PROFESSIONAL INFORMATION (APPROVED)

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

TESAR CO 40/12,5 mg tablets

TESAR CO 80/12,5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TESAR CO 40/12,5 mg: Each double-layered tablet contains 40 mg telmisartan and 12,5 mg hydrochlorothiazide.

TESAR CO 80/12,5 mg: Each double-layered tablet contains 80 mg telmisartan and 12,5 mg hydrochlorothiazide.

TESAR CO 40/12,5 mg contains sugar alcohol (mannitol 327,70 mg) and sugar (lactose monohydrate 99,67 mg) per tablet (see section 4.4).

TESAR CO 80/12,5 mg contains sugar alcohol (mannitol 327,70 mg) and sugar (lactose monohydrate 49,84 mg) per tablet (see section 4.4).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

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Tablets.

TESAR CO 40/12,5 mg tablets are round, bilayer tablets with white and yellow colour with a diameter of 12 mm.

TESAR CO 80/12,5 mg tablets are round, bilayer tablets with white and pink colour with a diameter of 10,5 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TESAR CO is indicated for the treatment of mild to moderate hypertension in patients whose blood pressure has been stabilised at the same dosage of the individual components given together.

4.2 Posology and method of administration

Posology

Adults:

TESAR CO should be taken once daily, with or without food. Two dosage strengths are available: 40/12,5 mg and 80/12,5 mg. The patient should be stabilised at the relevant dosage of the individual components given together, and then be changed to the appropriate combination dosage. When considering changing the patient's therapy with TESAR CO it must be born in mind that treatment needs to be continued for at least 4 to 8 weeks before the maximum effect is obtained. When necessary, TESAR CO may be administered with another antihypertensive medicine.

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Special populations

Renal impairment:

Due to the hydrochlorothiazide component, TESAR CO is not recommended for 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 (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment, the dosage should not exceed TESAR CO 40/12,5 mg once daily. TESAR CO is not indicated in patients with severe hepatic impairment. Thiazides, as in TESAR CO, should be used with caution in patients with impaired hepatic function.

Elderly:

No dosage adjustment is necessary.

Paediatric population

Children and adolescents up to 18 years:

There are no data on the safety and efficacy of TESAR CO in children and adolescents up to 18 years.

Method of administration

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TESAR CO tablets are for once-daily oral administration and should be taken with liquid, with or without food.

4.3 Contraindications

- Hypersensitivity to telmisartan, hydrochlorothiazide or other sulphonamide-derived medicines or to any of the ingredients of TESAR CO (see section 6.1)
- patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip
- severe renal function impairment (creatinine clearance < 30 ml/min) or anuria
- severe hepatic impairment, cholestasis and biliary cirrhosis
- refractory hyponatraemia, hypokalaemia, hypercalcaemia and symptomatic hyperuricaemia or gout
- bilateral renal artery stenosis or renal artery stenosis in the presence of a single kidney
- aortic valve stenosis and/or Hypertrophic Obstructive Cardiomyopathy (HOCM) (see section 4.4)
- angioedema on previous exposure to angiotensin receptor blockers (ARBs) or ACE inhibitors. These patients must never be given these medicines again
- hereditary or idiopathic angioedema
- biliary obstructive disorders
- concomitant therapy with potassium sparing diuretics such as amiloride, spironolactone, triamterene

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- Addison's disease
- porphyria
- lithium toxicity may occur when TESAR CO is used in combination with lithium therapy (see section 4.5)
- concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate to severe renal function impairment (creatinine clearance less than 30 ml/min) and in elderly patients
- concomitant use with aliskiren-containing medicines
- pregnancy and lactation (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking TESAR CO, the treatment must be stopped promptly and changed to a different medicine (see section 4.6). If a woman is contemplating pregnancy, a different class of medicine should be used (see section 4.6).

When pregnancy is diagnosed, treatment with TESAR CO should be stopped immediately and, if appropriate, alternative therapy should be started (see section 4.3).

Renovascular hypertension:

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral artery stenosis or stenosis of the artery to a single functioning kidney is treated with

medicines that affect the renin-angiotensin-aldosterone system (see section 4.3).

