hypersensitivity (including urticaria, allergic vasculitis and rare reports of angioedema), hypotension, myocardial infarction, pruritus, psoriasis, Raynaud's phenomenon, peripheral ischemia/claudication, somnolence, syncope, thrombocytopenia, various rashes and skin disorders, vertigo, and vomiting.

Telmisartan

The following adverse reaction is described elsewhere in labeling:

- Lichenoid keratosis
- Renal dysfunction upon use with ramipril

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Hypertension

Telmisartan has been evaluated for safety in more than 3700 patients, including 1900 treated for over 6 months and more than 1300 for over one year. Adverse experiences have generally been mild and transient in nature and have infrequently required discontinuation of therapy.

In placebo-controlled trials involving 1041 patients treated with various doses of Telmisartan (20 to 160 mg) monotherapy for up to 12 weeks, the overall incidence of adverse events was similar to that in patients treated with placebo.

Adverse events occurring at an incidence of ≥1% in patients treated with Telmisartan and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in the below table

Table: Adverse Events Occurring at an Incidence of ≥1% in Patients Treated with Telmisartan and at a Greater Rate Than Patients Treated with Placebo

	Telmisartan n=1455 %	Placebo n=380 %
Upper respiratory tract infection	7	6
Back pain	3	1
Sinusitis	3	2
Diarrhea	3	2
Pharyngitis	1	0

In addition to the adverse events in the table, the following events occurred at a rate of ≥1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema. Discontinuation of therapy because of adverse events was required in 2.8% of 1455 patients treated with Telmisartan tablets and 6.1% of 380 placebo patients in placebo-controlled clinical trials.

The incidence of adverse events was not dose-related and did not correlate with gender, age, or race of patients.

The incidence of cough occurring with telmisartan in 6 placebo-controlled trials was identical to that noted for placebo-treated patients (1.6%).

In addition to those listed above, adverse events that occurred in more than 0.3% of 3500 patients treated with Telmisartan monotherapy in controlled or open trials are listed below. It cannot be determined whether these events were causally related to Telmisartan tablets:

Autonomic Nervous System: impotence, increased sweating, flushing.

Body as a Whole: allergy, fever, leg pain, malaise.

Cardiovascular: palpitation, dependent edema, angina pectoris, tachycardia, leg edema, abnormal ECG.

CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoesthesia.

Gastrointestinal: flatulence, constipation, gastritis, vomiting, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders.

Metabolic: gout, hypercholesterolemia, diabetes mellitus.

Musculoskeletal: arthritis, arthralgia, leg cramps.

Psychiatric: anxiety, depression, nervousness.

Resistance Mechanism: infection, fungal infection, abscess, otitis media.

Respiratory: asthma, bronchitis, rhinitis, dyspnea, epistaxis.

Skin: dermatitis, rash, eczema, pruritus.

Urinary: micturition frequency, cystitis.

Vascular: cerebrovascular disorder;

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

During initial clinical studies, a single case of angioedema was reported (among a total of 3781 patients treated).

Clinical Laboratory Findings

In placebo-controlled clinical trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of Telmisartan tablets.

Hemoglobin:

A greater than 2 g/dL decrease in hemoglobin was observed in 0.8% telmisartan patients compared with 0.3% placebo patients. No patients discontinued therapy because of anemia.

Creatinine:

A 0.5 mg/dL rise or greater in creatinine was observed in 0.4% telmisartan patients compared with 0.3% placebo patients. One telmisartan-treated patient discontinued therapy because of increases in creatinine and blood urea nitrogen.

Liver Enzymes:

Occasional elevations of liver chemistries occurred in patients treated with telmisartan; all marked elevations occurred at a higher frequency with placebo. No telmisartan-treated patients discontinued therapy because of abnormal hepatic function.

