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

TORCILIN-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 the developing fetus.

1. Generic Name

Telmisartan 40 mg and Cilnidipine 10 mg Tablets

2. Qualitative and quantitative composition

Each film coated Tablet contains:

Telmisartan I.P. 40 mg

Cilnidipine 10 mg

Excipients q.s.

Colours: Ferric Oxide (Red) USP-NF & Titanium Dioxide I.P

3. Dosage form and strength

Dosage form: Film coated tablet.

Strength: Telmisartan 40 mg and Cilnidipine 10 mg

4. Clinical particulars

4.1 Therapeutic indication

Torcilin-T is indicated for the treatment of hypertension.

4.2 Posology and method of administration

Posology

The usual dose is 1 tablet of Torcilin-T to be administered once daily. Adjust dosage according to blood pressure goals. If adequate response is not achieved after 2 to 4 weeks of therapy, dose may be increased to 2 tablets once daily. The dosage, however, must be individualized.

Dosage of individual agents should not exceed the recommended maximum daily doses.

- Cilnidipine is effective over the range of 5 to 20 mg once daily; maximum recommended daily dose is 20 mg.
- Telmisartan efficacy is dose-related over the range of 20 to 80 mg per day; maximum recommended daily dose is 80 mg.

If blood pressure remains uncontrolled, consider a change to more appropriate treatment.

Torcilin-T Tablets can be administered regardless of meal. The tablet should be swallowed whole with water.

Method of administration

Torcilin-T may be administered with or without food. Torcilin-T is usually recommended

after breakfast.

4.3 Contraindications

- Hypersensitivity to cilnidipine or to telmisartan or to any component of the
- formulation.
- Cardiogenic shock.
- Severe aortic stenosis.
- Recent history of unstable angina or acute myocardial infarction, heart failure,
- hypotension.
- Second and third trimesters of pregnancy.
- Severe hepatic impairment and 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).

4.4 Special warnings and precautions for use

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 ACEinhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered 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 approptiate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkaliemia

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 reninangiotensin- 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 reninangiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including

selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

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

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

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists. These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, telmisartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially `sodium free´.

Cilnidipine

Cardiovascular Disorders: Cilnidipine should be used with caution in patients with hypotension, heart failure, and poor cardiac reserve. Cilnidipine should be discontinued immediately in patients who feel chest pain following the administration of the drug.

Abrupt Cessation of Therapy: In case of angina, cilnidipine should not be discontinued abruptly to avoid withdrawal symptoms.

Grapefruit Juice: Grapefruit juice may intensify the effect of cilnidipine. Thus, avoid drinking grapefruit juice as much as possible while on cilnidipine therapy.

Laboratory Test: Cilnidipine therapy may interfere with the results of vanillyl mandelic acid test which is used to detect tumour's such as pheochromocytoma and neuroblastoma. Therefore, cilnidipine should be avoided for 72 hours before sample collection, but the patient should be monitored intensively in a clinical setting.

4.5 Drugs interactions

Telmisartan

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.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. 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 if precautions for use are strictly followed.

Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements.

Angiotensin II receptor antagonists such as telmisartan attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia they should be used with caution and with frequent monitoring of serum potassium.

Lithium

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

Concomitant use requiring caution.

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

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

Diuretics (thiazide or loop diuretics)

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

concomitant use

Other antihypertensive agents

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

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

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

Corticosteroïds (systemic route)

Reduction of the antihypertensive effect.

Cilnidipine

Antipsychotic Drugs

Co-administration of antipsychotic drugs with cilnidipine may result in low blood pressure. Thus, caution should be exercised while concomitant use of these drugs with cilnidipine.

Antidiabetic Drugs

Co-administration of cilnidipine with antidiabetic drugs may result in changes in glucose levels, thus, monitoring of blood glucose levels may be required.

Other Drugs

Antiepileptic drugs (such as phenytoin and carbamazepine), rifampin, quinidine, erythromycin, other anti-hypertensive drugs, and aldesleukin should also be used with caution along with cilnidipine.

4.6 Use in special populations.

Telmisartan

Pregnancy

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

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

Epidemiological 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 drugs. 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.

Exposure to Angiotensin II receptor antagonist therapy during the second and third trimesters is known to induce human fetotoxicity (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

Because no information is available regarding the use of Telmisartan during breastfeeding, 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.

Fertility

In preclinical studies, no effects of Telmisartan on male and female fertility were observed.

Cilnidipine

Pregnant Women

Hypertension in pregnancy increases the maternal risk for pre-eclampsia, gestational diabetes, premature delivery, and delivery complications (e.g., need for cesarean section, post-partum hemorrhage). Hypertension increases the fetal risk for intrauterine growth restriction and intrauterine death. Thus, pregnant women with hypertension should be carefully monitored and managed accordingly. The safety of cilnidipine in human pregnancy has not been established. Thus, TORCILIN Tablets are not recommended during pregnancy.

Lactating Women

It is not known whether cilnidipine is secreted in breast milk. As a precautionary measure, it is advised that the nursing mother not breastfeed her child while on cilnidipine therapy. Accordingly, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Patients

Safety and efficacy of cilnidipine in paediatric patients has not been established. Thus, cilnidipine are not recommended in children.

