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

TORCILIN TRIO

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

Cilnidipine 10 mg, Telmisartan 40 mg & Chlorthalidone 6.25 mg Tablets

2. Qualitative and quantitative Composition:

Each film coated tablet contains:

Cilnidipine I.P. …… 10 mg

Telmisartan I.P. ……... 40 mg

Chlorthalidone I.P. ….. 6.25 mg

Colours: Iron Oxide of Yellow & Titanium Dioxide I.P.

The excipients used are starch, lactose, Sodium starch glycolate, Polyvinyl pyrrolidone, Isopropyl Alcohol, Microcrystalline cellulose, Talcum, Magnesium stearate, Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Polyethylene glycol, Titanium dioxide and Iron oxide of yellow.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: Cilnidipine, Telmisartan and Chlorthalidone (10 mg+ 40 mg + 6.25 mg)

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of essential hypertension.

4.2 Posology and method of administration

Posology

Dose: As directed by the Physician.

The recommended adult oral dosage of Torcilin Trio is one tablet per day.

Torcilin Trio may be administered in patients whose Blood Pressure (BP) is not adequately controlled with monotherapy of cilnidipine/telmisartan/chlorthalidone or dual therapy.

Method of administration

Tablet for oral administration.

4.3 Contraindications

FDC of Cilnidipine + Telmisartan + Chlorthalidone is contraindicated in:

- Cardiogenic shock
- Recent MI or acute unstable angina
- Severe aortic stenosis.
- Known hypersensitivity to active ingredients or any of the excipients.
- Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min),

- Hypersensitivity to chlortalidone and other sulphonamide derivatives,
- Refractory hypokalaemia, hyponatremia and hypercalcemia, symptomatic hyperuricemia (history of gout or uric acid calculi).
- Pregnancy
- Untreated Addison's disease
- Concomitant lithium therapy
- Biliary obstructive disorders
- The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).
  The concomitant use of Telmisartan and Cilnidipine with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

4.4 Special warnings and precautions for use

Cilnidipine

Careful Administration (cilnidipine should be administered with care in the following patients.): Patients with serious hepatic dysfunction [The plasma concentration may become elevated]. Patients with a history of serious adverse reactions to calcium antagonists. Elderly patients: Cilnidipine should be administered carefully under close observation of the patient's condition, taking such measures as starting with a lower dose (e.g. 5 mg). Use in the Elderly is generally acknowledged that excessive hypotensive action should be avoided in the elderly.

Important Precautions:

- As it has been reported that sudden withdrawal of a calcium antagonist caused aggravation of certain symptoms. Therefore, if the discontinuation of cilnidipine is necessary, the dosage should be gradually decreased under close observation.
- If Cilnidipine is withdrawn from a daily dose of 5 mg, appropriate measures, such as replacement with other antihypertensive agents, should be taken.
- Direct the patient not to discontinue this drug without the physician's instructions.

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 rennin 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, diarrhea, or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected before the 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, hyperkalemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers, or aliskiren is therefore not recommended. If dual blockade therapy is considered 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, hypoglycemia may occur under Telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalemia

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

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, hyperkalemia may be fatal.

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

The main risk factors for hyperkalemia to be considered are:

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

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

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

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

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

Ethnic differences: As observed for angiotensin-converting enzyme inhibitors, Telmisartan and the other angiotensin II receptor antagonists are less effective in lowering blood pressure in black people than in non-blacks, possibly because of the 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.

Chlorthalidone

- Plasma electrolyte should be periodically determined at inappropriate intervals to detect possible electrolyte imbalance especially hypokalaemia and hyponatraemia.
- Hypokalaemia and hyponatraemia may occur. Measurement of electrolytes is recommended, especially in the older patient, those receiving digitalis preparations for cardiac failure, those taking an abnormal (low in potassium) diet, or those suffering from gastrointestinal complaints. Hypokalaemia may predispose to arrhythmias in patients receiving digitalis.
- Impaired glucose tolerance may occur and diabetic patients should be aware of the potential for increased glucose levels. Close monitoring of glycemia is recommended in the initial phase of therapy and prolonged therapy test for glucosuria should be carried out at regular intervals.
- In patients with impaired hepatic function or progressive liver disease, minor alterations in fluid and electrolyte balance may precipitate hepatic coma.
- Hyperuricaemia may occur. Only a minor increase in serum uric acid usually occurs but in cases of prolonged elevation, the concurrent use of a uricosuric agent will reverse the hyperuricemia.

