

Telmisartan

PritorTM Tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Telmisartan (PritorTM) 40 mg Tablet: Each tablet contains 40 mg Telmisartan.

Telmisartan (PritorTM) 80 mg Tablet: Each tablet contains 80 mg Telmisartan.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Telmisartan is an orally effective and specific angiotensin II receptor (type AT₁) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT₁ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT₁ receptor. Telmisartan selectively binds the AT₁ receptor. The binding is long lasting.

Telmisartan does not show affinity for other receptors, including AT₂ and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by Telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore it is not expected to potentiate bradykinin-mediated adverse effects.

In man, an 80 mg dose of Telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Treatment of essential hypertension

After the first dose of Telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by trough to peak ratios consistently above 80% seen after doses of 40 and 80 mg of Telmisartan in placebo controlled clinical studies.

There is an apparent trend to a dose relationship to a time to recovery of baseline SBP. In this respect data concerning DBP are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of Telmisartan has been compared to antihypertensive drugs such as amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan.

Upon abrupt cessation of treatment with Telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.

Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.

The incidence of dry cough was significantly lower in patients treated with Telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of cardiovascular high risk patients.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years. The population studied was 73 % male, 74 % Caucasian, 14 % Asian and 43 % were 65 years of age or older. Hypertension was present in nearly 83 % of randomized patients: 69 % of patients had a history of hypertension at randomization and an additional 14 % had actual blood pressure readings above 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76 %), statins (62 %), beta-blockers (57 %), calcium channel blockers (34 %), nitrates (29 %) and diuretics (28 %).

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure.

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Telmisartan had similar efficacy to ramipril in reducing the primary endpoint. The incidence of the primary endpoint was similar in the telmisartan (16.7 %), ramipril (16.5 %) and telmisartan plus ramipril combination (16.3 %) arms. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019). The treatment effect was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint based on age, gender, race, baseline therapies or underlying disease.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril

vs. placebo. The hazard ratio of telmisartan vs. ramipril for this endpoint in ONTARGET was 0.99 (97.5 % CI 0.90 - 1.08, p (non-inferiority) = 0.0004).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Paediatric Population

The blood pressure lowering effects of two doses of telmisartan were assessed in hypertensive patients aged 6 to <18 years (n =76) after taking telmisartan 1 mg/kg (n = 30 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. After adjustment for age group effects and baseline SBP values an average placebo-corrected SBP change from baseline (primary objective) of 8.5 mmHg was observed in the telmisartan 2 mg/kg group, and a -3.6 mmHg SBP change was found in the telmisartan 1 mg/kg group. The adjusted and placebo-corrected DBP changes from baseline were 4.5 mmHg and -4.8 mmHg in the telmisartan 1mg/kg and 2 mg/kg groups, respectively. The change was dose dependent. The safety profile appeared generally comparable to that observed in adults.

Pharmacokinetics

Absorption of Telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for Telmisartan is about 50%.

When Telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of Telmisartan varies from approximately 6% (40mg dose) to approximately 19% (160mg dose). By 3 hours after administration plasma concentrations are similar whether Telmisartan is taken fasting or with food.

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

Gender differences in plasma concentrations were observed, C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.

Telmisartan is largely bound to plasma protein (>99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{ss}) is approximately 500L.

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, area under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of Telmisartan.

After oral (and intravenous) administration Telmisartan is nearly exclusively excreted with the faeces, exclusively as unchanged compound. Cumulative urinary excretion is <2% of dose.

Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min) compared with hepatic blood flow (about 1,500 mL/min).

Elderly patients

The pharmacokinetics of Telmisartan does not differ between young and elderly patients.

Patients with renal impairment

Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Patients with hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not changed in patients with hepatic impairment.

Paediatric population

The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to <18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age-related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max} .

TOXICOLOGY

In pre-clinical safety studies doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit) and changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated side effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II antagonists, were prevented by oral saline supplementation.

In both species increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of ACE-inhibitors and other angiotensin II antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed; at toxic doses levels, however, non-clinical studies indicated some hazardous potential of telmisartan to fetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

INDICATIONS

- Treatment of essential hypertension.
- Prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease (see Pharmacological properties).

DOSAGE AND ADMINISTRATION

Adults

Treatment of essential hypertension

The recommended dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, Telmisartan dose can be increased to a maximum of 80 mg once daily. Alternatively, Telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide which has been shown to have an additive blood pressure lowering effect with Telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

In patients with severe hypertension treatment with Telmisartan at doses up to 160 mg alone and in combination with hydrochlorothiazide 12.5 - 25 mg daily was well tolerated and effective.

Prevention of cardiovascular morbidity and mortality

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of telmisartan are effective in preventing cardiovascular morbidity and mortality.

When initiating telmisartan therapy for the prevention of cardiovascular morbidity and mortality, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Telmisartan (*PritorTM*) may be taken with or without food.

Renal Impairment

No posology adjustment is required for patients with renal impairment, including those on haemodialysis.

Telmisartan is not removed from blood by haemofiltration.

Hepatic Impairment

In patients with mild to moderate hepatic impairment the posology should not exceed 40mg once daily.

Elderly

No dosing adjustment is necessary.

Children and Adolescents

The safety and efficacy of Telmisartan (*PritorTM*) for use in children below 18 years have not been established.