Cardiovascular Risk Reduction

Because common adverse reactions were well characterized in studies of telmisartan in hypertension, only adverse events leading to discontinuation and serious adverse events were recorded in subsequent studies of telmisartan for cardiovascular risk reduction. In TRANSCEND (N=5926, 4 years and 8 months of follow-up), discontinuations for adverse events were 8.4% on telmisartan and 7.6% on placebo. The only serious adverse events at least 1% more common on telmisartan than placebo were intermittent claudication (7% vs 6%) and skin ulcer (3% vs 2%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Telmisartan. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Anemia, eosinophilia, thrombocytopenia

Gastrointestinal Disorders: Abdominal pain, diarrhea, dyspepsia, nausea

General Disorders and Administration Site Conditions: Asthenia, chest pain, edema, face edema, fatigue, lower limb edema, pain, weakness

Hepato-biliary: Abnormal hepatic function/liver disorder

Immune System Disorders: Anaphylactic reaction, hypersensitivity

Investigations: Increased CPK, uric acid increased

Metabolism and Nutrition Disorders: Hyperkalemia, hypoglycemia (in diabetic patients), hyponatremia

Musculoskeletal and Connective Tissue Disorders: Myalgia

Nervous System Disorders: Dizziness, headache, syncope

Renal and Urinary Disorders: Renal impairment including acute renal failure.

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Coughing

Skin and Subcutaneous Tissue Disorders: Angioedema (with fatal outcome), angioneurotic edema, drug eruption (toxic skin eruption mostly reported as toxicoderma, rash, and urticaria), erythema, sweating increased, urticaria.

Vascular Disorder: Hypotension (including postural hypotension)

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including Telmisartan.

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

In clinical trials and worldwide postmarketing experience there were reports of Nebivolol overdose. The most common signs and symptoms associated with Nebivolol overdosage are bradycardia and hypotension. Other important adverse reactions reported with Nebivolol overdose include cardiac failure, dizziness, hypoglycemia, fatigue and vomiting. Other adverse reactions associated with β-blocker overdose include bronchospasm and heart block.

The largest known ingestion of Nebivolol worldwide involved a patient who ingested up to 500 mg of Nebivolol along with several 100 mg tablets of acetylsalicylic acid in a suicide attempt. The patient experienced hyperhydrosis, pallor, depressed level of consciousness, hypokinesia, hypotension, sinus bradycardia, hypoglycemia, hypokalemia, respiratory failure and vomiting. The patient recovered.

Because of extensive drug binding to plasma proteins, hemodialysis is not expected to enhance nebivolol clearance.

If overdose occurs, provide general supportive and specific symptomatic treatment. Based on expected pharmacologic actions and recommendations for other β-blockers, consider the following general measures, including stopping Nebivolol, when clinically warranted:

Bradycardia:

Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Hypotension:

Administer IV fluids and vasopressors. Intravenous glucagon may be useful.

Heart Block (second or third degree):

Monitor and treat with isoproterenol infusion. Under some circumstances, transthoracic or transvenous pacemaker placement may be necessary.

Congestive Heart Failure:

Initiate therapy with digitalis glycoside and diuretics. In certain cases, consider the use of inotropic and vasodilating agents.

Bronchospasm:

Administer bronchodilator therapy such as a short acting inhaled β2-agonist and/or aminophylline.

Hypoglycemia:

Administer IV glucose. Repeated doses of IV glucose or possibly glucagon may be required.

Supportive measures should continue until clinical stability is achieved. The half-life of low doses of nebivolol is 12-19 hours.

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with Telmisartan tablets would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemofiltration and is not dialyzable.

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 centres, (4) suppression of renin activity and (5) vasodilation and decreased peripheral vascular resistance.

Telmisartan

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT1 receptor than for the AT2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

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-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 beta 1-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 a 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 hospitalizations 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 *vitro* and in *vivo* experiments in animals showed that Nebivolol has no intrinsic sympathomimetic activity. In vitro and in vivo experiments in animals showed that at pharmacological doses nebivolol has no membrane stabilising action.

In healthy volunteers, nebivolol has no significant effect on maximal exercise capacity or endurance. Available preclinical and clinical evidence in hypertensive patients has shown that nebivolol has no detrimental effect on erectile function.

