

# Telmitrust-H<sup>™</sup>

Tablets

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## Composition:

Each film-coated tablet contains

Telmisartan	20/ 40 mg
Hydrochlorothiazide IP	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.

Hydrochlorothiazide is fairly rapidly absorbed from the gastrointestinal tract. It is reported to have a bioavailability of about 65 to 70%. It has been estimated to have a plasma half-life of between about 5 and 15 hours and appears to be preferentially bound to red blood cells. It is excreted mainly unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and is distributed into breast milk.

## Mechanism of Action

Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT<sub>1</sub>-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 PPAR<sub>γ</sub>, 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 PPAR<sub>γ</sub> activators.

Hydrochlorothiazide, a thiazide diuretic, inhibits water reabsorption in the nephron by inhibiting the sodium-chloride symporter (SLC12A3) in the distal convoluted tubule, which is responsible for 5% of total sodium reabsorption. Normally, the sodium-chloride symporter transports sodium and chloride from the lumen into the epithelial cell lining the distal convoluted tubule. The energy for this is provided by a sodium gradient established by sodium-potassium ATPases on the basolateral membrane. Once sodium has entered the cell, it is transported out into the basolateral interstitium via the sodium-potassium ATPase, causing an increase in the osmolarity of the interstitium, thereby



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establishing an osmotic gradient for water reabsorption. By blocking the sodium-chloride symporter, hydrochlorothiazide effectively reduces the osmotic gradient and water reabsorption throughout the nephron.

**Other pharmacodynamic properties:**

Telmisartan is an orally active nonpeptide angiotensin II antagonist that acts on the AT<sub>1</sub> receptor subtype. It has the highest affinity for the AT<sub>1</sub> receptor among commercially available ARBS and has minimal affinity for the AT<sub>2</sub> receptor. New studies suggest that telmisartan may also have PPAR<sub>γ</sub> agonistic properties that could potentially confer beneficial metabolic effects, as PPAR<sub>γ</sub> 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.

Thiazides such as hydrochlorothiazide promote water loss from the body (diuretics). They inhibit Na<sup>+</sup>/Cl<sup>-</sup> reabsorption from the distal convoluted tubules in the kidneys. Thiazides also cause loss of potassium and an increase in serum uric acid. Thiazides are often used to treat hypertension, but their hypotensive effects are not necessarily due to their diuretic activity. Thiazides have been shown to prevent hypertension-related morbidity and mortality although the mechanism is not fully understood. Thiazides cause vasodilation by activating calcium-activated potassium channels (large conductance) in vascular smooth muscles and inhibiting various carbonic anhydrases in vascular tissue.

**Indication:**

Telmitrust® H (telmisartan and hydrochlorothiazide) tablets are indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy

**Contraindication:**

- TELMITRUST H tablets are contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan, hydrochlorothiazide, or any other component of this product
- Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.
- Do not co-administer aliskiren with TELMITRUST H in patients with diabetes

**Drug Interaction:**

**Telmisartan**



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- Aliskiren: Do not co-administer aliskiren with TELMITRUST H in patients with diabetes. Avoid use of aliskiren with TELMITRUST H 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 C<sub>max</sub> and AUC of ramipril 2.3 and 2.1 fold, respectively, and C<sub>max</sub> and AUC of ramiprilat 2.4 and 1.5 fold, respectively. In contrast, C<sub>max</sub> 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.

### **Hydrochlorothiazide**

When administered concurrently, the following drugs may interact with thiazide diuretics:

- Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.
- Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.



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- Other antihypertensive drugs: Additive effect or potentiation.
- Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.
- Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.
- Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.
- Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.
- Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Telmitrust® H (telmisartan and hydrochlorothiazide) tablets.
- Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when TELMITRUST H tablets and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained

#### **Adverse effects:**

- Back pain, dyspepsia, vomiting, tachycardia, hypokalemia, bronchitis, pharyngitis, rash, hypotension postural, abdominal pain.
- Pain, headache, cough, urinary tract infection.

#### **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® H (telmisartan and hydrochlorothiazide) tablets. 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.
- Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.
- Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Acute Myopia and Secondary Angle-Closure Glaucoma: Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain



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and typically occur within hours to weeks of drug initiation. Untreated angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy

- **Symptomatic Hypotension:** A patient receiving Telmitrust® H (telmisartan and hydrochlorothiazide) 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 H 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.
- **Potassium Supplements:** A patient receiving TELMITRUST H 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.

#### **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 of telmisartan/hydrochlorothiazide 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 H 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® H (telmisartan and hydrochlorothiazide) tablets may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so TELMITRUST H tablets are not recommended.
5. **Pregnancy and lactation:** Pregnancy Category D: When pregnancy is detected, discontinue TELMITRUST H 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. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to



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discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Dosage:**

As directed by physician.

**Presentation:**

Telmitrust H Tablet is available in the following packages and strengths

Telmitrust H Tablet - Packages: 14 Tablet

Telmitrust H Tablet - Strengths: 20MG+12.5MG, 40+12.5

**Storage and handling:**

Store in cool and dry place.



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