SCHEDULING STATUS: S3

PROPRIETARY NAMES AND DOSAGE FORM:

TREMISTAN PLUS 40/12,5 (film-coated tablets)
TREMISTAN PLUS 80/12,5 (film-coated tablets)
TREMISTAN PLUS 80/25 (film-coated tablets)

COMPOSITION:

Active ingredient:

Tremistan Plus 40/12,5: Each film-coated tablet contains 40 mg telmisartan and 12,5 mg hydrochlorothiazide.
Tremistan Plus 80/12,5: Each film-coated tablet contains 80 mg telmisartan and 12,5 mg hydrochlorothiazide.
Tremistan Plus 80/25: Each film-coated tablet contains 80 mg telmisartan 25 mg and hydrochlorothiazide.

Inactive ingredients:

Each Tremistan Plus 40/12,5 film-coated tablet contains citric acid monohydrate, ferric oxide (yellow 10) E172, ferric oxide (red 30) E172, lactose anhydrous, ludipress (lactose based excipient)*, macrogol poly (vinyl alcohol) grafted copolymer, magnesium stearate, meglumine, povidone K25 and sodium hydroxide.

Each Tremistan Plus 80/12,5 film-coated tablet contains citric acid monohydrate, lactose anhydrous, ludipress (lactose based excipient)*, macrogol poly (vinyl alcohol) grafted copolymer, magnesium stearate, meglumine, povidone K25 and sodium hydroxide

Each Tremistan Plus 80/25 film-coated tablet contains citric acid monohydrate, ferric oxide (yellow 10) E172, lactose anhydrous, ludipress (lactose based excipient)*, macrogol poly (vinyl alcohol) grafted copolymer, magnesium stearate, meglumine, povidone K25 and sodium hydroxide.

* Ludipress consists of 93 % lactose monohydrate, 3,5 % povidone K30 and 3,5 % crospovidone type A.

Each Tremistan Plus 40/12,5 tablet contains sugar (lactose 155,24 mg).
Each Tremistan Plus 80/12,5 tablet contains sugar (lactose 310,48 mg).
Each Tremistan Plus 80/25 tablet contains sugar (lactose 310,48 mg).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular Medicines – other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Telmisartan and hydrochlorothiazide 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.

Telmisartan:

Telmisartan is an orally effective and specific angiotensin II receptor subtype 1 (AT_1) antagonist. It displaces angiotensin II from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds at the AT_1 receptor. The binding is long lasting. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. In healthy volunteers, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase.

After administration of the first dose of telmisartan and hydrochlorothiazide, onset of antihypertensive activity occurs within 3 hours. The maximum reduction in blood pressure is generally attained 4 – 8 weeks after the start of treatment and is sustained during long-term therapy.

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

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect 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.

Pharmacokinetic properties:

Concomitant administration of hydrochlorothiazide and telmisartan does not appear to affect the pharmacokinetics of either substance in healthy volunteers.

Absorption:

Telmisartan:

Following oral administration peak concentrations of telmisartan are reached in 0,5 to 1,5 hours after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42 % and 58 %, respectively.

The pharmacokinetics of orally administered telmisartan is non-linear over doses from 20 to 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 in healthy volunteers.
When telmisartan and hydrochlorothiazide is taken with food, the reduction in the area under the plasma-concentration curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). After 3 hours post administration plasma concentrations are similar whether telmisartan is taken fasting or with food.

Hydrochlorothiazide:
Following oral administration of telmisartan and hydrochlorothiazide, peak concentrations of hydrochlorothiazide are reached in approximately 1,0 to 3,0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60 %.
Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance.

Distribution:
Telmisartan:
Telmisartan is highly bound to plasma protein (> 99,5 %), mainly albumin and alpha-1 acid glycoprotein. The apparent volume of distribution (V_{dss}) is approximately 500 ℓ indicating additional tissue binding.

Hydrochlorothiazide:
Hydrochlorothiazide is 68 % protein bound in the plasma and its apparent volume of distribution is 0,83 – 1,14 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 > 1 500 mℓ/min. Terminal elimination half-life was > 20 hours.

Hydrochlorothiazide:
Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged medicine in urine. About 60 % of the oral dose is eliminated as unchanged medicine within 48 hours. Renal clearance is about 250 to 300 mℓ/min in healthy volunteers. The terminal pharmaceutical elimination half-life of hydrochlorothiazide is 10 to 15 hours, although the biological effects last longer.

