

Telmisartan Hydrochlorothiazide

PritorPlusTM Tablets

FORMULATION

Telmisartan/Hydrochlorothiazide (PritorPlusTM) 40 mg/12.5 mg Tablet: Each tablet contains 40 mg Telmisartan and 12.5 mg Hydrochlorothiazide

Telmisartan/Hydrochlorothiazide (PritorPlusTM) 80 mg/12.5 mg Tablet: Each tablet contains 80 mg Telmisartan and 12.5 mg Hydrochlorothiazide

Telmisartan/Hydrochlorothiazide (PritorPlusTM) 80 mg/25 mg Tablet: Each tablet contains 80 mg Telmisartan and 25 mg Hydrochlorothiazide

CLINICAL PHARMACOLOGY

Pharmacodynamics

Telmisartan/Hydrochlorothiazide (PritorPlusTM) is a combination of an angiotensin II receptor antagonist, Telmisartan and a thiazide diuretic, Hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Telmisartan/Hydrochlorothiazide (PritorPlusTM) once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan:

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.

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.

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.

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.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides effect the renal tubular mechanisms of electrolyte re-absorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity, increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics.

With hydrochlorothiazides, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6 - 12 hours.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

Pharmacokinetics

Concomitant administration of hydrochlorothiazide and telmisartan has no effect on the pharmacokinetics of either drug.

Absorption:

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 – 1.5 hours after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42% and 58%, respectively. 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 19% after a 160 mg 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.

The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Following oral administration of Telmisartan/Hydrochlorothiazide (*PriorPlusTM*) peak concentrations of hydrochlorothiazide are reached in approximately 1.0 – 3.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60%.

Distribution:

Telmisartan: Telmisartan is highly bound to plasma proteins (> 99.5%) mainly albumin and alpha1-acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Hydrochlorothiazide: Hydrochlorothiazide is 64% protein bound in the plasma and its apparent volume of distribution is 0.8 ± 0.3 L/kg.

Biotransformation and elimination:

Telmisartan: Following either intravenous or oral administration of 14 C-labelled telmisartan most of the administered dose (> 97%) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine.

Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans.

After a single dose of 14 C-labelled telmisartan 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 after oral administration is > 1500 mL/min. Terminal elimination half-life was > 20 hours.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged drug in urine. About 60% of the oral dose are eliminated as unchanged drug within 48 hours. Renal clearance is about 250 – 300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10–15 hours.

Elderly patients:

Pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Gender:

Plasma concentrations of telmisartan are generally 2–3 times higher in females than in males. In clinical trials however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Patients with renal impairment:

Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30–60 mL/min, mean about 50 mL/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced.

In a typical study in patients with a mean creatinine clearance of 90 mL/min, the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

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.

TOXICOLOGY

In non-clinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional

findings not already observed with administration of either substance alone. There were no toxicological findings observed of relevance to human therapeutic use.

Toxicological findings also well known from non-clinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury.

Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in *in vitro* studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

There is no clear evidence of a teratogenic or embryotoxic potential for either telmisartan or hydrochlorothiazide administered as single entities or in combination. At toxic dose levels, however, animal 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.

INDICATIONS

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is indicated for the treatment of essential hypertension.

As fixed dose combination Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is indicated in patients whose blood pressure is not adequately controlled on telmisartan or hydrochlorothiazide alone.

DOSAGE AND ADMINISTRATION

Adults

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) should be taken once daily. The dose of telmisartan could be up-titrated before switching to Telmisartan/Hydrochlorothiazide (*PritorPlusTM*). Direct change from monotherapy to the fixed combinations may be considered.

- Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 40 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan (*PritorTM*) 40 mg or hydrochlorothiazide.
- Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 80 mg/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan (*PritorTM*) 80 mg or by Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 40 mg/12.5 mg.
- Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 80 mg/25 mg may be administered in patients whose blood pressure is not adequately controlled by Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 80 mg/12.5 mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

The maximum antihypertensive effect is generally attained with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 4 – 8 weeks after the start of treatment.

When necessary, Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) may be administered with another antihypertensive drug.

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.

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) may be taken with or without food.

Renal impairment: Due to the hydrochlorothiazide component, Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) should not be used in patients with severe renal dysfunction (creatinine clearance < 30 mL/min). Loop diuretics are preferred to thiazides in this population. Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised.

Hepatic impairment: In patients with mild to moderate hepatic impairment the posology should not exceed Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 40mg /12.5 mg once daily. Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

Elderly

No dosage adjustment is necessary.

Children and adolescents

Safety and efficacy of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) have not been established in children and in adolescents up to 18 years.

CONTRAINDICATIONS

Hypersensitivity to the active ingredient, to any of the excipients, or to other sulphonamide-derived substances (hydrochlorothiazide is a sulphonamide-derived substance).