Renal artery stenosis:

TESAR CO may increase serum creatinine and blood urea in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, which could lead to an increased risk of severe hypotension (see section 4.3).

Renal impairment and kidney transplantation:

Patients with severe renal function (creatinine clearance < 30 ml/min) should not take TESAR CO (see section 4.3).

Uraemia, associated with hydrochlorothiazide, as in TESAR CO, may occur in patients with renal impairment.

The periodic monitoring of potassium, creatinine and uric levels is mandatory in patients with mild to moderate renal impairment.

There is no experience with respect to the administration of TESAR CO in patients with a recent kidney transplant or severe renal impairment (see section 4.3).

Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Intravascular volume depletion:

In patients with intravascular volume and/or sodium depletion caused by vigorous diuretic therapy, diarrhoea, vomiting or dietary salt restriction, hypotension may occur, especially after the first dose of TESAR CO. The use of TESAR CO is not recommended until this condition has been corrected.

Isolated cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) have been observed with the use of hydrochlorothiazide.

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Dual blockade of the renin-angiotensin-aldosterone system:

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or alikiren may increase the risk of hypotension, hyperkalaemia and decrease renal function (including acute renal failure). Dual blockade of Renin-Angiotensin-Aldosterone System (RAAS) through the combined use of TESAR CO and aliskiren is therefore contraindicated (see section 4.3). TESAR CO should not be used concomitantly with aliskiren (see section 4.3).

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Other conditions which stimulate the renin-angiotensin-aldosterone system:

Treatment with other medicines that affect the renin-angiotensin-aldosterone system, including TESAR CO, in patients whose vascular tone and renal function depend on this system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis) has been linked to hyperazotaemia, oliguria, acute hypotension, or rarely acute renal failure.

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors /angiotensin receptor blockers, whether used separately and/or in combination.

Primary aldosteronism:

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Patients with primary aldosteronism do not normally respond to antihypertensive medicines which act through inhibition of the renin-angiotensin system. Administration of TESAR CO is therefore not recommended in these patients.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy:

Special caution is recommended in patients suffering from obstructive hypertrophic cardiomyopathy or mitral or aortic valve stenosis (see section 4.3).

Hyperkalaemia:

Although clinically significant hyperkalaemia has not been documented with telmisartan/hydrochlorothiazide in combination, hyperkalaemia may occur during treatment with other medicines that affect the renin-angiotensin-aldosterone system, especially in the presence of heart failure and/or renal impairment and diabetes mellitus.

Co-administration of TESAR CO with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines which may increase potassium levels (e.g. heparin) should be taken with caution.

Hepatic impairment:

Telmisartan, as in TESAR CO, is mostly eliminated in the bile. Patients with biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, TESAR CO should not be given to these patients (see section 4.3).

TESAR CO should be used with caution in patients with progressive liver disease or mild to moderate hepatic impairment, since minor alterations of electrolyte balance and fluid may induce hepatic coma. There is no clinical experience with TESAR CO in patients with hepatic impairment.

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Metabolic and endocrine effects:

Treatment with TESAR CO may impair glucose tolerance, therefore dose adjustment of antidiabetic medicines (including insulin) may be necessary. Latent diabetes mellitus may occur during TESAR CO treatment. Increases in triglyceride and cholesterol levels have been associated with hydrochlorothiazide (as in TESAR CO) therapy, however, at the 12,5 mg dose, minimal or no effects were reported.

Hydrochlorothiazide, as in TESAR CO, may increase serum uric acid concentration and may lead to gout in patients who are susceptible.

Serum electrolyte changes:

Periodic monitoring of serum electrolytes should be performed at appropriate intervals in patients receiving hydrochlorothiazide, as in TESAR CO.

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines which may increase potassium levels (e.g. heparin) should be taken 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 those experiencing brisk diuresis, in those receiving inadequate oral intake of electrolytes and in those receiving concomitant therapy with corticosteroids or ACTH. Conversely, due to the antagonism of the angiotensin II (AT1) receptors by the telmisartan component of TESAR CO, hypokalaemia may occur. Frequent monitoring of serum potassium is recommended.

