Telmitrust® LN

Tablets

Composition:

Each film-coated tablet contains

Telmisartan	40mg
Cilnidipine	10 mg

Pharmacokinetic properties:

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose dependent and is about 42% after a 40-mg dose and 58% after a 160-mg dose. Peak plasma concentrations of telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours.

A 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 and when it was coadministered with valsartan 160 mg. For example, the total exposure to cilnidipine was comparable, ie, the GMR (90% confidence interval [CI]) of Cmax and AUC last for cilnidipine with and without valsartan was 0.91 (0.83–1.00) and 1.04 (0.98– 1.10), respectively, 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)

Mechanism of Action

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.

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 hypertensiveassociated 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.

Other pharmacodynamic properties:

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT_1 receptor subtype. It has the highest affinity for the AT_1 receptor among commercially available ARBS and has minimal affinity for the AT_2 receptor. New studies suggest that telmisartan may also have PPARγ agonistic properties that could potentially confer beneficial metabolic effects, as PPARγ is a nuclear receptor that regulates specific gene transcription, and whose target genes are involved in the regulation of glucose and lipid metabolism, as well as anti-inflammatory responses. This observation is currently being explored in clinical trials. Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan works by blocking the vasoconstrictor and aldosterone secretory effects of angiotensin II.

A pharmacodynamic assessment study showed, all treatment groups, both SBP and DBP were decreased after a single administration of cilnidipine or valsartan alone and in combination. The greatest decreases in both SBP and DBP were seen at approximately 6 hours after study drug administration, when coadministered cilnidipine and valsartan 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).

Indication:

- TELMITRUST LN is indicated for diabetic patient with hypertension.

Contraindication:

- TELMITRUST LN tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) component of this product

Drug Interaction:

Telmisartan

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

- Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.
- Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists including telmisartan. Because lithium should not be used with diuretics, the use of lithium with telmisartan and hydrochlorothiazide is not recommended.
- Non-Steroidal Anti-Inflammatory Agents including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists, including telmisartan, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving telmisartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists, including telmisartan may be attenuated by NSAIDs including selective COX-2 inhibitors.
- Ramipril and Ramiprilat: Co-administration of telmisartan 80 mg once daily and ramipril 10 mg once daily to healthy subjects increases steady-state Cmax and AUC of ramipril 2.3 and 2.1 fold, respectively, and Cmax and AUC of ramiprilat 2.4 and 1.5 fold, respectively. In contrast, Cmax and AUC of telmisartan decrease by 31% and 16%, respectively. When co-administering telmisartan and ramipril, the response may be greater because of the possibly additive pharmacodynamic effects of the combined drugs, and also because of the increased exposure to ramipril and ramiprilat in the presence of telmisartan.
- Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).
- Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects in vitro on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Cilnidipine

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

Adverse effects:

Telmitrust Ln Tablet tablets may not lead to any side effects in some patients; other can suffer from side effects like-

- Fatigue
- Eye Pain
- Headache
- Pain in the chest area
- Nausea and dizziness
- flushing of the face, neck and even ears
- Edema

Warnings and Precautions:

- Hypotension in Volume-Depleted Patients: Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of Telmitrust® CT. Treatment should be started under close medical supervision If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.
- Symptomatic Hypotension: A patient receiving Telmitrust® CT tablets should be cautioned that light-headedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician.
- The patients should be told that if syncope occurs, TELMITRUST LN tablets should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of light headedness and possible syncope.
- Hyperkalemia Hyperkalemia may occur in patients on ARBs, particularly in patients with advanced renal impairment, heart failure, on renal replacement therapy, or on potassium supplements, potassium-sparing diuretics, potassium-containing salt substitutes or other drugs that increase potassium levels. Consider periodic determinations of serum electrolytes to detect possible electrolyte imbalances, particularly in patients at risk.
- Dual Blockade of the Renin-Angiotensin-Aldosterone System: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should include close monitoring of renal function.
- Potassium Supplements: A patient receiving TELMITRUST LN tablets should be told not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing physician
- Hypotension, poor cardiac reserve and heart failure. Sudden withdrawal may exacerbate angina.

Use in special population:

1. **Pediatric:** Safety and effectiveness in pediatric patients have not been established.
2. **Geriatric:** No overall differences in effectiveness and safety were observed in these patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
3. **Liver impairment:** TELMITRUST LN tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination
4. **Renal failure:** The usual regimens of therapy with Telmitrust® LN tablets may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment TELMITRUST LN tablets are not recommended.
5. **Pregnancy and lactation:** Pregnancy Category D: When pregnancy is detected, discontinue TELMITRUST LN as soon as possible. These adverse outcomes are usually associated with use of these drugs in the second and third trimester of pregnancy.
   It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Not recommended for use in breastfeeding.

Dosage:

As directed by physician.

Presentation:

Telmitrust LN Tablet - Packages: 10 Tablet
Strengths: 40MG+10MG

Storage and handling:

Store in cool and dry place.