- Second and third trimesters of pregnancy
- Lactation
- Cholestasis and biliary obstructive disorders
- Severe hepatic impairment
- Severe renal impairment (creatinine clearance < 30 mL/min)
- Refractory hypokalaemia, hypercalcaemia
- The concomitant use of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²)

In case of rare hereditary conditions that may be incompatible with an excipient of the product 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.

Hepatic Impairment:

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) 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. There is no clinical experience with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) in patients with hepatic impairment.

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:

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see Contraindications).

There is no experience regarding the administration of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) in patients with severe renal impairment or with a recent kidney transplant. Experience with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is modest in the patients with mild to moderate renal impairment, therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function.

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, diarrhoea or vomiting. Such conditions should be corrected before the administration of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*).

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 other 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/Hydrochlorothiazide (*PritorPlusTM*) 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.

Metabolic and endocrine effects:

Thiazide therapy may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may manifest during thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in Telmisartan/Hydrochlorothiazide (*PritorPlusTM*), minimal or no effects were reported.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance:

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloroemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea or vomiting.

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of liver, in patients experiencing brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH). Conversely, due to the antagonism of the angiotensin II (AT₁) receptors by the telmisartan component of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*), hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*), risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*).

There is no evidence that Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

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

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Sorbitol:

The maximum recommended daily dose of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) contains 169 mg sorbitol in the dose strength 40mg /12.5 mg and 338 mg sorbitol on the dose strength 80mg /12.5 mg and 80mg /25mg. 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/Hydrochlorothiazide (*PritorPlusTM*).

Lactose:

The maximum recommended daily dose of Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) contains 112 mg of lactose monohydrate in the dose strengths 40mg /12.5 mg and 80mg /12.5 mg, and 99mg lactose monohydrate in the dose strength 80mg /25mg.

Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

Other:

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.

General:

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.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

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 and typically occur within hours to weeks of drug initiation. Untreated acute 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.

DRUG INTERACTIONS

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. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*). Lithium and Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) should only be co-administered under medical supervision and serum lithium level monitoring is advisable during concomitant use.

The potassium-depleting effect of hydrochlorothiazide is attenuated by the potassium-sparing effect of telmisartan. However, this effect of hydrochlorothiazide on serum potassium would be expected to be potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, corticosteroids, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives).

If these drugs are to be prescribed with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*), monitoring of potassium plasma levels is advised.

Conversely, based on the experience with the use of other drugs that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.

If these drugs are to be prescribed with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*), monitoring of potassium plasma levels is advised.

Periodic monitoring of serum potassium is recommended when Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is administered with drugs affected by serum potassium disturbances, e.g. digitalis glycosides, anti-arrhythmic agents and drugs known to induce torsades de pointes.

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid (ASA) 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/Hydrochlorothiazide (*PritorPlusTM*) should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.

Telmisartan 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.

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 insulins): Dosage adjustment of the antidiabetic drug may be required;

Metformin: There is a risk of lactic acidosis when co-administered with hydrochlorothiazide;

Cholestyramine and colestipol resins: absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias;

Pressor amines (e.g. noradrenaline): The effect of pressor amines may be decreased;

Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;

Treatment for gout: Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol;

Calcium salts: Thiazide diuretics may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;

Other interactions: The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastro-intestinal motility and stomach emptying rate.

Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

PREGNANCY AND LACTATION

Telmisartan:

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.

Preclinical 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.

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.

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) is contraindicated during lactation. It is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk.

Thiazides appear in human milk and may inhibit lactation.

Fertility:

No studies on fertility in humans have been performed.

In non-clinical studies, an effect of telmisartan and hydrochlorothiazide on male and female fertility was not observed.

Effects on 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 should be taken into account that dizziness or drowsiness may occur when taking antihypertensive therapy.

ADVERSE EFFECTS

The overall incidence of adverse events reported with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) was comparable to those reported with telmisartan alone in randomised controlled trials involving 1,471 patients receiving telmisartan plus hydrochlorothiazide or telmisartan alone. There was no dose-relationship to undesirable effects and there was no correlation with gender, age or race of the patients.

Adverse reactions reported in clinical trials with telmisartan plus hydrochlorothiazide are shown below according to system organ class. Adverse reactions not observed in clinical trials with telmisartan plus hydrochlorothiazide but expected during treatment with Telmisartan/Hydrochlorothiazide (*PritorPlusTM*) based on the experience with telmisartan or hydrochlorothiazide alone have been included and are detailed in separate sections below:

Infections and infestations: Bronchitis, pharyngitis, sinusitis

Immune system disorders: Exacerbation or activation of systemic lupus erythematosus

Metabolism and nutrition disorders: Hypokalaemia, hyponatraemia, hyperuricaemia

Psychiatric disorders: Anxiety, depression

Nervous system disorders: Dizziness, syncope/faint, paraesthesia, sleep disturbances, insomnia,