4.5 Drugs interactions

Cilnidipine

Cilnidipine is chiefly metabolized by the drug-metabolizing enzyme CYP3A4 and in part by CYP2C19.

Precautions for co-administration (Cilnidipine and the following drugs should be co-administered with care)		
Name of the drug	**Signs, Symptoms and Treatment**	**Mechanism and Risk factor**
Other antihypertensive drugs	Blood pressure may be excessively lowered.	Additive or synergistic potentiation of the effect has been implicated
Digoxin	It has been reported that some other calcium antagonists (eg: Nifedipine) increased the plasma concentration of digoxin. If any toxic signs/symptoms attributable	The mechanism is not completely clarified yet, but is thought to lie in decreased renal and extra renal clearances.

	to digoxin (eg: nausea, vomiting, headache, abnormal vision, arrhythmia) are observed. Appropriate measure should be instituted such as digoxin dose adjustment or discontinuation of cilnidipine, depending on patients condition.	
Cimetidine	It has been reported that the effect of other Ca Antagonist (eg: Nifedipine etc) were enhanced.	It is thought that cimetidine decreases the hepatic blood flow with the consequent suppression of the enzymatic metabolism of calcium antagonists in liver microsomes, and at the same time, cimetidine lowers gastric acid output and thus increases absorption of calcium antagonists.
Rifampicin	It has been reported that effects of other Ca Antagonist (like Nifedipine etc.) were reduced.	It is generally thought that hepatic drug metabolizing enzyme (Cytochrome P-450) induced by rifampicin facilitates metabolism of Ca antagonists and thus increases the clearances of these agents.
Antifungal azoles: Itraconazole, Miconazole etc.	The blood concentration of cilnidipine may be elevated.	Antimycotic azoles are thought to inhibit CYP3A4, a drug-metabolizing enzyme for cilnidipine.
Grapefruit Juice	It has been demonstrated that the plasma concentration of cilnidipine is elevated.	Details of the underlying mechanism remain to be elucidated, but some constituents in grapefruit juice may inhibit CYP3A4, a drug-metabolizing enzyme for cilnidipine.

Telmisartan

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

As with other medicinal products acting on the renin-angiotensin-aldosterone system, Telmisartan may provoke hyperkalemia. The risk may increase in case of treatment combined with other medicinal products that may also provoke hyperkalemia (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, immunosuppressive (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalemia depends on associated risk factors. The risk is increased in the case of the abovementioned treatment combinations. The risk is particularly high in

combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended.

Potassium-sparing diuretics or potassium supplements: Angiotensin II receptor antagonists such as Telmisartan, attenuate diuretic-induced potassium loss. Potassium-sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium- containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalemia 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 the 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 (a thiazide diuretic) may result in volume depletion and is 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, hyperkalemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent. Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including Telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route): Reduction of the antihypertensive effect.

<u>Chlorthalidone</u>

Chlorthalidone may be combined with all medicinal products used for the treatment of hypertension, the action of which is potentiated by Chlorthalidone. It can also be combined with medicinal products used for the treatment of heart failure.

The administration of Chlorthalidone may affect the action of the following drugs:

Diuretics may reduce lithium excretion and thus increase its plasma levels. Since diuretics raise blood lithium levels, the latter must be monitored in patients under lithium therapy who are taking Chlorthalidone at the same time. Where lithium has induced polyuria, diuretics may exert a paradoxical antidiuretic effect.

Diuretics potentiate the action of curare derivatives. Antihypertensive drugs action may be potentiated by diuretics (e.g. guanethidine, methyldopa, ß-blockers, vasodilators, calcium antagonists, ACE inhibitors). The combination of diuretics and ACE inhibitors may lead to severe hypotension. It is recommended that the dosage of Chlorthalidone be reduced or administration interrupted 2 to 3 days before starting treatment with an ACE inhibitor and/or that this treatment is started with a low dose of the ACE inhibitor. It may prove necessary to readjust the dosage of insulin and oral antidiabetic agents due to the risk of reduction of the hypoglycaemic effect, caused by the possible reduction of insulin release by the pancreas due to the hypokalaemic effect. Thiazide-induced hypokalaemia or hypomagnesaemia may favor the occurrence of digitalis- induced cardiac arrhythmias.

Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate), and potentiate their myelosuppressive effects.

Administration of thiazide diuretics with vitamin D or with calcium salts may potentiate the increase in serum calcium, due to an inhibition of urinary excretion.

The action of chlorthalidone may be affected by the administration of the following drugs:

The hypokalaemic effect of diuretics may be increased by corticosteroids, ACTH, ß 2–agonists, amphotericin, and carbenoxolone with the risk of heart and/or muscle disorders.

Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indomethacin) may weaken the diuretic and antihypertensive activity of diuretics, and there have been isolated reports of a deterioration in renal function in predisposed patients.

The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.

Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as cholestyramine. A decrease in the pharmacological effect may be expected.

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

By analogy with all the other diuretics, it is noted that there is a decrease in the anticoagulant effect of oral anticoagulants when combined with Chlorthalidone.

Concomitant administration of ketanserin increases the risk of hypokalaemia and a prolonged QT interval.

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

Pregnancy

Pregnancy and Lactation

The FDC of Cilnidipine + Telmisartan + Chlorthalidone should not be initiated during pregnancy and lactation.

The use of angiotensin II antagonists is not recommended during the first trimester of pregnancy. The use of angiotensin II antagonists is contra-indicated during the 2nd and 3rd trimester of pregnancy.

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

Renal impairment

Limited experience is available in patients with severe renal impairment or hemodialysis. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

FDC of Cilnidipine + Telmisartan + Chlorthalidone is contraindicated in patients with Severe Hepatic impairment.

Pediatric population: The safety and efficacy of FDC of Cilnidipine + Telmisartan + Chlorthalidone in children and adolescents aged below 18 years have not been established.

Elderly (age 65 years or over)

The FDC of Cilnidipine + Telmisartan + Chlorthalidone should be administered carefully under close observation in elderly patients.

4.7 Effects on ability to drive and use machines

Telmisartan and Hydrochlorothiazide can have influence on the ability to drive and use machines. Dizziness or drowsiness may occasionally occur when taking Telmisartan and Hydrochlorothiazide.

4.8 Undesirable effects

Cilnidipine

(1) Clinical significant adverse reactions:

- Hepatic function disorder and jaundice accompanied by increased AST (GOT), ALT (GPT), and γ-GTP may occur. Therefore, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.
- Thrombocytopenia (incidence: <0.1%): Since thrombocytopenia may occur, close observation should be made, and if any abnormality is observed, appropriate measures, such as discontinuation of cilnidipine, should be taken.

(2) Other adverse reactions-

If any of the following adverse reactions occur, appropriate measures should be taken depending on the symptoms.

	Less than 0.1 ~ 5%	**Less than 0.1%**	**Frequency unknown**
Hepatic	Increase in AST (GOT), ALT (GPT), LDH etc.	ALP increased	
Renal	Increase in Creatinine or Urea Nitrogen, Urinary Protein positive	Urine Sediment present	
Psycho neurological	Headache, Headache dull, Dizziness, Dizziness on standing	Sleepiness, Insomnia, Tremor finger, Forgetfulness	Numbness

	up, Shoulder muscle stiffness		
Cardiovascular	Flushed face, Palpitation, Feeling hot, ECG abnormal (ST depressed, inverted T waves), Decrease in blood pressure	Chest pain, cardiothoracic ratio increased, tachycardia, AV block, feeling cold	Extra systole
Gastrointestinal	Nausea, Vomiting, Abdominal pain	Constipation, bloating, thirst, gingival hypertrophy, heartburn, diarrhea	
Hypersensitivity	Rash	Redness, Itching	Photosensitivity
Hematologic	Up or down in WBC, Neutrophil, Hemoglobin	Up or down in RBC, Hematocrit, Eosinophil, Lymphocytes	
Other	Oedema (Face, Lower leg etc), General Malaise, pollakiuria, Increase in serum cholesterol, Up or down in CK (CPK), Uric acid, Serum K, and Serum P	Feeling of weakness, gastrocnemius muscle cramps, periophthalmic dryness, ocular hyperemia and feeling of irritation, dysgeusia, urine sugar positive, up or down in fasting blood sugar, total protein, serum Ca and CRP, cough	Tinnitus
Note 1): The patient should be carefully monitored for these symptoms and if any abnormality is noted, cilnidipine should be discontinued. Note 2): If any such symptoms appear, cilnidipine should be discontinued.			