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Hypochloroaemic alkalosis and hyponatraemia:

Hypochloroaemic alkalosis and hyponatraemia have been linked to treatment with hydrochlorothiazide, as in TESAR CO.

Hypercalcaemia:

Hydrochlorothiazide, as in TESAR CO, may decrease urinary calcium excretion and cause irregular and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Increased hypercalcaemia may be a sign of hyperparathyroidism. Discontinue TESAR CO therapy before performing tests for parathyroid function.

Hypomagnesaemia:

Hydrochlorothiazide, as in TESAR CO, may lead to hypomagnesaemia, due to an increase in the urinary excretion of magnesium.

Symptoms which warn against electrolyte and fluid imbalance, irrespective of cause, include thirst, dry mouth, lethargy, weakness, restlessness, drowsiness, confusion, muscle pains or cramps, seizures, muscular fatigue, oliguria, tachycardia, hypotension and gastro-intestinal disturbances such as vomiting and nausea.

Systemic lupus erythematosus:

Hydrochlorothiazide, as in TESAR CO, has been reported to worsen or activate systemic lupus erythematosus.

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 medicine such as ARBs or ACE-inhibitors (such as TESAR CO). In patients with diabetes mellitus, CAD may be asymptomatic and therefore undiagnosed. These patients should undergo appropriate diagnostic evaluation prior initiation of treatment e.g. exercise stress testing, to detect and to treat CAD accordingly, before initiating treatment with TESAR CO.

Choroidal Effusion, Acute Myopia and Angle-Closure Glaucoma

Hydrochlorothiazide, a sulphonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, 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 sulphonamide or penicillin allergy.

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 (HCTZ) exposure has been observed in two epidemiological studies. Photosensitising actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking TESAR CO 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 UV rays and, in case of exposure, adequate protection 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 examinations of biopsies.

TESAR CO should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Ethnic differences:

As with all other angiotensin II receptor antagonists, telmisartan (as in TESAR CO) is apparently less effective in lowering blood pressure in black patients than in non-black patients, possibly because of higher prevalence of low renin states in the black hypertensive population.

Acute Respiratory Toxicity:

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, TESAR CO should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Other:

An excessive decrease in blood pressure in patients with ischaemic cardiovascular disease or ischaemic cardiopathy could result in a stroke or myocardial infarction when these

patients take TESAR CO.

General:

Patients with or without a history of allergy or bronchial asthma, may experience hypersensitivity reactions to hydrochlorothiazide, as in TESAR CO, but are more likely to occur in those patients with a history.

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If a photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Lactose:

TESAR CO contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take TESAR CO.

TESAR CO contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Mannitol:

TESAR CO contains mannitol which may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

The antihypertensive effect of telmisartan, as in TESAR CO, may increase the hypotensive effects of other antihypertensive medicines

Telmisartan, as in TESAR CO, has no clinically significant interaction with digoxin,

hydrochlorothiazide, warfarin, ibuprofen, glibenclamide, paracetamol, amlodipine and simvastatin, when co-administered. Monitoring of plasma digoxin levels should be considered, since a 20 % increase in median plasma digoxin trough concentration has been observed.

Although the clinical relevance is unknown, co-administration of telmisartan (as in TESAR CO) and ramipril led to an increase of up to 2,5-fold in the AUC_{0-24} and C_{max} of ramipril and ramiprilat during a single study.

Lithium:

Toxicity and reversible increases in serum lithium concentrations have been reported during concomitant use of lithium with telmisartan, as in TESAR CO. Renal clearance is also decreased by hydrochlorothiazide, as in TESAR CO, increasing the risk of lithium toxicity. Co-administration of lithium and TESAR CO is contraindicated (see section 4.3).

Fluoroquinolones and ACE inhibitors/angiotensin receptor blockers:

Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

Iodinated contrast products

In the event of dehydration caused by diuretics, there is an increased risk of acute functional renal failure, particularly during use of high doses of iodinated contrast products. Rehydration before administration of the iodinated product is required.