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

5.3. Pharmacokinetic properties

Nebivolol

Nebivolol is metabolized by a number of routes, including glucuronidation and hydroxylation by CYP2D6. The active isomer (d-nebivolol) has an effective half-life of about 12 hours in CYP2D6 extensive metabolizers (most people), and 19 hours in poor metabolizers and exposure to d-nebivolol is substantially increased in poor metabolizers. This has less importance than usual, however, because the metabolites, including the hydroxyl metabolite and glucuronides (the predominant circulating metabolites), contribute to β-blocking activity.

Plasma levels of d–nebivolol increase in proportion to dose in EMs and PMs for doses up to 20mg. Exposure to l-nebivolol is higher than to d-nebivolol but l-nebivolol contributes little to the drug's activity as d-nebivolol's beta receptor affinity is > 1000-fold higher than l-nebivolol. For the same dose, PMs attain a 5-fold higher Cmax and 10-fold higher AUC of d-nebivolol than do EMs. d-Nebivolol accumulates about 1.5-fold with repeated once-daily dosing in EMs.

Absorption

Absorption of Nebivolol is similar to an oral solution. The absolute bioavailability has not been determined.

Mean peak plasma nebivolol concentrations occur approximately 1.5 to 4 hours post-dosing in EMs and PMs.

Food does not alter the pharmacokinetics of nebivolol. Under fed conditions, nebivolol glucuronides are slightly reduced. Nebivolol may be administered without regard to meals.

Distribution

The in *vitro* human plasma protein binding of nebivolol is approximately 98%, mostly to albumin, and is independent of nebivolol concentrations.

Metabolism

Nebivolol is predominantly metabolized via direct glucuronidation of parent and to a lesser extent via N-dealkylation and oxidation via cytochrome P450 2D6. Its stereospecific metabolites contribute to pharmacologic activity.

Elimination

After a single oral administration of 14C-nebivolol, 38% of the dose was recovered in urine and 44% in feces for EMs and 67% in urine and 13% in feces for PMs. Essentially all nebivolol was excreted as multiple oxidative metabolites or their corresponding glucuronide conjugates.

Pharmacokinetics in Special Populations

Hepatic Disease

d-Nebivolol peak plasma concentration increased 3-fold, exposure (AUC) increased 10-fold, and the apparent clearance decreased by 86% in patients with moderate hepatic impairment (Child-Pugh Class B). No formal studies have been performed in patients with severe hepatic impairment and nebivolol should be contraindicated for these patients.

Renal Disease

The apparent clearance of nebivolol was unchanged following a single 5 mg dose of Nebivolol in patients with mild renal impairment (ClCr 50 to 80 mL/min, n=7), and it was reduced negligibly in patients with moderate (ClCr 30 to 50 mL/min, n=9), but clearance was reduced by 53% in patients with severe renal impairment (ClCr< 30 mL/min, n=5). No studies have been conducted in patients on dialysis.

Drug-Drug Interactions

Drugs that inhibit CYP2D6 can be expected to increase plasma levels of nebivolol. When Nebivolol is co-administered with an inhibitor or an inducer of this enzyme, monitor patients closely and adjust the nebivolol dose according to blood pressure response. In vitro, studies have demonstrated that at therapeutically relevant concentrations, d- and l-nebivolol do not inhibit any cytochrome P450 pathways.

Digoxin:

Concomitant administration of Nebivolol (10 mg once daily) and digoxin (0.25 mg once daily) for 10 days in 14 healthy adult individuals resulted in no significant changes in the pharmacokinetics of digoxin or nebivolol.

Warfarin:

Administration of Nebivolol (10 mg once daily for 10 days) led to no significant changes in the pharmacokinetics of nebivolol or R- or S-warfarin following a single 10 mg dose of warfarin. Similarly, nebivolol has no significant effects on the anticoagulant activity of warfarin, as assessed by Prothrombin time and INR profiles from 0 to 144 hours after a single 10 mg warfarin dose in 12 healthy adult volunteers.