Telmisartan:

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

Tabulated summary of adverse reactions:

The adverse reactions reported with Telmisartan as mentioned in the table below.
Adverse reactions have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations	**Uncommon:** Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis **Rare:** Sepsis including fatal outcome
Blood and the lymphatic system disorders	**Uncommon:** Anaemia **Rare:** Eosinophilia, thrombocytopenia

Immune system disorders	**Rare:** Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	**Uncommon:** Hyperkalaemia **Rare:** Hypoglycemia (in diabetic patients)
Psychiatric disorders	**Uncommon:** Insomnia, depression **Rare:** Anxiety
Nervous system disorders	**Uncommon:** Syncope **Rare:** Somnolence
Eye disorders	**Rare:** Visual disturbance
Ear and labyrinth disorders	**Uncommon:** Vertigo
Cardiac disorders	**Uncommon:** Bradycardia **Rare:** Tachycardia
Vascular disorders	**Uncommon:** Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	**Uncommon:** Dyspnoea, cough **Very rare:** Interstitial lung disease
Gastrointestinal disorders	**Uncommon:** Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting **Rare:** Dry mouth, stomach discomfort, Dysgeusia
Hepato-biliary disorders	**Rare:** Hepatic function abnormal/liver disorder
Skin and subcutaneous tissue disorders	**Uncommon:** Pruritus, hyperhidrosis, rash **Rare:** Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Musculoskeletal and connective tissue disorders	**Uncommon:** Back pain (e.g. sciatica), muscle spasms, myalgia **Rare:** Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	**Uncommon:** Renal impairment including acute renal failure
General disorders and administration site conditions	**Uncommon:** Chest pain, asthenia (weakness) **Rare:** Influenza-like illness
Investigations	**Uncommon:** Blood creatinine increased **Rare:** Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

Chlorthalidone

The following adverse drug reactions which have been derived from multiple sources,

including post-marketing experience with Chlorthalidone, are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. Frequency estimate: very rare < 0.01%; rare ≥ 0.01% to < 0.1%; uncommon ≥ 0.1% to < 1%; common ≥1% to < 10%; very common ≥10%, not known: cannot be estimated from the available data.

Blood and lymphatic system disorders

Rare: thrombocytopenia, leukopenia, agranulocytosis, and eosinophilia. Immune system disorders

Not Known: Hypersensitivity to chlorthalidone, other sulphonamide derivatives, or any of the excipients.

Metabolism and nutrition disorders

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and hyperlipidaemia.

Common: hyponatraemia, hypomagnesaemia, hyperglycaemia and decreased appetite. **Rare**: hypercalcaemia, worsening of diabetic metabolic state, and gout.

Very rare: alkalosis hypochloraemic, alkalosis hypokalaemic. Nervous system disorders **Common**: dizziness, vertigo, weakness.

Rare: paraesthesia, headache.

Eye disorders

Rare: disturbances of vision.

Cardiac disorders

Rare: arrhythmia.

Vascular disorders

Common: orthostatic hypotension, which may be aggravated by alcohol, anaesthetics or sedatives.

Very rare: vasculitis.

Respiratory, thoracic, and mediastinal disorders

Very rare: idiosyncratic/ non-cardiogenic pulmonary oedema.

Gastrointestinal disorders

Common: minor gastrointestinal distress.

Rare: mild nausea and vomiting, abdominal pain upper, constipation, and diarrhoea.

Very rare: pancreatitis.

Hepatobiliary disorders

Rare: cholestasis or jaundice.

Skin and subcutaneous tissue disorders Common: urticaria and other forms of skin rash. **Rare**: photosensitivity reaction.

Renal and urinary disorders

Rare: glycosuria.

Very rare: allergic tubulointerstitial nephritis.