CONTRAINDICATIONS

- Hypersensitivity to the active ingredient or to any of the excipients
- Second and third trimesters of pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment
- The concomitant use of Telmisartan (*PritorTM*) with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60ml/min/1.73 m²)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see Warnings and Precautions), the use of the product is contraindicated.

WARNINGS AND PRECAUTIONS

Pregnancy:

Angiotensin II receptor antagonists should not be initiated during pregnancy.

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and if appropriate, alternative therapy should be started.

Renovascular hypertension:

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplant:

When Telmisartan (*PritorTM*) is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan (*PritorTM*) in patients with a recent kidney transplant.

Intravascular volume depletion:

Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, and diarrhoea or vomiting. Such conditions, especially volume and/or sodium depletion should be corrected before the administration of Telmisartan (*PritorTM*).

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 in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor antagonist) should therefore be limited to individually defined cases with close monitoring of renal function (see Contraindications).

Other conditions with stimulation of the renin-angiotensin-aldosterone system:

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of Telmisartan (*PritorTM*) is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Hyperkalaemia:

During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on the experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with Telmisartan (*PritorTM*).

Hepatic impairment:

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. Telmisartan (*PritorTM*) should be used with caution in these patients.

Sorbitol:

This product contains 338 mg of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Diabetes mellitus:

In diabetic patients with an additional cardiovascular risk, i.e. patients with diabetes mellitus and coexistent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with Telmisartan (*PritorTM*).

Other:

As observed for angiotensin converting enzyme inhibitors, angiotensin receptor blockers including Telmisartan (*PritorTM*) are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

DRUG INTERACTIONS

Telmisartan (*PritorTM*) may increase the hypotensive effect of other antihypertensive agents. Other interactions of clinical significance have not been identified.

Co-administration of Telmisartan did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, ibuprofen, paracetamol, simvastatin and amlodipine. For digoxin a 20% increase in median plasma digoxin trough concentration has been observed (39% in a single case), monitoring of plasma digoxin levels should be considered.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC₀₋₂₄ and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

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 (*PritorTM*). Therefore, serum lithium level monitoring is advisable during concomitant use.

Treatment with NSAIDs (at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like Telmisartan may have synergistic effects. Patients receiving NSAIDs and Telmisartan (*PritorTM*) should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive drugs like Telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

PREGNANCY AND LACTATION

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started. The use of angiotensin II receptor antagonists is contraindicated during the second and third trimester of pregnancy.

Non-clinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity.

Angiotensin II receptor antagonists exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

Should exposure to angiotensin II receptor antagonists have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension.

Telmisartan (*PritorTM*) is contraindicated during lactation since it is not known whether it is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.

Fertility

No studies on fertility in humans have been performed. In preclinical studies, an effect of Telmisartan (*PritorTM*) on male and female fertility was not observed.

Effects on the Ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

ADVERSE EFFECTS

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials in patients treated for hypertension. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients.

The safety profile of Telmisartan (*PritorTM*) in patients treated for prevention of cardiovascular morbidity and mortality was consistent with that obtained in hypertensive patients.

The adverse drug reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse events and adverse events leading to discontinuation reported in three clinical long-term studies including 21642 patients treated with telmisartan for prevention of cardiovascular morbidity and mortality for up to six years.

Infections and infestations:

Sepsis including fatal outcome, urinary tract infections (including cystitis), upper respiratory tract infections

Blood and lymphatic system disorders:

Anaemia, eosinophilia, thrombocytopenia

Immune system disorders:

Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:

Hyperkalaemia, hypoglycaemia (in diabetic patients)

Psychiatric disorders:

Anxiety, insomnia, depression

Nervous system disorders:

Syncope (faint)

Eye disorders:

Visual disturbance

Ear and labyrinth disorders:

Vertigo

Cardiac disorders:

Bradycardia, tachycardia

Vascular disorders:

Hypotension, orthostatic hypotension

Respiratory disorders:

Dyspnoea

Gastro-intestinal disorders:

Abdominal pain, diarrhoea, dry mouth, dyspepsia, flatulence, stomach discomfort, vomiting

Hepatobiliary disorders:

Hepatic function abnormal/liver disorder*

*Most cases of hepatic function abnormal/liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse effects.

Skin and subcutaneous tissue disorders:

Angioedema (with fatal outcome), eczema, erythema, pruritis, hyperhidrosis, urticaria, drug eruption, toxic skin eruption, rash

Musculoskeletal, connective tissue and bone disorders:

Arthralgia, back pain, muscle spasms (cramps in legs) or pain in extremity (leg pain), myalgia, tendon pain (tendonitis-like symptoms)

Renal and urinary tract disorders:

Renal impairment including acute renal failure (see Warnings and Precautions)

General disorders and administration site conditions:

Chest pain, influenza-like illness, asthenia (weakness)

Investigations:

Haemoglobin decreased, blood uric acid increased, blood creatinine increased, hepatic enzymes increased, blood creatinine phosphokinase (CPK) increased

OVERDOSAGE AND TREATMENT

Limited information is available with regard to overdose in humans. The most prominent manifestations of Telmisartan overdose were hypotension and tachycardia, bradycardia also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

STORAGE

Store at temperatures not exceeding 30°C.

AVAILABILITY

Telmisartan (*PritorTM*) 40 mg tablet: Box of 28's.

Telmisartan (*PritorTM*) 80 mg tablet: Box of 28's

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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