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

TELSAR LN

1. Generic Name

Telmisartan and Cilnidipine Tablets

2. Qualitative and quantitative composition

TELSAR LN 5

Each film coated tablet contains:

Telmisartan I.P. ……. 40 mg

Cilnidipine I.P……. 5 mg

Excipients…….…... q.s.

Colours: Erythrosine & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Erythrosine.

TELSAR LN 10

Each film coated tablet contains:

Telmisartan I.P. ……. 40 mg

Cilnidipine I.P……. 10 mg

Excipients…….…... q.s.

Colours: Ponceau 4R & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Ponceau 4R.

3. Dosage form and strength

Dosage form: Film coated Tablet

Strength: Telmisartan I.P. 40 mg and Cilnidipine I.P 5mg/10 mg

4. Clinical particulars

4.1 Therapeutic indication

In mild to moderate hypertension

4.2 Posology and method of administration

Posology

Dose: As directed by physician

Renal impairment

Limited experience is available in patients with severe renal impairment or haemodialysis. A lower starting dose of 20 mg of telmisartan with cilnidipine is recommended in these patients. No posology adjustment is required for patients with mild to moderate renal impairment.

Hepatic impairment

TELSAR LN is contraindicated in patients with severe hepatic impairment (see section 4.3).

In patients with mild to moderate hepatic impairment, the posology should not exceed 40 mg of telmisartan with cilnidipine once daily (see section 4.4).

Elderly

No dose adjustment is necessary for elderly patients.

Paediatric population

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

Method of administration

Tablet for oral administration.

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

4.3 Contraindications

• Hypersensitivity to the active substance, dihydropyridine derivatives, Cilnidipine or to any of the excipients

• Second and third trimesters of pregnancy

• Biliary obstructive disorders

• Severe hepatic impairment

• Severe hypotension.

The concomitant use of **TELSAR LN with** aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m)

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 ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended. If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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

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

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

Primary aldosteronism

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

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

Diabetic patients treated with insulin or antidiabetics

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

Hyperkalaemia

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

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

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

The main risk factors for hyperkalaemia to be considered are:

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

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

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

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

Sorbitol

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Telmisartan.

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.

Cilnidipine

Hypotension, poor cardiac reserve and heart failure. Sudden withdrawal may exacerbate angina. Discontinue in patients who experience ischemic pain following administration. Pregnancy and lactation.

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. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment

combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

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

Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements

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

Lithium

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

Concomitant use requiring caution.

Non-steroidal anti-inflammatory medicinal products

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

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

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and ramipril at. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

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

To be taken into account with concomitant use.

Other antihypertensive agents

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

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

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

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

Cilnidipine

Cilnidipine can interact with aldesleukin, quinidine, phenytoin, rifampicin, erythromycin, other anti-hypertensive drugs and anti-psychotic drugs.

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

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.

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, and 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 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.

Fertility

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

Cilnidipine

No specific information about USFDA pregnancy category. Caution should be exercised during Cilnidipine use in pregnancy. Consult a physician before taking Cilnidipine

Lactation

Nursing mothers should consult a physician before taking Cilnidipine.

4.7 Effects on ability to drive and use machines

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

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 reported 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.

Tabulated list of adverse reactions

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

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

Infections and infestations	
Uncommon: Rare:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia
Immune system disorders	
Rare:	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	
Uncommon: Rare:	Hyperkalaemia Hypoglycaemia (in diabetic patients)
Psychiatric disorders	
Uncommon:	Insomnia, depression
Rare:	Anxiety
Nervous system disorders	
Uncommon: Rare:	Syncope Somnolence
Eye disorders	
Rare:	Visual disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Bradycardia
Rare:	Tachycardia
Vascular disorders	
Uncommon:	Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon: Very rare:	Dyspnoea, cough Interstitial lung disease[4]
Gastrointestinal disorders	
Uncommon: Rare:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting Dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders	
Rare:	Hepatic function abnormal/liver disorder[3]

Skin and subcutaneous tissue disorders	
Uncommon: Rare:	Pruritus, hyperhidrosis, rash Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Muscoloskeletal and connective tissue disorders	
Uncommon: Rare:	Back pain (e.g. sciatica), muscle spasms, myalgia 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: Rare:	Chest pain, asthenia (weakness) Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

[1,2,3,4]: for further descriptions, please see sub-section *"Description of selected adverse reactions"*

Description of selected adverse reactions

Sepsis

In the reported 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.

Cilnidipine

• Dizziness

• Flushing

• Headache

• Hypotension

• Peripheral oedema

• Tachycardia

• Palpitations

• GI disturbances

• Increased micturition frequency

• Lethargy

- **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product 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 over dosage. 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

Not Available

5. Pharmacological properties

5.1 Mechanism of Action

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 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 calcium antagonist and its calcium antagonistic activity is lasting longer than those of Nifedipine and Nicardipine. Cilnidipine has been used for the treatment of hypertension and hypertensive-associated vascular disorders. Its adult dose is about 40 to 80 mg once daily. Cilnidipine has a very low solubility (BCS Class-II drug Low solubility high permeability) and compliance to the medication is always very poor.

