Telmitrust® CT Tablets

Composition:

Each film-coated tablet contains

Telmisartan	40/ 80 mg
Chlorthalidone	12.5 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.

The major portion of the drug is excreted unchanged by the kidneys. Non renal routes of elimination have yet to be clarified. Data are not available regarding percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood-brain barrier.

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.

Chlorthalidone produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The diuretic effects of chlorthalildone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not wholly clear, sodium and water depletion appear to provide a basis for its antihypertensive effect.

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.

Indication:

- TELMITRUST CT contains an angiotensin II receptor blocker (ARB) and a thiazide-like diuretic and is indicated for the treatment of hypertension, to lower blood pressure.
- TELMITRUST CT may be used in patients whose blood pressure is not adequately controlled on monotherapy.
- Hypertension with cardiovascular risk
- TELMITRUST CT may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure goals.

Contraindication:

- TELMITRUST CT 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 CT in patients with diabetes. Avoid use of aliskiren with TELMITRUST CT 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.

Chlorthalidone

- Loop diuretics, including furosemide (Lasix), bumetanide (Bumex), and torsemide (Demadex)
- Digoxin (Lanoxin)
- Drugs containing lithium
- Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen (Motrin or Advil), naproxen (Naprosyn), and nabumetone (Relafen)
- Diabetes medications

Adverse effects:

- The common side effects of Telmitrust CT Tablet are diarrhea, headache, vomiting, nausea, chest congestion, fatigue, body and muscle aches. These side effects are minor and usually disappear within a week or two. If they continue for a prolonged period, consult your doctor.

- The major side effects include dizziness, nausea, swelling of the hands, ankles, or feet and sudden weight gain.

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 CT 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 lightheadedness 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.
- Potassium Supplements: A patient receiving TELMITRUST CT tablets should be told not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing physician
- 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.
- Chlorthalidone may make you drowsy, so you should not drive or operate machinery until you know how it will affect you.

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 CT 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® CT tablets may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment so TELMITRUST CT tablets are not recommended.
5. **Pregnancy and lactation:** Pregnancy Category D: When pregnancy is detected, discontinue TELMITRUST CT 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 in breatfeeding.

Dosage:

As directed by physician.

Presentation:

Telmitrust CT Tablet is available in the following packages and strengths
Telmitrust CT Tablet - Packages: 10 Tablet
Telmitrust CT Tablet - Strengths: 40MG+12.5MG, 80+12.5

Storage and handling:

Store in cool and dry place.