Diuretics:

No pharmacokinetic interactions were observed in healthy adults between nebivolol (10 mg daily for 10 days) and furosemide (40 mg single dose), hydrochlorothiazide (25 mg once daily for 10 days), or spironolactone (25 mg once daily for 10 days).

Ramipril:

Concomitant administration of Nebivolol (10 mg once daily) and ramipril (5 mg once daily) for 10 days in 15 healthy adult volunteers produced no pharmacokinetic interactions.

Losartan:

Concomitant administration of Nebivolol (10 mg single dose) and losartan (50 mg single dose) in 20 healthy adult volunteers did not result in pharmacokinetic interactions.

Fluoxetine:

Fluoxetine, a CYP2D6 inhibitor, administered at 20 mg per day for 21 days prior to a single 10 mg dose of nebivolol to 10 healthy adults, led to an 8-fold increase in the AUC and 3-fold increase in Cmax for d-nebivolol.

Histamine-2 Receptor Antagonists:

The pharmacokinetics of nebivolol (5 mg single dose) were not affected by the co-administration of ranitidine (150 mg twice daily). Cimetidine (400 mg twice daily) causes a 23% increase in the plasma levels of d-nebivolol.

Charcoal:

The pharmacokinetics of nebivolol (10 mg single dose) were not affected by repeated co-administration (4, 8, 12, 16, 22, 28, 36, and 48 hours after nebivolol administration) of activated charcoal.

Sildenafil:

The co-administration of nebivolol and sildenafil decreased AUC and Cmax of sildenafil by 21 and 23% respectively. The effect on the Cmax and AUC for d-nebivolol was also small (< 20%). The effect on vital signs (e.g., pulse and blood pressure) was approximately the sum of the effects of sildenafil and nebivolol.

Other Concomitant Medications:

Utilizing population pharmacokinetic analyses, derived from hypertensive patients, the following drugs were observed not to have an effect on the pharmacokinetics of nebivolol: acetaminophen, acetylsalicylic acid, atorvastatin, esomeprazole, ibuprofen, levothyroxine sodium, metformin, sildenafil, simvastatin, or tocopherol.

Protein Binding:

No meaningful changes in the extent of in vitro binding of nebivolol to human plasma proteins were noted in the presence of high concentrations of diazepam, digoxin, diphenylhydantoin, enalapril, hydrochlorothiazide, imipramine, indomethacin, propranolol, sulfamethazine, tolbutamide, or warfarin. Additionally, nebivolol did not significantly alter the protein binding of the following drugs: diazepam, digoxin, diphenylhydantoin, hydrochlorothiazide, imipramine, or warfarin at their therapeutic concentrations.

Telmisartan

Absorption

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 mg to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism and Elimination

Following either intravenous or oral administration of 14C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Specific Populations

Renal Insufficiency

No dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration and is not dialyzable

Hepatic Insufficiency

In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%.

Gender

Plasma concentrations of telmisartan are generally 2 to 3 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Geriatric Patients

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

Pediatric Patients

Telmisartan pharmacokinetics have not been investigated in patients.

Drug Interaction Studies

Ramipril and Ramiprilat:

Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3- and 2.1-fold, respectively, and Cmax and AUC of ramiprilat 2.4- and 1.5-fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.

Other Drugs:

Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin, or ibuprofen.

Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nebivolol

In a two-year study of nebivolol in mice, a statistically significant increase in the incidence of testicular Leydig cell hyperplasia and adenomas was observed at 40 mg/kg/day (5 times the maximally recommended human dose of 40 mg on a mg/m2 basis). Similar findings were not reported in mice administered doses equal to approximately 0.3 or 1.2 times the maximum recommended human dose. No evidence of a tumorigenic effect was observed in a 24-month study in Wistar rats receiving doses of nebivolol 2.5, 10 and 40 mg/kg/day (equivalent to 0.6, 2.4, and 10 times the maximally recommended human dose). Co-administration of dihydrotestosterone reduced blood LH levels and prevented the Leydig cell hyperplasia, consistent with an indirect LH-mediated effect of nebivolol in mice and not thought to be clinically relevant in man.