Reproductive system and breast disorders

Common: erectile dysfunction.

Investigations

Very rare: blood cholesterol increased.

Interference with the results of diagnostic tests: The concomitant administration of thiazide diuretics during the bentiromide test period will invalidate the results of it as thiazide diuretics are also metabolized to arylamines and therefore will increase the percentage of para aminobenzoic acid (PABA) recovered.

And with physiological/laboratory values:

- Bilirubin
- Calcium
- Cholesterol, low-density lipoproteins, and triglycerides
- Creatinine (serum concentrations may increase)
- Glucose in blood and urine
- Magnesium, potassium, and sodium
- Protein-bound iodine (serum concentrations may decrease)
- Uric acid • Calcium concentrations in urine (may decrease)

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.

4.9 Overdose

There is no experience of overdose with Cilnidipine and Telmisartan. Signs and symptoms of overdose are expected to be in line with exaggerated pharmacological effects of individual ingredients.

Cilnidipine:

Overdosage of Cilnidipine may cause an excessive reduction in blood pressure. If reduction in blood pressure is remarkable, appropriate measures such as lifting lower extremities, fluid therapy, and administration of vasopressors should be taken. Hemodialytical removal of cilnidipine is not effective because of its high rate of protein binding.

Telmisartan:

There is limited information available concerning overdose in humans.

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

Treatment: Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of 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.

Treatment:

Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since

ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of 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.

Chlorthalidone:

Symptoms

In poisoning, due to an overdosage, the following signs and symptoms may occur dizziness, nausea, somnolence, hypovolaemia, hypotension, and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.

Treatment

There is no specific antidote. Induction of vomiting or gastric lavage and administration of activated charcoal should be employed to reduce absorption if the patient is conscious. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures are taken. Intravenous fluid and electrolyte replacement may be indicated. Supplementation with artificial plasma may be required.

5. Pharmacological properties

5.1 Mechanism of Action

Cilnidipine

Cilnidipine acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of norepinephrine and suppressing the increase in stress blood pressure.

Telmisartan

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT_1-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance. Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels.

Studies also suggest that telmisartan is a partial agonist of PPARγ, which is an established target for antidiabetic drugs. This suggests that telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPARγ activators).

Chlorthalidone

Chlorthalidone prevents reabsorption of sodium and chloride through inhibition of the Na+/Cl- symporter in the cortical diluting segment of the ascending limb of the loop of Henle. Reduction of sodium reabsorption subsequently reduces extracellular fluid and plasma volume via an osmotic, sodium-driven diuresis. By increasing the delivery of sodium to the distal renal tubule, Chlorthalidone indirectly increases potassium excretion via the sodium-potassium exchange mechanism. The exact mechanism of chlorthalidone's anti-hypertensive effect is under debate, however, it is thought that increased diuresis results in decreased plasma and extracellular fluid volume which therefore requires decreased cardiac output and overall lowers blood pressure.[5] Chlorthalidone has also been shown to decrease platelet aggregation and vascular permeability, as well as promote

angiogenesis in vitro, which is thought to be partly the result of reductions in carbonic anhydrase–dependent pathways. These pathways may play a role in chlorthalidone's cardiovascular risk reduction effects.

5.2 Pharmacodynamic properties

Cilnidipine

Experimental data suggest that cilnidipine binds to the dihydropyridine binding sites of the L-type voltage-dependent calcium channel and inhibits Ca2+ influx across the cell membranes of vascular smooth muscle cells via this channel (rabbits in vitro).

Consequently, vascular smooth muscle is relaxed, causing vasodilation. Through this mechanism, cilnidipine is considered to have a hypotensive action.

Cilnidipine inhibits Ca2+ influx via N-type voltage-dependent calcium channels in the sympathetic nerve cell membrane. The inhibition of Ca2+ influx via N-type voltage-dependent calcium channel was observed over a similar range of drug concentrations to those inhibiting L-type voltage-dependent Ca2+ channels (rats in vitro). Consequently, the release of norepinephrine from sympathetic nerve terminals would be inhibited. Cilnidipine is considered to suppress the reflex increase in heart rate which may be mediated by sympathetic activation after blood pressure reduction and to inhibit stress-related hypertension through this mechanism.