Eye disorders: Abnormal vision, transient blurred vision
Ear and labyrinth disorders: Vertigo
Cardiac disorders: Cardiac arrhythmias, tachycardia
Vascular disorders: Hypotension (including orthostatic hypotension)
Respiratory, thoracic and mediastinal disorders: Dyspnoea, respiratory distress (including pneumonitis and pulmonary oedema)
Gastro-intestinal disorders: Diarrhoea, dry mouth, flatulence, abdominal pain, constipation, dyspepsia, vomiting, gastritis
Hepato-biliary disorders: Abnormal hepatic function/liver disorder
Skin and subcutaneous tissue disorders: Angioedema, erythema, pruritis, rash, sweating increased, urticaria
Musculoskeletal, connective tissue and bone disorders: Back pain, muscle spasm, myalgia, arthralgia, leg pain, cramps in legs
Reproductive system and breast disorders: Impotence
General disorders and administration site conditions: Chest pain, influenza-like symptoms, pain
Investigations: Increase in uric acid, increase in creatinine, increase in liver enzymes, increase in blood creatine phosphokinase
Telmisartan:
Additional side effects reported in clinical trials with telmisartan monotherapy in the indication hypertension or in patients 50 years or older at high risk of cardiovascular events were as follows:
Infections and Infestations: Upper respiratory tract infections, urinary tract infections (including cystitis), sepsis including fatal outcome
Blood and lymphatic system disorders: Anaemia, thrombocytopenia, eosinophilia
Immune system disorders: Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders: Hyperkalaemia, hypoglycaemia (in diabetic patients)
Cardiac Disorders: Bradycardia
Gastro-intestinal disorders: Stomach upset
Skin and subcutaneous tissue disorders: Eczema, drug eruption, toxic skin eruption
Musculoskeletal, connective tissue and bone disorders: Arthrosis, tendon pain (tendinitis-like symptoms)
Renal and urinary disorders: Renal impairment including acute renal failure (see also under Warnings and Precautions)
General disorders and administration site conditions: Asthenia (weakness)
Investigations: Decrease in haemoglobin
Hydrochlorothiazide:
Additional side effects reported with hydrochlorothiazide monotherapy were as follows:
Infections and infestations: Sialadenitis
Blood and the lymphatic system disorders: Thrombocytopenia, aplastic anaemia, haemolytic anaemia, bone marrow depression, leukopenia, neutropenia/agranulocytosis
Immune system disorders: Anaphylactic reactions, allergy
Endocrine disorders: Loss of diabetic control
Metabolism and nutrition disorders: Cause or exacerbate volume depletion, electrolyte imbalance, anorexia, loss of appetite, hyperglycaemia, hypercholesterolaemia
Psychiatric disorders: Restlessness
Nervous system disorders: Light-headedness
Eye disorders: Xanthopsia, acute myopia, acute angle-closure glaucoma
Vascular disorders: Necrotizing angitis (vasculitis)
Gastro-intestinal disorders: Stomach upset, pancreatitis
Hepato-biliary disorders: Jaundice (hepatocellular or cholestatic jaundice)
Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, cutaneous vasculitis, photosensitivity reactions
Musculoskeletal, connective tissue and bone disorders: Weakness
Renal and urinary disorders: Interstitial nephritis, renal dysfunction, glycosuria
General disorders and administration site conditions: Fever
Investigations: Increase in triglycerides

OVERDOSAGE AND TREATMENT

Limited information is available for Telmisartan/Hydrochlorothiazide (*PritorPlus™*) with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred.

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloroemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasm and/or accentuate cardiac arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.

No specific information is available on the treatment of overdose with Telmisartan/Hydrochlorothiazide (*PritorPlus™*). The patient should be closely monitored, and the treatment should be symptomatic and supportive depending on the time since ingestion and the severity of the symptoms.

Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. Telmisartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

STORAGE

Pritor Plus™ 40 mg/12.5 mg tablet and 80 mg/12.5 mg tablet: Store at temperatures not exceeding 30°C.

Pritor Plus™ 80 mg/25 mg tablet: Store at temperatures not exceeding 25°C.

AVAILABILITY

Pritor Plus™ 40 mg/12.5 mg tablet: Alu/Alu blister pack x 7's (Box of 28's)

Pritor Plus™ 80 mg/12.5 mg tablet: Alu/Alu blister pack x 7's (Box of 28's)
Pritor Plus™ 80 mg/25 mg tablet: Alu/Alu blister pack x 7's (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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Version Number: PDS v. 8

Date: 17 June 2013



Imported by:

GlaxoSmithKline Philippines Inc

2266 Chino Roces Avenue, City of Makati 1231, Philippines

Tel no. 892-0761

Manufactured by:

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Strasse 173, D-55216 Ingelheim am Rhein, Germany

Packed by:

GlaxoSmithKline Australia Pty Ltd

1061 Mountain Highway, Boronia 3155, Australia

PH/TMSHC/0001/15

August 2015

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