Special population:
Elderly patients:
The pharmacokinetics of telmisartan does not differ between the elderly and those younger than 65 years.

Gender:
Telmisartan: Plasma concentrations of telmisartan are generally 2 to 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 toward higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Patients with renal impairment:
Telmisartan: Renal excretion does not contribute to the clearance of telmisartan. In patients with mild to moderate renal impairment (creatinine clearance of 30 to 60 mℓ/min, mean about 50 mℓ/min) no dosage adjustment is necessary, nor in patients with mildly decreased renal function. Telmisartan is not removed from blood by haemodialysis.

Hydrochlorothiazide: 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:
Telmisartan:
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.

INDICATIONS:
Treatment of essential hypertension.

TREMISTAN PLUS 80/25 fixed dose combination (80 mg telmisartan / 25 mg hydrochlorothiazide) is indicated in adults whose blood pressure is not adequately controlled on

TREMISTAN PLUS 80/12,5 (80 mg telmisartan / 12,5 mg hydrochlorothiazide) or adults who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

CONTRAINDICATIONS:

- Hypersensitivity to telmisartan, hydrochlorothiazide or any of the components of TREMISTAN PLUS.
- Hypersensitivity to other sulphonamide-derived substances (since hydrochlorothiazide is a sulphonamide-derived medicinal product).
- A history of angioedema related to previous therapy with ACE inhibitors or angiotensin receptor blockers (ARBs): Such patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Severe renal function impairment (creatinine clearance less than 30 mℓ/min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see “INTERACTIONS”).
- Potassium supplements, salt substitutes containing potassium or other medicines that may increase potassium levels, e.g. heparin (see “INTERACTIONS”).
- Porphyria.
- Lithium therapy: Concomitant administration with TREMISTAN PLUS may lead to toxic blood concentrations of lithium (see “INTERACTIONS”).
- Pregnancy and lactation (see “WARNINGS AND SPECIAL PRECAUTIONS” and “PREGNANCY AND LACTATION”).
- The concomitant use of TREMISTAN PLUS with renin inhibitors such as aliskiren-containing products is contraindicated (see **“**WARNINGS AND SPECIAL PRECAUTIONS” and “INTERACTIONS”).
- The concomitant use of TREMISTAN PLUS with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1,73 m^2) (see “WARNINGS AND SPECIAL PRECAUTIONS”).
- Biliary obstructive disorders.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia.

WARNINGS AND SPECIAL PRECAUTIONS:

Should a woman become pregnant while receiving TREMISTAN PLUS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see “CONTRAINDICATIONS” and “PREGNANCY AND LACTATION”).

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or renin inhibitors such as aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.
If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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 medicines that affect this system has been associated with acute hypotention, hyperuraemia, oliguria or rarely acute renal failure.

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 medicines that affect the renin-angiotensin-aldosterone system (see **"**CONTRAINDICATIONS").

Renal impairment and kidney transplant:
TREMISTAN PLUS must not be given to patients with severe renal impairment (creatinine clearance < 30 mℓ/min) (see **"**CONTRAINDICATIONS"). Thiazide diuretic-associated uraemia may occur in patients with impaired renal function.
In patients with mild to moderate renal impairment, periodic monitoring of potassium, creatinine and uric acid levels is mandatory. There is no experience regarding the administration of TREMISTAN PLUS in patients with severe renal impairment or with a recent kidney transplant (see **"**CONTRAINDICATIONS").

Intravascular volume depletion:
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by diuretic therapy, dietary salt restriction, diarrhoea or vomiting. Such conditions should be corrected before the administration of TREMISTAN PLUS.

Primary aldosteronism:
Patients with primary aldosteronism generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin system. Therefore, the use of TREMISTAN PLUS is not recommended.

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

Hyperkalaemia:
During treatment with other medicines that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment, diabetes mellitus and/or heart failure. Adequate monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of other medicines that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be used with caution. (see “CONTRAINDICATIONS” and “INTERACTIONS”.)

Serum electrolyte changes:
Periodic determination of serum electrolytes should be performed at appropriate intervals.

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) should therefore be used with caution.

Hypokalaemia:
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 the 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).