A randomized, double-blind, placebo- and active-controlled, parallel-group study in healthy male volunteers was conducted to determine the effects of nebivolol on adrenal function, luteinizing hormone, and testosterone levels. This study demonstrated that 6 weeks of daily dosing with 10 mg of nebivolol had no significant effect on ACTH-stimulated mean serum cortisol AUC0-120 min, serum LH, or serum total testosterone.

Effects on spermatogenesis were seen in male rats and mice at ≥ 40 mg/kg/day (10 and 5 times the MRHD, respectively). For rats the effects on spermatogenesis were not reversed and may have worsened during a four-week recovery period. The effects of nebivolol on sperm in mice, however, were partially reversible.

Mutagenesis: Nebivolol was not genotoxic when tested in a battery of assays (Ames, in vitro mouse lymphoma TK+/-, in vitro human peripheral lymphocyte chromosome aberration, in vivo Drosophila melanogaster sex-linked recessive lethal, and in vivo mouse bone marrow micronucleus tests).

Telmisartan

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella and E. coli (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

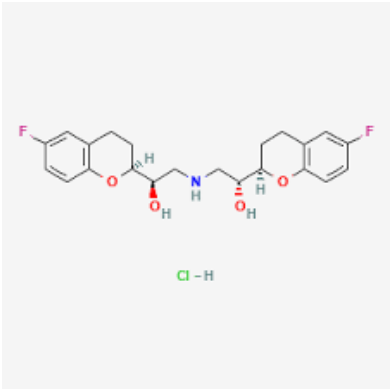
No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC

as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

7. Description

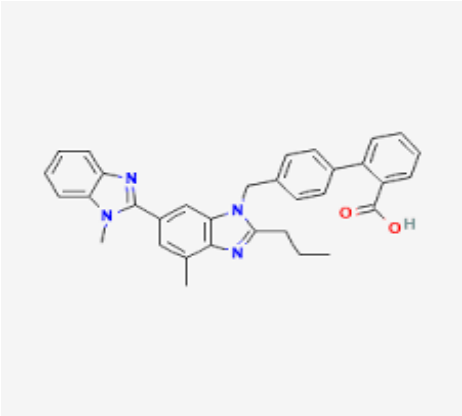
Nebivolol Hydrochloride

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



Telmisartan

Telmisartan is 4-{[4-methyl-6-(1-methyl-1H-benzimidazole-2yl)-2-propyl-1H-benzimidazol-1-yl] methyl}-2-biphenyl carboxylic acid. The empirical formula is $C_{33}H_{30}N_4O_2$, and its molecular weight is 514.6 g/mol. The chemical structure of Telmisartan is:



NEBICARD T 2.5 mg

Nebivolol Hydrochloride and Telmisartan Tablets are White to off white and light orange coloured, elongated, biconvex, bilayered, uncoated tablets, scored on one side and plain on other side.

The List of Excipients used are Mannitol, Sodium Hydroxide, N. Methyl D. Glucemine Meglumine, Povidone, crospovidone, Magnesium Stearate, Lactose, Microcrystalline Cellulose, Croscarmellose Sodium, Sunset Yellow Lake, Pregelatinized Starch, Hydroxypropyl Methyl Cellulose, Polysorbate 80, Sodium Lauryl Sulphate and Colloidal Silicon Dioxide.

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 2.5 mg is available in pack of 10 Tablets.

8.4. Storage and handing instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.

Keep out of reach of children.

Important : Moisture sensitive tablets -Do not remove from strip until immediately before administration.

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

Windlas Biotech 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, issue date:16.04.2026

12. Date of revision

NA

MARKETED BY

TORRENT PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/NEBICARD T 2.5 mg/40 mg/JUN 2026/01/PI