

TELMITRUST TABLETS

Telmisartan

COMPOSITION

Each uncoated tablet contains:
Telmisartan BP 20 mg/40 mg

PHARMACOLOGY

Pharmacodynamics

Telmisartan is a non-peptide Angiotensin II receptor (type AT₁) antagonist. 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.

Ace inhibitors block the renin-angiotensin system, thus inhibiting the biosynthesis of angiotensin II from angiotensin I. ACE inhibitors also inhibit the degradation of bradykinin. Because telmisartan does not inhibit ACE, it does not affect the response to bradykinin. Whether this difference has clinical relevance is not 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.

Pharmacokinetics

General

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour. 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.

The absolute bioavailability of telmisartan is dose dependent. At 40 mg the bioavailability is approximately 42%. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan has a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations.

Metabolism & Elimination

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.

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide which is the only metabolite that has been identified in human plasma and urine. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Distribution

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1 - acid glycoprotein. The volume of distribution for telmisartan is approximately 500 liters indicating additional tissue binding.

INDICATION

Hypertension

TELMITRUST is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Cardiovascular Risk Reduction

TELMITRUST is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events and who are unable to take ACE inhibitors.

High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin-dependent or non-insulin dependent) with evidence of end-organ damage. **TELMITRUST** can be used in addition to other needed treatment (such as antihypertensive, antiplatelet or lipid-lowering therapy).

DOSAGE & ADMINISTRATION

• Hypertension

Dosage must be individualized. The usual starting dose is **TELMITRUST-20mg / 40mg** once a day. Blood pressure response is dose-related over the range of 20-80 mg. Most of the antihypertensive effect is apparent within two weeks and maximal reduction is generally attained after four weeks. When additional blood pressure reduction beyond that achieved with 80 mg telmisartan is required, a diuretic may be added.

No initial dosing adjustment is necessary for elderly patients or patients with renal impairment, including those on hemodialysis. Patients on dialysis may develop orthostatic hypotension; their blood pressure should be closely monitored.

TELMITRUST may be administered with other antihypertensive agents.

TELMITRUST may be administered with or without food.

• Cardiovascular Risk Reduction

The recommended dose of **TELMITRUST** is 80 mg once a day and can be administered with or without food. It is not known whether doses lower than 80 mg of telmisartan are effective in reducing the risk of cardiovascular morbidity and mortality. When initiating **TELMITRUST** therapy for cardiovascular risk reduction, monitoring of blood pressure is recommended, and adjustment of medications that lower blood pressure may be necessary.

CONTRAINDICATION

TELMITRUST is contraindicated in patients who are hypersensitive to any component of this product.

WARNINGS

Fetal/Neonatal Morbidity & Mortality

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** (telmisartan) 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** tablets as soon as possible.

Hypotension in Volume-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may occur after initiation of therapy with **TELMITRUST** tablets. This condition should be corrected prior to administration of **TELMITRUST** tablets, or treatment should start 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.

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.

PRECAUTIONS

General

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 **TELMITRUST** at low doses and titrate slowly in these patients.

Impaired Renal Function: 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 and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with **TELMITRUST** tablets.

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 **TELMITRUST** tablets in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Pregnancy

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

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

Lactation

It is not known whether telmisartan is excreted 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

Digoxin: Digoxin levels should be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization, as coadministration 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. Therefore, monitor serum lithium levels during concomitant use.

Ramipril and 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.

UNDESIRABLE EFFECTS

Telmisartan is usually well tolerated. The side effects have been mild and transient in nature and have only infrequently required discontinuation of therapy. The commonly observed side effects are back pain, sinusitis, diarrhea, pharyngitis, headache, dizziness, pain, fatigue, nausea, intermittent claudication and skin ulcer.

OVERDOSAGE

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

PRESENTATION

TELMITRUST 20mg/ 40mg Tablets are available in strips of 10

STORAGE

Store between 15°-30°C.