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 an affinity for other receptors, including AT2 and other less characterized 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 humans, an 80 mg dose of Telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained for over 24 hours and still measurable for up to 48 hour.

Chlorthalidone

Chlorthalidone is a benzothiadiazine (thiazide)-related diuretic, chemically related to the sulphonamides, with a long duration of action.

Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting NaCl reabsorption (by antagonising the Na+ -Cl- cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collecting tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

In persons with normal renal function, diuresis is induced after the administration of 12.5 mg Chlorthalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose-dependent and occur both in normal and in edematous patients. The diuretic effect sets in after 2-3 hours, reaches its maximum after 4-24 hours and may persist for 2-3 days.

Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may become activated.

In hypertensive individuals, Chlorthalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pre-treatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated. On chronic administration, the antihypertensive effect of Chlorthalidone is dose-dependent between 12.5 and 50 mg/day. Raising the dose above 50 mg increases metabolic complications and is rarely of therapeutic benefit.

As with other diuretics, when Chlorthalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomized clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics, including chlorthalidone, reduce cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other anti-hypertensives potentiates the blood-pressure-lowering effects. In a large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.

Because thiazide diuretics including Chlorthalidone reduce Ca++ excretion, they have been used to prevent the formation of recurrent renal calcium oxalate stones. Besides, bone loss in elderly women was reduced.

Thiazide diuretics are useful in nephrogenic diabetes insipid us. The mechanism of action has not been elucidated.

5.3 Pharmacokinetic properties

Cilnidipine

Plasma Drug Levels

When a single dose of cilnidipine 5 mg, 10 mg, or 20 mg cilnidipine was orally administered to 6healthy male volunteers, the Cmax was found to be 4.7 ng/mL, 5.4 ng/ml, and 15.7 ng/mL, respectively, and the AUC 0-24 to be 23.7 ng*hr/mL, 27.5 ng*hr/mL and 60.1 ng*hr/mL, respectively.

Thus, both parameters increased in a dose-dependent manner.

When a single dose of cilnidipine 10 mg was repeatedly administered once a day to 6 healthy male volunteers, pharmacokinetic parameters of cilnidipine were indicated as follows. The plasma concentration reached a steady-state from Day 4 of the administration and there was no evidence of the accumulation.

Parameter Day of closing	**Cmax (ng/mL)**	**Tmax (hr)**	**T1/2(a) (hr)**	**T1/2(b) (hr)**	**AUC0-inf (ng*hr/mL)**
Day 1	9.5 ± 1.6	2.8±1.0	1.0 ± 0.2	5.2 ± 2.0	51.4 ± 12.7
Day 4	13.5 ± 5.0	3.7 ± 0.8	-	-	101.8 ±29.0
Day 7	16.5± 7.9	3.0±13	1.1 ± 0.6	8.1 ± 2.7	95.5 ± 34.5

Metabolism and Excretion:

From the metabolites identified in the plasma and urine of healthy male volunteers, it is considered that the major route of cilnidipine metabolism is demethylation of the methoxyethyl group followed by hydrolysis of the cinnamyl ester and oxidation of the

dihydropyridine ring. It is considered that CYP3A4 is mainly involved and CYP2C19 is partly involved in the demethylation of the methoxyethyl group (in vitro).

The calcium channel blocking the action of the metabolite with the demethylated methoxyethyl group was only 1/00 of that of the parent compound (in rabbits). When a single oral dose of cilnidipine 10 mg was repeatedly administered to healthy male volunteers once a day for 7 days, no unchanged compound of cilnidipine but 5.2% of the dose was excreted in the urine as metabolites. (The approved administration of cilnidipine is orally once a day after breakfast.)

An in vitro experiment showed that cilnidipine was 99.3% bound to human serum protein.

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 to whether Telmisartan is taken fasting or with food.

Linearity/non-linearity:

The small reduction in AUC is not expected to cause a reduction in 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 metabolized by conjugation to the glucuronide of the parent compound. No pharmacological activity has-been shown for the conjugate.

Elimination:

Telmisartan is characterized by bi-exponential 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), increases 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 feces, mainly as an unchanged compound. Cumulative urinary excretion is < 1% of the dose. Total plasma clearance (Cltot) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Special Population

Elderly

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

Renal impairment

In patients with mild to moderate and severe renal impairment, the doubling of plasma

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

Hepatic impairment

Pharmacokinetic 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.