Medicines affecting potassium:

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The potassium-depleting effect of hydrochlorothiazide, as in TESAR CO, could be increased by other medicines associated with hypokalaemia and potassium loss (e.g. other kaliuretic diuretics, corticosteroids, ACTH, laxatives, carbenoxolone, amphotericin, salicylic acid and derivatives, penicillin G sodium). Monitoring of potassium plasma levels is advised if these medicines are prescribed with TESAR CO.

Equally, concomitant use of TESAR CO and ACE inhibitors, potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium, cyclosporin or other medicines that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium and should therefore be co-administered cautiously with TESAR CO, and potassium plasma levels monitored (see section 4.3).

Duel blockade of the RAAS with ARBs, ACE inhibitors or aliskiren:

Study data has shown that blockage 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 sections 4.3 and 4.4).

Medicines affected by serum potassium disturbances:

Monitoring of serum potassium is recommended when TESAR CO is administered with medicines affected by serum potassium disturbances (e.g. digitalis glycosides, anti-dysrhythmics and medicines known to induce torsade's de pointes, such as:

- dolasetron, erythromycin, clarithromycin, halofantrine, moxifloxacin, pimozide, chlorpromazine, ziprasidone and mizolastine).
- class Ia anti-dysrythmics (e.g. quinidine, hydroquinidine, disopyramide)

- class III anti-dysrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)

- some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride,

sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)

- others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV.)). Hypokalaemia being a predisposing factor to torsades de pointes.

Non-steroidal anti-inflammatory drugs (NSAIDs):

The concomitant use of NSAIDs, including aspirin, should be used with caution in patients taking telmisartan, as in TESAR CO, as the risk of acute renal insufficiency may be increased, especially in those patients who are not adequately hydrated.

NSAIDs may also intensify the hypotensive effects of telmisartan, as in TESAR CO. The diuretic, natriuretic and antihypertensive effects of hydrochlorothiazide, as in TESAR CO, are blunted by NSAIDs.

Patients taking NSAIDs and TESAR CO should be sufficiently hydrated and be monitored for renal function at the beginning of, and during, combined treatment.

Additional information on TESAR CO interaction:

The pharmacokinetics of telmisartan, as in TESAR CO, are not affected by the hydrochlorothiazide in TESAR CO.

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

Alcohol, barbiturates or narcotics:

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Orthostatic hypotension may become aggravated by simultaneous intake of alcohol, barbiturates, anaesthetics or opioids.

Antidiabetic medicines (oral agents and insulin):

Treatment with hydrochlorothiazide, as in TESAR CO, may impair glucose tolerance. Dosage adjustment of antidiabetic medicines, including insulin, may be required.

Metformin:

There is a risk of lactic acidosis when hydrochlorothiazide, as in TESAR CO is co-administered with metformin.

Cholestyramine and colestipol resins:

The gastrointestinal absorption of hydrochlorothiazide, as in TESAR CO, is reduced by colestipol or cholestyramine.

Digitalis glycosides:

Hypokalaemia or hypomagnesaemia, induced by hydrochlorothiazide, as in TESAR CO, favours the onset of digitalis-induced cardiac dysrhythmias.

Digoxin:

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49 %) and in trough concentration (20 %) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

Pressor amines (e.g. noradrenaline):

Hydrochlorothiazide, as in TESAR CO, has been reported to cause the arterial response to pressor amines (e.g. noradrenaline) to decrease.

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Non-depolarizing skeletal muscle relaxants (e.g. tubocurarine):

The effect on non-depolarizing skeletal muscle relaxants (e.g. tubocurarine) may be increased by hydrochlorothiazide, as in TESAR CO.

Treatment for gout (e.g. probenecid, sulfinpyrazone and allopurinol):

Hydrochlorothiazide, as in TESAR CO, may increase levels of serum uric acid, therefore dosage adjustment of uricosuric medicines probenecid or sulfinpyrazone may be necessary.