Hyperkalaemia:
Conversely, due to the antagonism of the angiotensin II (AT_1) receptors by the telmisartan component of TREMISTAN PLUS, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with TREMISTAN PLUS, 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 with caution with TREMISTAN PLUS.Frequent monitoring of serum potassium is recommended (see “CONTRAINDICATIONS”).

Hyponatraemia and hypochloroaemic alkalosis:
There is no evidence that TREMISTAN PLUS would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

Hypercalcaemia:
Thiazides may decrease urinary calcium excretion and cause 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.

Hypomagnesaemia:
Hydrochlorothiazide, as in TREMISTAN PLUS, increases the urinary excretion of magnesium, which may result in hypomagnesaemia.

Electrolyte imbalance:
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including hypokalaemia, hyponatraemia and hypochloraemic alkalosis). Irrespective of cause, include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

Ethnic differences:
As with all other angiotensin II receptor antagonists, telmisartan is apparently less effective in lowering blood pressure in black patients than in non-blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

Hepatic impairment:
Telmisartan is mostly eliminated in the bile. Patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, telmisartan should not be given to these patients (see “CONTRAINDICATIONS”).
TREMISTAN PLUS should be used only with caution in patients with mild to moderate hepatic impairment or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with TREMISTAN PLUS in patients with hepatic impairment.

Metabolic and endocrine effects:
Hydrochlorothiazide, as in TREMISTAN PLUS, may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic medicines may be required. Latent diabetes mellitus may become manifest during TREMISTAN PLUS therapy.
An increase in cholesterol and triglyceride levels has been associated with hydrochlorothiazide, as in TREMISTAN PLUS.
Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving hydrochlorothiazide, as in TREMISTAN PLUS.

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 infarctions and unexpected cardiovascular death may be increased when treated with blood pressure lowering medicines 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 TREMISTAN PLUS.

Systemic lupus erythematosus:
Thiazide diuretics, including hydrochlorothiazide, as in TREMISTAN PLUS, has been reported to exacerbate or activate systemic lupus erythematosus.

Non-melanoma skin cancer:
An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed. The risk for NMSC appears to increase with long-term use. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC. Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and adequate protection when exposed to sunlight should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined, potentially including histological examination of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have previously experienced NMSC.

Other:
Excessive reduction in blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

General:
Hypersensitivity reactions to hydrochlorothiazide, as in TREMISTAN PLUS, may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Hydrochlorothiazide, as in TREMISTAN PLUS, rarely causes dermatological (photosensitivity, skin rashes) disorders.

Acute myopia and angle-closure glaucoma:
Hydrochlorothiazide, a sulphonamide, 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 medicine

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 treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulphonamide or penicillin allergy.

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, it should be taken into account that dizziness or drowsiness may occasionally occur when taking TREMISTAN PLUS.

Lactose:
TREMISTAN PLUS contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take TREMISTAN PLUS.
TREMISTAN PLUS contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

INTERACTIONS:
Interactions relating to Telmisartan:
***Lithium*:**
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor antagonists, including telmisartan (as in TREMISTAN PLUS). Co-administration of lithium and TREMISTAN PLUS is not recommended. If this combination proves essential, careful monitoring of serum lithium level is recommended during concomitant use.

***Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren*:**
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see “CONTRAINDICATIONS” and “WARNINGS AND SPECIAL PRECAUTIONS”).

Telmisartan, as in TREMISTAN PLUS, may increase the hypotensive effect of other antihypertensive medicines.

The concomitant use of TREMISTAN PLUS with aliskiren-containing products should be avoided in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min) (see “WARNINGS AND SPECIAL PRECAUTIONS”).

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs):
Concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin is associated with the potential for acute renal insufficiency, especially in patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function). This combination should be administered with caution, especially in the elderly. Patients receiving NSAIDs and TREMISTAN PLUS should be adequately hydrated and be monitored for renal function at the beginning of, and during combined treatment.
The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of TREMISTAN PLUS.

Co-administration of telmisartan, as in TREMISTAN PLUS, 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 (in a single case a 49 %); 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 AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Additional information on TREMISTAN PLUS interaction:
The pharmacokinetics of telmisartan is not affected by co-administration of hydrochlorothiazide.

