

TELMITRUST CT® Tablets

Composition

TELMITRUST CT -40 Tablets

Each film-coated tablet contains

Telmisartan Potassium 40 mg

Chlorthalidone 12.5 mg

TELMITRUST CT -80 Tablets

Each film-coated tablet contains

Telmisartan Potassium 80 mg

Chlorthalidone 12.5 mg

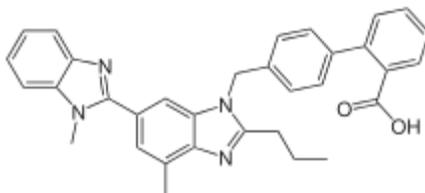
TELMISARTAN

Generic name: Telmisartan

Chemical name: 4'-[(1, 4'-dimethyl-2'- propyl[2,6'-bi-1H-benzimidazol]-1'- yl)methyl]-[1,1'- biphenyl]-2-carboxylic acid

Molecular mass: 514.63 g/mol

Structural formula:



Empirical formula: C₃₃H₃₀N₄O₂

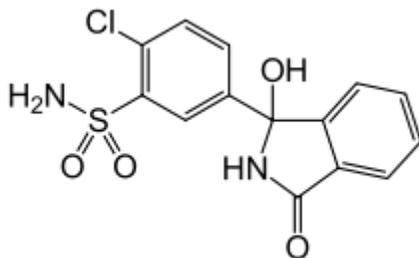
CHLORTHALIDONE

Generic name: Chlorthalidone

Chemical name: 2-chloro-5(1-hydroxy-3-oxo-1- isoindolinyl) benzenesulfonamide

Molecular mass: 338.766 g/mol

Structural formula:



Empirical formula: C₁₄H₁₁ClN₂O₄S.

CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because Telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of Telmisartan on blood pressure.

SSD Technology

Telmisartan is Hydrophilic and does not dissolve in water readily. The unique SSD technology in the Telmitrust, Telmisartan is made soluble. This is done by addition of Meglumine and Poloxamer as excipients with Telmisartan.

Chlorthalidone

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 chlorthalidone 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.

Pharmacokinetics

Telmisartan

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5 to 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 and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20 to 160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10% to 25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1 - acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

Metabolism and Elimination

Following either intravenous or oral administration of ^{14}C -labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acyl glucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Chlorthalidone

The major portion of the drug is excreted unchanged by the kidneys. Nonrenal 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.

Pharmacodynamics

Telmisartan

In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an intravenous infusion of angiotensin II by about 90% at peak plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Chlorthalidone

The diuretic effect of chlorthalidone occurs in approximately 2.6 hours and continues for up to 72 hours.

INDICATIONS

- 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 CV risk
- TELMITRUST CT may be used as initial therapy if a patient is likely to need multiple drugs to achieve blood pressure goals.

DOSAGE AND ADMINISTRATION

The recommended starting dose of TELMITRUST CT is 40/12.5 mg taken orally once daily. Most of the antihypertensive effect is apparent within 1 to 2 weeks.

Patients not controlled with telmisartan medoxomil 80 mg may have an additional systolic / diastolic clinic blood pressure reduction of 13/6 mm Hg when switched to TELMITRUST CT 40/12.5 mg. Patients not controlled with chlorthalidone 25 mg may have an additional clinic blood pressure reduction of 10/7 mm Hg when switched to TELMITRUST CT 40/12.5 mg.

CONTRAINDICATIONS

Telmisartan is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis or angioedema) to telmisartan or any other component of this product.

WARNINGS AND PRECAUTIONS

Telmisartan

Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Telmisartan as soon as possible.

Hypotension

In patients with an activated renin-angiotensin system, such as volume- or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with Telmisartan. Either correct this condition prior to administration of Telmisartan, or start treatment under close medical supervision with a reduced dose.

If hypotension does occur, the patient 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.

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.

Impaired Hepatic Function

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. Initiate telmisartan at low doses and titrate slowly in these patients.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, anticipate changes in renal function 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 or renal dysfunction), treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results have been reported 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. There has been no long term use of Telmisartan in patients with unilateral or bilateral renal artery stenosis, but anticipate an effect similar to that seen with ACE inhibitors.

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.

The ONTARGET trial enrolled 25,620 patients \geq 55 years old with atherosclerotic disease or diabetes with end-organ damage, randomizing them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of Telmisartan and ramipril did not obtain any additional benefit compared to monotherapy, but experienced an increased incidence of renal dysfunction (e.g., acute renal failure) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of Telmisartan and ramipril is not recommended.

Chlorthalidone

Chlorthalidone cross the placental barrier and appear in cord blood. Adverse reactions include fetal or neonatal jaundice and thrombocytopenia.

OVERDOSAGE**Telmisartan**

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage with Telmisartan tablets 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.

Chlorthalidone

Symptoms of acute overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. The oral LD50 of the drug in the mouse and the rat is more than 25,000 mg/kg body weight. The minimum lethal dose (MLD) in humans has not been established. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose-saline with potassium, administered with caution.

SHELF-LIFE -**PACKAGING INFORMATION -**