Geriatric Patients

In general, a lower starting dose is recommended in elderly patients given their greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease and/or other drug therapy. Dosage up-titration, if required, should be done with caution.

4.7 Effects on ability to drive and use machines.

For cilnidipine and telmisartan combination therapy, studies have not been performed on effects on the ability to drive and use machines. It is advised not to operate machinery or drive a vehicle if patient experience side effects such as drowsiness, dizziness, fatigue, headache, or hypotension while taking antihypertensive drug therapy.

4.8 Undesirable effects

Telmisartan

Summary of the safety profile

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

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

The adverse reactions listed below have been accumulated from 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.

Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table: List of Adverse Events

System Organ Class	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)	Very rare (< 1/10,000)
Infections and	Urinary tract	Sepsis including fatal	
infestations	infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis	outcome[1]	
Blood and the lymphatic system disorders	Anaemia	Eosinophilia, thrombocytopenia	
Immune system disorders		Anaphylactic reaction, hypersensitivity	
Metabolism and nutrition disorders	Hyperkalaemia	Hypoglycaemia (in diabetic patients)	
Psychiatric disorders	Insomnia, depression	Anxiety	
Nervous system disorders	Syncope	Somnolence	

System Organ	Uncommon (≥	Rare (≥ 1/10,000 to	Very rare (<
Eye disorders		Visual disturbance	
Ear and labyrinth disorders	Vertigo		
Cardiac disorders	Bradycardia	Tachycardia	
Vascular disorders	Hypotension[2], orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough		Interstitial lung disease[4]
Gastrointestinal disorders	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting	Dry mouth, stomach discomfort, dysgeusia	
Hepato-biliary disorders		Hepatic function abnormal/liver disorder[3]	
Skin and subcutaneous tissue disorders	Pruritus, hyperhidrosis, rash	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption	
Musculoskeletal and connective tissue disorders	Back pain (e.g. sciatica), muscle spams, myalgia,	Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)	
Renal and urinary disorders	Renal impairment including acute renal failure		

System Organ	Uncommon (≥	Rare (≥ 1/10,000 to	Very rare (<
General disorders and administration site conditions	Chest pain, asthenia (weakness)	Influenza-like illness	
Investigations	Blood creatinine increased	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood	
		creatine phosphokinase increased	

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.

Hepatic function abnormal / liver disorder

Most 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.

Interstitial lung disease

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.

Intestinal angioedema

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists.

Cilnidipine

Cilnidipine may cause following adverse reactions:

General: Edema (face, limb, etc.), facial flush, thickening of gums, heat sensation, lethargy, generalized fatigue, frequent urination, impotence, liver dysfunction, jaundice, thrombocytopenia (nose/gum bleeding), allergic reaction, etc.

Gastrointestinal: Nausea, vomiting, anorexia, stomachache, gastrointestinal reflux disease

(GERD).

Eye: Transient blindness, eye pain.

Musculoskeletal: Muscle ache, tremors.

Cardiovascular System: Hypotension, palpitations, ischemic chest pain.

Central Nervous System: Dizziness, headache, depression, cerebral ischemia.

Dermatological: Rashes, itching, photosensitivity.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

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.

Management

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 overdosage. 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.

Cilnidipine

In humans, experience with cilnidipine overdose is limited. Overdose symptoms include confusion, dizziness, headache, fatigue, and sedation. If overdose occurs, it might cause excessive peripheral vasodilation with marked hypotension. If overdose should occur, initiate active cardiac and respiratory monitoring. Frequent blood pressure measurements are essential. Should hypotension occur, provide cardiovascular support including elevation of the extremities and the judicious administration of fluids. If hypotension remains unresponsive to these conservative measures, consider administration of vasopressors (such as phenylephrine) with attention to circulating volume and urine output.

5. Pharmacological properties

5.1 Mechanism of Action

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 effects.

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.

Cilnidipine

Cilnidipine is a novel dihydropyridine class of calcium-channel blocker (CCB)/antagonist used for the management of hypertension. Cilnidipine inhibits the transmembrane influx of calcium ions (Ca++) into cardiac and vascular smooth muscle. However, it has greater selectivity for vascular smooth muscle. Antihypertensive action of cilnidipine is due to a direct relaxant effect on vascular smooth muscle. Cilnidipine has little or no action at the SA or AV nodes and negative inotropic activity is rarely seen at therapeutic doses. Like most of the other CCBs, cilnidipine acts on the L-type of calcium channels present on blood vessels.

Cilnidipine blocks entry of calcium ions and thus, suppresses contraction of blood vessels, thereby reducing blood pressure. Cilnidipine possesses both, L- and N-type calcium channel blocking activity. Since N-type calcium channels are distributed along the sympathetic nerve endings and in the brain, cilnidipine exerts specific antisympathetic effect i.e., it inhibits the release of norepinephrine, a sympathomimetic hormone. Thus, cilnidipine reduces blood pressure which is associated with sympathetic overactivity.