Interactions relating to Hydrochlorothiazide:
Hydrochlorothiazide, as in TREMISTAN PLUS, may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Based on their pharmacological properties it can be expected that the following medicinal product may potentiate the hypotensive effects of all antihypertensives including telmisartan: baclofen, amifostine.

Concurrent hypovolaemia may induce acute renal failure.

There have been reports in the literature of haemolytic anaemia occurring with concomitant use with hydrochlorothiazide, as in TREMISTAN PLUS, and methyldopa.

Hydrochlorothiazide, as in TREMISTAN PLUS, may increase the risk of adverse effects caused by amantadine.

When administered concurrently, the following medicines may interact with hydrochlorothiazide (as in TREMISTAN PLUS):

Alcohol, barbiturates, narcotics or antidepressants: potentiation of orthostatic hypotension may occur;
Metformin: there is a risk of lactic acidosis when co-administered with hydrochlorothiazide (as in TREMISTAN PLUS);
Cholestyramine and colestipol resins: absorption of hydrochlorothiazide as in TREMISTAN PLUS is impaired in the presence of anionic exchange resins;
Digoxin: thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digoxin-induced cardiac dysrhythmias;
Pressor amines (e.g. epinephrine (noradrenaline)): the effect of pressor amines may be decreased;
Non-depolarising skeletal muscle relaxants: the effect of non-depolarising skeletal muscle relaxants may be potentiated by hydrochlorothiazide as in TREMISTAN PLUS;
Treatment for gout: dosage adjustment of uricosuric medicines may be necessary as hydrochlorothiazide, as in TREMISTAN PLUS, may raise the level of serum uric acid. Co-administration of hydrochlorothiazide, as in TREMISTAN PLUS, may increase the incidence of hypersensitivity reactions of allopurinol;
Calcium salts: hydrochlorothiazide, as in TREMISTAN PLUS, 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. Administration of hydrochlorothiazide, as in TREMISTAN PLUS, with vitamin D may potentiate a rise in serum calcium.

Other interactions:
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by hydrochlorothiazide, as in TREMISTAN PLUS. Anticholinergic medicines (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics, as in TREMISTAN PLUS, by decreasing gastrointestinal motility and stomach emptying rate.

Antidiabetic medicines (oral medicines and insulins):
Dosage adjustment of the antidiabetic medicine may be required.

Medicines affected by serum potassium disturbances:
Periodic monitoring of serum potassium is recommended when TREMISTAN PLUS is administered with medicines affected by serum potassium disturbances (e.g. digoxin, antidysrhythmics and medicines known to induce torsades de pointes, such as erythromycin, halofantrine, dolasetron, clarithromycin, moxifloxacin, chlorpromazine, pimozide, ziprasidone and mizolastine).

Medicines affecting potassium:
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 medicines associated with potassium loss and hypokalaemia

(e.g. other kaliuretic diuretics, laxatives, corticosteroids, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives). If these medicines are to be prescribed with TREMISTAN PLUS, monitoring of potassium plasma levels is advised.

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

PREGNANCY AND LACTATION:

TREMISTAN PLUS is contraindicated during pregnancy and lactation (see "CONTRAINDICATIONS" and "WARNINGS AND SPECIAL PRECAUTIONS"). TREMISTAN PLUS should not be initiated during pregnancy. When pregnancy is confirmed, treatment with TREMISTAN PLUS should be stopped and, if appropriate, alternative therapy should be started.

Safety in pregnancy and lactation has not been established (see "CONTRAINDICATIONS"). When pregnancy is planned or confirmed TREMISTAN PLUS should be discontinued and patients should be changed to alternative antihypertensive treatments, which have an established safety profile for use in pregnancy.

Medicines affecting the renin-angiotensin system, such as TREMISTAN PLUS, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. Women of childbearing age should ensure effective contraception.

Exposure to an angiotensin II receptor antagonist, such as TREMISTAN PLUS, during pregnancy is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to TREMISTAN PLUS have occurred during pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken TREMISTAN PLUS should be closely observed for hypotension.

Hydrochlorothiazide, as in TREMISTAN PLUS, cross the placental barrier and appear in cord blood. They may cause foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopaenia and foetal, or neonatal, jaundice have been reported with maternal hydrochlorothiazide.

TREMISTAN PLUS is contraindicated during lactation. It is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breastmilk. Hydrochlorothiazide appears in human milk and may inhibit lactation.