Chlorthalidone

Chlorthalidone is administered orally. The drug is 75% bound to plasma proteins and is also highly bound to red blood cells (blood to plasma ratio 72.5), with carbonic anhydrate as the binding site. Chlorthalidone crosses the placenta and is distributed into human breast milk. The onset of action is about 2 hours, with peak effects occurring in 2-6 hours and the duration olfaction lasting 48-72 hours. The majority of the drug is excreted unchanged in the urine (50-74%), with some potential biliary excretion. The mean half-life of Chlorthalidone is approximately 40 to 60 hours. Chlorthalidone is absorbed from the GI tract following oral administration, with a bioavailability of about 65%.

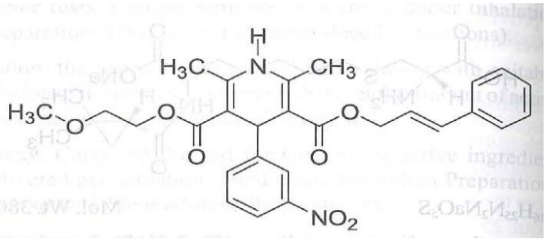
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

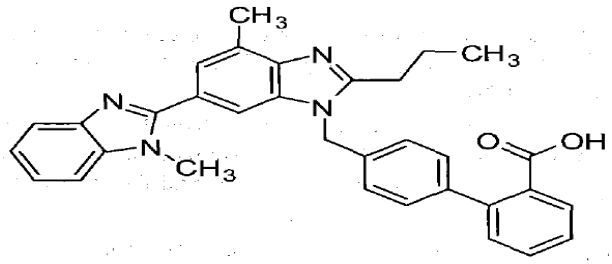
None known

7. Description

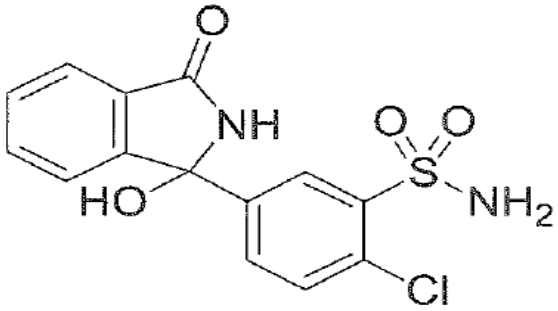
Cilnidipine is l, 4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid 2-methoxyethyl (2*E*)-3-phenyl-2-propenyl ester. The empirical formula is $C_{27}H_{28}N_2O_7$ and its molecular weight is 492.5 g/mol. The chemical structure of Cilnidipine is:



Telmisartan is 4'-{[4-methyl-6-(1-methyl-l*H*-benzimidazol-2-yl)-2-propyl-l*H*-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:



Chlorthalidone is (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzene-sulphonamide. The empirical formula is $C_{14}H_{11}ClN_2O_4S$ and its molecular weight is 338.8 g/mol. The chemical structure of Chlorthalidone is:



TORCILIN TRIO is Yellow colour, round, biconvex, both side plain and film coated tablets. The excipients used are starch, lactose, Sodium starch glycolate, Polyvinyl pyrrolidone, Isopropyl Alcohol, Microcrystalline cellulose, Talcum, Magnesium stearate, Colloidal silicon dioxide, Hydroxy propyl methyl cellulose, Polyethylene glycol, Titanium dioxide and Iron oxide of yellow.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

TORCILIN TRIO is packed in Aluminium-PVC blister of 10 tablets.

8.4 Storage and handing instructions

Store protect from light & moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

Important: Moisture sensitive tablet. 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

Pure and Cure Healthcare Pvt. Ltd.

(A subsidiary of Akums Drugs & Pharmaceuticals Ltd.)

Plot no. 26A, 27-30, Sector-8A, IIE, SIDCUL, Ranipur,

Haridwar-249403 (Uttarakhand)

11. Details of permission or licence number with date

13/UA/2013 issued on 07.11.2019

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TORCILIN TRIO/Aug-2025/01/PI