Co-administration of hydrochlorothiazide, as in TESAR CO, may increase the incidence of hypersensitivity reactions of allopurinol.

Calcium salts:

Hydrochlorothiazide, as in TESAR CO, may increase serum calcium levels due to the reduced ability to excrete excess calcium. If calcium supplements or Vitamin D must be taken, serum calcium levels should be monitored and dosage adjusted accordingly.

Other interactions:

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by concurrent use with hydrochlorothiazide, as in TESAR CO. Anticholinergic agents (e.g. biperiden, atropine) may increase the bioavailability of hydrochlorothiazide, as in TESAR CO, by decreasing stomach-emptying rate and gastrointestinal motility.

Hydrochlorothiazide, as in TESAR CO, may increase the risk of adverse effects caused by amantadine.

Hydrochlorothiazide, as in TESAR CO, may reduce the renal excretion of cytotoxic agents (e.g. methotrexate, cyclophosphamide) and increase their myelosuppressive effects.

Concurrent hypovolaemia may cause acute renal failure when taking TESAR CO.

Administration of thiazide diuretics, as in TESAR CO, with vitamin D may potentiate a rise in serum calcium.

Haemolytic anaemia occurring with co-administration of hydrochlorothiazide, as in TESAR CO, and methyldopa has been reported.

Concurrent therapy with cyclosporin may increase the risk of gout-type complications and hyperuricaemia.

Food does not affect the bioavailability of telmisartan, as in TESAR CO.

Based on their pharmacological properties it can be expected that baclofen and amifostine may potentiate the hypotensive effects of all antihypertensives including telmisartan.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age should ensure effective contraception.

Pregnancy

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed, TESAR CO should be discontinued.

Preclinical studies indicate that telmisartan, as in TESAR CO, does not indicate teratogenic effect, but has shown fetotoxicity.

Medicines affecting the renin-angiotensin system, such as TESAR CO, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Should exposure to TESAR CO have occurred during pregnancy, ultrasound check of renal

function and skull is recommended.

Infants whose mothers have taken TESAR CO should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide, as contained in TESAR CO, crosses the placental barrier and appears in cord blood. They may cause foetal electrolyte disturbances and possibly other reactions that have occurred in adults. Cases of neonatal thrombocytopenia and foetal, or neonatal, jaundice have been reported with maternal thiazide therapy.

Breastfeeding

TESAR CO is contraindicated during breastfeeding (see section 4.3). Although animal studies have shown excretion of telmisartan in breastmilk, it is unknown whether telmisartan, as in TESAR CO, is excreted in human milk. Hydrochlorothiazide appears in human milk and may inhibit lactation.

Fertility

No fertility studies in humans have been performed. In pre-clinical studies, an effect of telmisartan and hydrochlorothiazide on male and female fertility was not observed.

4.7 Effects on ability to drive and use machines

TESAR CO can have influence on the ability to drive and use machines. Dizziness, syncope or vertigo may occasionally occur when taking antihypertensive therapy such as TESAR CO.

4.8 Undesirable effects

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Summary of the safety profile

The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely.

Tabulated list of adverse effects

Fixed-dose combination (TESAR CO):

System Organ Class	Frequency	Side effects
Infections and infestations	Less frequent Frequency unknown	Bronchitis Pharyngitis*, sinusitis*
Immune system disorders	Frequency unknown	Exacerbation or activation of systemic lupus erythematosus*
Metabolism and nutrition disorders	Less frequent	Hyponatraemia, hyperuricaemia, hypokalaemia, hypoglycaemia
Psychiatric disorders	Less frequent	Depression, anxiety
Nervous system disorders	Frequent Less frequent	Dizziness Insomnia, sleep disturbances, syncope/fainting, paraesthesia
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

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Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders	Less frequent Frequency unknown	Diarrhoea, dry mouth, flatulence, abdominal pain, constipation, dyspepsia, vomiting Gastritis*
Hepatobiliary disorders	Less frequent	Abnormal hepatic function/liver disorder
Skin and subcutaneous tissue disorders	Less frequent	Angioedema (with fatal outcome), erythema, pruritus, rash, increased sweating, urticaria
Musculoskeletal, connective tissue and bone disorders	Less frequent	Back pain, muscle spasm, myalgia, arthralgia, leg cramps, leg pain
Reproductive system and breast disorders	Less frequent	Impotence
General disorders and administrative site conditions	Less frequent	Chest pain, influenza-like symptoms, pain
Investigations	Less frequent	Increase in uric acid, increase in creatinine, blood creatinine phosphokinase increase, increase in liver enzymes

*Post-marketing side effects reported with TESAR CO.