Fertility:
No studies on fertility in humans have been performed.

DOSAGE AND DIRECTIONS FOR USE:
Adults:
TREMISTAN PLUS should be taken once daily, with or without food.
Three dosage strengths are provided; 40/12,5 mg, 80/12,5 mg and 80/25 mg. The patient should be stabilised at the relevant dosage of the individual components given together and then changed to the appropriate combination dosage.
When considering changing the patient's therapy with TREMISTAN PLUS it must be borne in mind that treatment needs to be continued for at least 4 to 8 weeks before the maximum effect is obtained. When necessary, TREMISTAN PLUS may be administered with another antihypertensive medicine.

Renal impairment:
Due to the hydrochlorothiazide component, TREMISTAN PLUS is contraindicated for patients with severe renal dysfunction (creatinine clearance < 30 mℓ/min. Experience in patients with mild to moderate renal impairment is modest 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 dosage should not exceed TREMISTAN PLUS 40/12,5 mg once daily. TREMISTAN PLUS is not indicated in patients with severe hepatic impairment. Hydrochlorothiazide should be used with caution in patients with impaired hepatic function.

Elderly:
No dosage adjustment is necessary.

Children and adolescents up to 18 years:
There are no data on the safety and efficacy of TREMISTAN PLUS in children and adolescents up to 18 years.

SIDE EFFECTS:

Fixed dose TREMISTAN PLUS:

Infections and Infestations:

Less frequent:	Bronchitis.
Frequency unknown:	Pharyngitis, sinusitis.

Immune system disorders:

Frequency unknown:	Exacerbation or activation of systemic lupus erythematosus.

Metabolism and nutrition disorders:

Less frequent:	Hypokalaemia, hypoglycaemia, hyponatraemia, hyperuricaemia.

Psychiatric disorders:

Less frequent:	Anxiety, depression.

Nervous system disorders:

Frequent:	Dizziness.
Less frequent:	Syncope/fainting, paraesthesia, insomnia, sleep disturbances.

Eye disorders:

Less frequent:	Abnormal vision, transient blurred vision.

Ear and labyrinth disorders:

Less frequent:	Vertigo.

Cardiac disorders:

Less frequent:	Tachycardia, cardiac dysrhythmias.

Vascular disorders:

Less frequent:	Hypotension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:

Less frequent:	Dyspnoea, respiratory distress (including pneumonitis and pulmonary oedema).

Gastrointestinal disorders:

Less frequent:	Diarrhoea, dry mouth, flatulence, abdominal pain, constipation, dyspepsia, vomiting, gastritis.

Hepato-biliary disorders:

Less frequent:	Abnormal hepatic function/liver disorder.

Skin and subcutaneous tissue disorders:

Less frequent:	Angioedema (often with fatal outcome), erythema, pruritus, rash, increased sweating, urticaria.

Musculoskeletal, connective tissue and bone disorders:

Less frequent:	Back pain, muscle spasm, myalgia, arthralgia, cramps in legs, leg pain.

Reproductive system and breast disorders:

Less frequent:	Impotence.

General disorders and administration site conditions:

Less frequent:	Chest pain, influenza-like symptoms, pain.

Investigations:

Less frequent:	Increase in blood uric acid, increase in blood creatinine, increased blood creatine phosphokinase, increase in liver enzymes.

Additional information on individual components - Telmisartan:

Infections and Infestations:

Less frequent:	Urinary tract infections (including cystitis), upper respiratory tract infections.
Frequency unknown:	Sepsis including fatal outcome.

Blood and the lymphatic system disorders:

Less frequent:	Anaemia, thrombocytopaenia.
Frequency unknown:	Eosinophilia.

Nervous system disorders:

Less frequent:	Somnolence.

Immune system disorders:

Less frequent:	Hypersensitivity, angioedema.
Frequency unknown:	Anaphylactic reaction.

Metabolism and nutrition disorders:

Less frequent:	Hyperkalaemia, hypoglycaemia (in diabetic patients).

Cardiac disorders:

Less frequent:	Bradycardia.

Gastrointestinal disorders:

Less frequent: Stomach discomfort.

Skin and subcutaneous tissue disorders:

Less frequent: Eczema, drug eruption, toxic skin eruption.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Arthrosis, tendon pain (tendinitis-like symptoms).

