

TELMITRUST-H

Telmisartan & Hydrochlorothiazide

COMPOSITION

Each uncoated tablet contains:

Telmisartan BP 40 mg

Hydrochlorothiazide BP 12.5 mg

CLINICAL PHARMACOLOGY

Telmisartan: 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 blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁ receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT₁ receptor than for the AT₂ receptor.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium salt and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacokinetics

General

Telmisartan: Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet dose. The absolute bioavailability of telmisartan is approximately 42% with a 40 mg tablet. Telmisartan has a terminal elimination half-life of approximately 24 hours.

Hydrochlorothiazide: After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours. The plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism & Elimination

Telmisartan: Following oral administration, most of the administered dose (>97%) of telmisartan is eliminated unchanged in feces via biliary excretion; only minute amounts are found in the urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

Distribution

Telmisartan: Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1 - acid glycoprotein.

Hydrochlorothiazide: Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

INDICATIONS

TELMITRUST-H tablets (telmisartan and hydrochlorothiazide) tablets are indicated for the treatment of hypertension. This combination is not indicated for initial therapy.

DOSAGE & ADMINISTRATION

The usual starting dose of telmisartan is 20-40 mg once a day; blood pressure response is dose related over the range of 20-80 mg.

Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy with **TELMITRUST-H** tablets only after the patient has failed to achieve the desired effect with monotherapy.

TELMITRUST-H tablets may be administered with other antihypertensive agents.

TELMITRUST-H tablets may be administered with or without food.

Patients with Renal Impairment

The usual regimens of therapy with **TELMITRUST-H** tablets may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, **TELMITRUST-H** tablets are not recommended.

Patients with Hepatic Impairment

TELMITRUST-H tablets are not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency may be treated with **TELMITRUST-H** tablets under close medical supervision.

CONTRAINDICATIONS

TELMITRUST-H tablets are contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, **TELMITRUST-H** tablets is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity & Mortality

Telmisartan: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, **TELMITRUST-H** (telmisartan and hydrochlorothiazide) tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Patients and physicians should be aware, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist during the first trimester should be so informed that most reports of fetal toxicity have been associated with second and third trimester exposure. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of **TELMITRUST-H** (telmisartan and hydrochlorothiazide) tablets as soon as possible.

Hydrochlorthiazide: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

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 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.

Hydrochlorothiazide

Hepatic Impairment: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be given with thiazides.

PRECAUTIONS

Serum Electrolytes

Telmisartan & Hydrochlorothiazide

In controlled trials using the telmisartan/hydrochlorothiazide combination treatment, no patient had a decrease in potassium ≥ 1.4 mEq/L, and no patient experienced hyperkalemia. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. **TELMITRUST-H** tablets should therefore be used with caution in these patients.

Impaired Renal Function

Telmisartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia. Similar results may be anticipated in patients treated with telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. An

effect similar to that seen with ACE inhibitors should be anticipated with telmisartan.

Hydrochlorothiazide: Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Dual Blockade of the Renin-angiotensin-aldosterone System

Telmisartan: 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. Concomitant use of telmisartan and ramipril is not recommended.

Pregnancy

Pregnancy Categories C (first trimester) and D (second & third trimesters)

See **WARNINGS, Fetal/Neonatal Morbidity & Mortality.**

Nursing Mothers

It is not known whether telmisartan is excreted in human milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness and safety were observed in clinical studies, as compared to younger patients, but greater sensitivity of some older individuals cannot be ruled out.

DRUG INTERACTIONS

Telmisartan

Digoxin: Digoxin levels should be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization, as co-administration of telmisartan and digoxin increases the plasma levels of digoxin.

Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium 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.

Ramipril & Ramiprilat: When telmisartan and ramipril are coadministered, 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. Concomitant use of telmisartan and ramipril is not recommended.

Other Drugs: Co-administration of telmisartan does not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, simvastatin, hydrochlorothiazide, warfarin or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system.

Hydrochlorothiazide

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

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Oral Antidiabetic drugs & insulin: Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine & colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins.

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.

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.

ADVERSE REACTIONS

Telmisartan and hydrochlorothiazide tablets has been evaluated for safety in over 1700 patients, including 716 treated for over six months and 420 for over one year. In clinical trials with the combination, adverse experiences have been limited to those that have been previously reported with telmisartan and/or hydrochlorothiazide. Most adverse experiences were mild in intensity and transient in nature and did not require discontinuation of therapy.

The commonly observed side effects are fatigue, influenza-like symptoms, dizziness, diarrhea, nausea, back pain, sinusitis, pharyngitis, headache, pain, fatigue, dry mouth, flatulence, constipation, insomnia, somnolence, electrolyte disturbances etc.

OVERDOSAGE

Telmisartan: Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Hydrochlorothiazide: The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hyponatremia, hypochloremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD50 of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

PRESENTATION

Tablets should not be removed from blisters until immediately before administration.

STORAGE

Store at 15°-30°C (59°-86°F)