5.2 Pharmacodynamic properties

Telmisartan

Telmisartan is an angiotensin receptor antagonist class of antihypertensive drugs. The antihypertensive effect of telmisartan persists constantly over 24 hours after dosing which includes the last 4 hours before the next dose. In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

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 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 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 pretreatment 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.

Cardiovascular prevention

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n=8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or, hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 – 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6% and 11.8% among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 – 1.08), p (non –inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death), non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0% in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 – 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 – 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported

with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension, and syncope in the combination arm. Therefore, the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33%) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE inhibitor with an angiotensin II receptor blocker.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage.

VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.

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

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension, and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric population

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

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary

hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The safety data from this study in patients aged 6 to < 18 years appeared generally like that observed in adults. The safety of long-term treatment of telmisartan in children and adolescents was not evaluated.

An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance are unknown.

These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

Cilnidipine

Cilnidipine is a calcium channel blocker class of antihypertensive drugs. Cilnidipine decreases blood pressure safely and effectively without excessive blood pressure reduction or tachycardia. With chronic once daily oral administration of cilnidipine, antihypertensive effectiveness is maintained for about 24 hours.

5.3 Pharmacokinetic properties

Telmisartan

Absorption:

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

Linearity/non-linearity:

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

Distribution:

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

Biotransformation:

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

Elimination:

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (Cmax) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of

telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

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

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 study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for Cmax.

Gender:

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

Elderly:

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

Renal impairment:

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

Hepatic impairment:

Pharmacokinetic 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.

Cilnidipine:

Absorption

After oral administration of cilnidipine, absorption is very rapid with peak plasma concentration reached after 2 hours.

Distribution

Distribution of cilnidipine tends to be higher in the liver as well as in kidneys, plasma, and other tissues. Cilnidipine has a large volume of distribution. Plasma protein binding of cilnidipine is very high i.e., 98% of the administered dose.

Metabolism

Cilnidipine is metabolized by both liver and kidney. It is rapidly metabolized by liver microsomes by a dehydrogenation process. The major enzymatic isoform involved in cilnidipine dehydrogenation of the dihydropyridine ring is CYP3A.

Excretion

Approximately 20% of the administered dose of cilnidipine gets eliminated through the urine, with the remainder (about 80%) being eliminated in feces.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Telmisartan

In 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 saline 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 antagonists, do not appear to have clinical significance.

No clear evidence of 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 evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

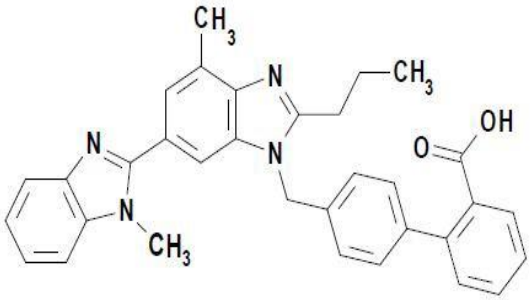
Cilnidipine

No relevant information available.

7. Description

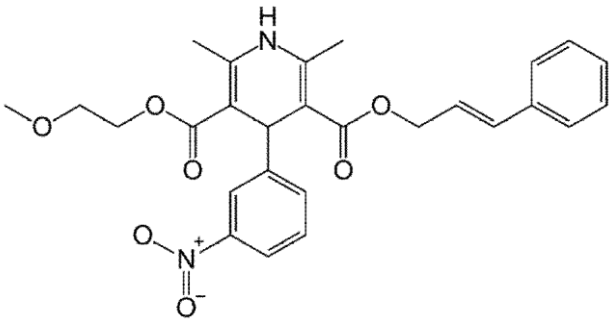
Telmisartan

Telmisartan is a non-peptide angiotensin II receptor (type AT1) antagonist. Telmisartan, a nonpeptide molecule, is chemically described as 4'- [[4-Methyl- 6-(1-methyl-1H-benzimidazol-2- yl)-2-propyl-1H-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid. It has empirical formula $C_{33}H_{30}N_4O_2$ and molecular weight is 514.6. The chemical structure of Telmisartan is:



Cilnidipine

Cilnidipine is the novel calcium antagonist accompanied with L-type and N-type calcium channel blocking function and belonging to the chemical class (1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid 2-methoxyethyl (2E)-3-phenyl-2-propenyl ester. Clinidipine is crystalline powder of pale yellow which has not taste and smell. Its molecular formula is $C_{27}H_{28}N_2O_7$ and its molecular weight is 492.52. The structural formula is:



8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

Torcilin–T Tablets are available in Blister Strip of 10 Tablets.

8.4 Storage and handing instructions.

Store at a temperature not exceeding 25°C, Protected from light & moisture.

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

Manufactured in India by:

M/s. Acme Generics LLP

Plot No. 115, HPSIDC, Industrial Area, Vill. Davni, P.O. Gurumajra,

Tehsil Nalagarh, Distt. Solan, H.P.-174101

11. Details of permission or licence number with date

Mfg. Lic. No.:MNB/15/880

12. Date of revision

Feb- 2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORCILIN-T/Feb-2026/03/PI