Renal and urinary disorders:

Less frequent: Renal impairment including acute renal failure.

General disorders and administration site conditions:

Less frequent: Asthenia (weakness).

Investigations:

Less frequent: Decreased haemoglobin.

Additional information on individual components - Hydrochlorothiazide:

Infections and Infestations:

Frequency unknown: Sialoadenitis.

Blood and the lymphatic system disorders:

Less frequent: Thrombocytopaenia (sometimes with purpura).

Frequency unknown: Aplastic anaemia, haemolytic anaemia, bone marrow depression, leukopenia, neutropenia, agranulocytosis.

Immune system disorders:

Frequency unknown: Hypersensitivity, allergy, anaphylactic reactions.

Endocrine disorders:

Frequency unknown: Inadequate diabetes mellitus control.

Metabolism and nutrition disorders:

Frequent: Electrolyte imbalance, volume depletion.

Frequency unknown: Anorexia, loss of appetite, hypercholesterolaemia, hyperglycaemia.

Psychiatric disorders:

Frequency unknown: Restlessness.

Nervous system disorders:

Less frequent: Headache.

Frequency unknown: Light-headedness.

Eye disorders:

Frequency unknown: Xanthopsia, acute myopia, acute angle-closure glaucoma.

Vascular disorders:

Frequency unknown: Necrotising angiitis (vasculitis).

Gastrointestinal disorders:

Less frequent: Nausea.

Frequency unknown: Pancreatitis, stomach discomfort.

Hepato-biliary disorders:

Less frequent: Hepatocellular jaundice, cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Frequency unknown: Cutaneous lupus erythematosus-like reactions (or reactivation of lupus erythematosus), photosensitivity reactions, cutaneous vasculitis, toxic epidermal necrolysis, erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Weakness.

Renal and urinary disorders:

Frequency unknown: Interstitial nephritis, renal dysfunction, glycosuria.

General disorders and administration site conditions:

Frequency unknown: Fever.

Investigations:

Less frequent: Increase in triglycerides.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

The most prominent manifestations of telmisartan overdose are hypotension and tachycardia; bradycardia, dizziness, vomiting, increase in serum creatinine, and acute renal failure have also been reported. Overdose with hydrochlorothiazide is associated with electrolyte depletion

(hypokalaemia, hypochloraemia) and dehydration (hypovolaemia) 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 dysrhythmias associated with the concomitant use of digoxin or certain anti-dysrhythmic medicines.

Treatment:
No specific information is available on the treatment of overdosage with TREMISTAN PLUS. 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. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. 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.

IDENTIFICATION:
Tremistan Plus 40/12,5: red, oval, biconvex film-coated tablet debossed with 40 on one side and with 12,5 on the other side.
Tremistan Plus 80/12,5: white to off-white, oval, biconvex film-coated tablet debossed with 80 on one side and with 12,5 on the other side.
Tremistan Plus 80/25: yellow, oval, biconvex film-coated tablet debossed with 80 on one side and with 25 on the other side.

PRESENTATION:
Tremistan Plus 40/12,5: Silver aluminium/aluminium blister strips containing 7 tablets each or silver aluminium/aluminium blister strips containing 14 tablets each.
Pack size 28’s.
Tremistan Plus 80/12,5: Silver aluminium/aluminium blister strips containing 7 tablets each or silver aluminium/aluminium blister strips containing 14 tablets each.
Pack size 28’s.
Tremistan Plus 80/25: Silver aluminium/aluminium blister strips containing 7 tablets each or silver aluminium/aluminium blister strips containing 14 tablets each.
Pack size 28’s.

STORAGE INSTRUCTIONS:
Store at or below 25 °C.
Keep blisters in the outer carton until required for use.
TREMISTAN PLUS tablets should not be removed from the blister strips until required for use in order to protect from moisture.
KEEP OUT OF THE REACH OF CHILDREN

REGISTRATION NUMBERS:

Tremistan Plus 40/12,5: 46/7.1.3/0927
Tremistan Plus 80/12,5: 46/7.1.3/0928
Tremistan Plus 80/25: 46/7.1.3/0929

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Sandoz SA (Pty) Ltd[1]
72 Steel Road
Spartan
Kempton Park
1619

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 11 June 2018
Date of most recent approval of professional information: 11 June 2018

[1]Company Reg. No.: 1990/001979/07