5.2 Pharmacodynamics properties

Telmisartan

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

Mechanism of action

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

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 agent's representative of other classes of antihypertensive medicinal products (demonstrated in reported clinical trials comparing telmisartan to Cilnidipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

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

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

Paediatric population

In the reported study 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 reported investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 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 similar to 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 is unknown.

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

Cilnidipine

A pharmacodynamics assessment study showed, all treatment groups, both SBP and DBP were decreased after a single administration of cilnidipine. The greatest decreases in both SBP and DBP were seen at approximately 6 hours after study drug administration, when coadministered cilnidipine resulted in a 2.9-fold significantly larger decrease in SBP (14.7 vs 5.0 mmHg for SBP) and a 2.1-fold significantly larger decrease in DBP than did cilnidipine alone (16.3 vs 7.9 mmHg for DBP) (P<0.001, RM-ANOVA test).

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 ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3

hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

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

Distribution

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

Biotransformation

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

Elimination

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

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

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 C_{max}.

Gender

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

Elderly

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

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma

protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment

Pharmacokinetic 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

In a reported PK analysis study with 51 subjects was planned. The mean plasma concentration–time profiles of cilnidipine after a single oral administration at 10 mg did not significantly differ when it was administered alone. For example, the total exposure to cilnidipine was comparable, ie, the GMR (90% confidence interval [CI]) of Cmax and AUC last for cilnidipine 1.04 (0.98–1.10),, although cilnidipine was absorbed slightly slower when it was coadministered with valsartan than when it was administered alone (median tmax: 2.0 vs 2.5 hours for cilnidipine alone and in combination, respectively).

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Telmisartan

In reported preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral 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 receptor antagonists, do not appear to have clinical significance.

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

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

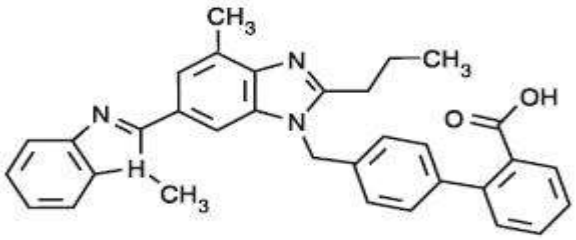
Cilnidipine

Not Available

7. Description

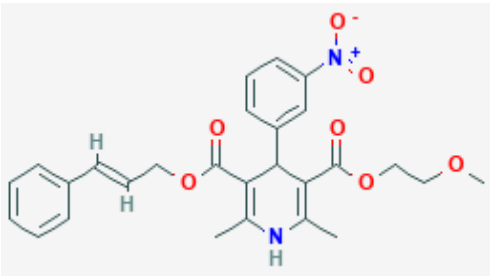
Telmisartan

Telmisartan is chemically described as 4'-{[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and its structural formula is:



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

Cilnidipine is l, 4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine dicarboxylic acid 2-methoxyethyl (2E)-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:



TELSAR LN-5

Telmisartan and Cilnidipine Tablets are pink colour circular biconvex film coated tablets plain on both sides. The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Erythrosine.

TELSAR LN-10

Telmisartan and Cilnidipine Tablets are red colour circular biconvex film coated tablets plain on both sides. The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Ponceau 4R.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TELSAR LN tablets available in blister strips of 10 tablets

8.4 Storage and handing instructions

Store in a dry place below 30°C. Protect from light.

Keep all medicines out of reach of children.

9. Patient Counselling Information

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet?

9.1.What TELSAR LN are **and what they are used for.**

TELSAR LN is combination of Telmisartan and Cilnidipine. Telmisartan belongs to a class of medicines known as angiotensin II receptor antagonists. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow, thus increasing your blood pressure. Telmisartan blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered. **Cilnidipine** calcium channel blocker acting by blocking both L- and N-type calcium channels.

TELSAR LN is used in mild to moderate hypertension

9.2.What you need to know before you take TELSAR LN

- If you are allergic to telmisartan, cilnidipine or any other ingredients of this medicine.
- If you are more than 3 months pregnant. (It is also better to avoid TELSAR LN in early pregnancy)
- If you have severe liver problems such as cholestasis or biliary obstruction (problems with drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren. If any of the above applies to you, tell your doctor or pharmacist before taking TELSAR LN.

Warnings and precautions

Talk to your doctor before taking TELSAR LN if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.
- Talk to your doctor before taking TELSAR LN:
- if you are taking any of the following medicines used to treat high blood pressure:
- an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have
- Diabetes-related kidney problems.
- Aliskiren.
- Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (E.g. potassium) in your blood at regular intervals. See also information under the heading

  "Do Not take TELSAR LN".
- If you are taking digoxin.
- You must tell your doctor if you think you are (or might become) pregnant. TELSAR LN is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage.
- In case of surgery or anaesthesia, you should tell your doctor that you are taking TELSAR LN.
- TELSAR LN may be less effective in lowering the blood pressure in black patients.
- **Children and adolescents**
- The use of TELSAR LN in children and adolescents up to the age of 18 years is not recommended.

Other medicines and TELSAR LN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may need to change the dose of these other medicines or take other precautions. In some cases, you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with TELSAR LN:

- Lithium containing medicines to treat some types of depression.
- Medicines that may increase blood potassium levels such as salt substitutes containing

Potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor antagonists, NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressive (e.g. cyclosporin or tacrolimus), and the antibiotic trimethoprim.

- Diuretics ('water tablets'), especially if taken in high doses together with TELSAR LN, may lead to excessive loss of body water and low blood pressure (hypotension).
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take TELSAR LN" and "Warnings and precautions").
- Digoxin.
- aldesleukin,
- quinidine,
- phenytoin,
- rifampicin,
- erythromycin

The effect of TELSAR LN may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.

TELSAR LN may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine).

Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics or antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking TELSAR LN.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking TELSAR LN before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of TELSAR LN. TELSAR LN is not recommended in early pregnancy, and must not be taken when more than 3 months pregnant, as it may cause serious harm to your baby if used after the third month of pregnancy.

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. TELSAR LN is not recommended for mothers who are breast-feeding, and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is newborn, or was born prematurely.

Driving and using machines

Some people feel dizzy or tired when taking TELSAR LN. If you feel dizzy or tired, do not drive or operate machinery.

9.3 How to use TELSAR LN

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

Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms:

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory

Response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated they could be fatal.

If you forget to take TELSAR LN

If you forget to take a dose, do not worry. Take it as soon as you remember then carry on as before. If you do not take your tablet on one day, take your normal dose on the next day. *Do not* take a double dose to make up for forgotten individual doses.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

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

Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms:

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory

Response), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated they could be fatal.

Possible side effects of TELSAR LN

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

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

Dizziness, flushing, headache, Abnormal heart rate (bradycardia), irregular and/or forceful beating of the heart. GI disturbances, increased urination, laziness or lack of energy

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

Urinary tract infections, upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia), high potassium levels, difficulty falling asleep, feeling sad (depression), fainting (syncope), feeling of spinning (vertigo), low blood pressure (hypotension) in users treated for high blood pressure, on standing up (orthostatic hypotension), shortness of breath, cough, abdominal pain, diarrhoea, discomfort in the abdomen, bloating, vomiting, itching, increased sweating, drug rash, back pain, muscle cramps, muscle pain (myalgia), kidney impairment including acute kidney failure, pain in the chest, feeling of weakness, and increased level of creatinine in the blood.

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

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death), increase in certain white blood cells (eosinophilia), low platelet count (thrombocytopenia), severe allergic reaction (anaphylactic reaction), allergic

reaction (e.g. rash, itching, difficulty breathing, wheezing, swelling of the face or low blood pressure), low blood sugar levels (in diabetic patients), feeling anxious, somnolence, impaired vision, fast heart beat (tachycardia), dry mouth, upset stomach, taste disturbance (dysgeusia), abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin and mucosa which can also lead to death (angioedema also with fatal outcome), eczema (a skin disorder), redness of skin, hives (urticaria), severe drug rash, joint pain (arthralgia), pain in extremity, tendon pain, flulike- illness, decreased haemoglobin (a blood protein), increased levels of uric acid, increased hepatic enzymes or creatine phosphokinase in the blood.

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

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

* The event may have happened by chance or could be related to a mechanism currently not known.

** Cases of progressive scarring of lung tissue have been reported during intake of telmisartan.

However, it is not known whether telmisartan was the cause.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store TELSAR LN

Store in a dry place below 30°C. Protect from light.

Keep all medicines out of reach of children.

9.6 Contents of the pack and other information

TELSAR LN 5

Each film coated tablet contains:

Telmisartan I.P. 40 mg

Cilnidipine I.P 5 mg

The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Erythrosine. Colours: Erythrosine & Titanium Dioxide I.P.

TELSAR LN 10

Each film coated tablet contains:

Telmisartan I.P. 40 mg

Cilnidipine I.P 10 mg

The excipients used are Microcrystalline Cellulose, Lactose, Croscarmellose Sodium, Sodium Hydroxide Pellets, PVP K-30, Purified Water, Sodium Starch Glycolate, Dibasic Calcium Phosphate Anhydrous, Talc, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, PEG 6000, Titanium Dioxide and Ponceau 4R. Colours: Ponceau 4R & Titanium Dioxide I.P.

10 Details of manufacturer

Manufactured in India by:

Swiss Garnier Genexiaa Sciences Private Limited

Plot No. 54 & 78, Mamring Bhasti, Rangpo Post, South Sikkim – 737132.

11. Details of permission or licence number with date

Mfg Lic No. M/605/2012 issued on 29.12.2017

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ TELSAR LN 40, 5/10 mg/Apr-20/01/PI