Telmisartan monotherapy:

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System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Less frequent Frequency unknown	Urinary tract infections (including cystitis), upper respiratory tract infections Sepsis, including fatal outcome*
Blood and lymphatic system disorders	Less frequent Frequency unknown	Anaemia, thrombocytopenia Eosinophilia*
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity Anaphylactic reaction*
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia, hypoglycaemia (in diabetic patients), hyponatraemia
Psychiatric disorders	Less frequent	Anxiety, depression, insomnia
Nervous system disorders	Less frequent	Somnolence, syncope
Eye disorders	Less frequent	Visual impairment
Ear and labyrinth disorders	Less frequent	Vertigo
Cardiac disorders	Less frequent	Bradycardia, tachycardia
Vascular disorders	Less frequent	Hypotension, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Cough, dyspnoea Interstitial lung disease

Gastrointestinal disorders	Less frequent	Stomach discomfort, taste disturbance, taste loss, diarrhoea, dry mouth, flatulence, abdominal pain, dyspepsia, vomiting
Hepatobiliary disorders	Less frequent	Abnormal hepatic function/liver disorder*
Skin and subcutaneous tissue disorders	Less frequent	Eczema, drug eruption, toxic skin eruption, angioedema (including fatal outcome), erythema, pruritus, rash, hyperhidrosis, urticaria
Musculoskeletal, connective tissue and bone disorders	Less frequent Frequency unknown	Back pain, muscle spasm (cramps in legs), myalgia, arthralgia, pain in extremity Arthrosis*, tendon pain (tendinitis like symptoms)*, rhabdomyolysis
Renal and urinary disorders	Less frequent	Renal impairment including acute renal failure
General disorders and administrative site conditions	Less frequent	Asthenia, chest pain, influenza-like illness
Investigations	Less frequent	Haemoglobin decreased, blood uric acid increased, blood creatinine increased, blood creatinine phosphokinase increased, hepatic enzyme increased

Hydrochlorothiazide monotherapy (Post-marketing experience):

System Organ Class	**Frequency**	**Side effects**

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Infections and infestations	Frequency unknown	Sialadenitis
Neoplasms benign and malignant (including cysts and polyps)	Frequency unknown	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	Less frequent	Leukopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
Immune system disorders	Less frequent	Hypersensitivity, allergy, anaphylactic reactions
Endocrine disorders	Frequency unknown	Loss of diabetic control
Metabolism and nutrition disorders	Less frequent Frequency unknown	Electrolyte imbalance, volume depletion Anorexia, loss of appetite, hypercholesterolaemia, hyperglycaemia
Psychiatric disorders	Less frequent	Restlessness, depression
Nervous system disorders	Less frequent Frequency unknown	Headache, paraesthesia Light-headedness
Eye disorders	Frequency unknown	Yellow vision (xanthopsia), acute myopia, acute angle-closure glaucoma, choroidal effusion
Cardiac disorders	Less frequent	Dysrhythmias

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Vascular disorders	Frequent Frequency unknown	Orthostatic hypotension Necrotising angitis (vasculitis)
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Respiratory distress, pneumonitis, pulmonary oedema, acute respiratory distress syndrome (ARDS) (see section 4.4)
Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Nausea, vomiting Upset stomach, constipation, abdominal discomfort Pancreatitis
Hepatobiliary disorders	Less frequent	Jaundice hepatocellular, jaundice cholestatic
Skin and subcutaneous tissue disorders	Frequent Less frequent Frequency unknown	Rash, urticaria Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions (or reactivation of cutaneous lupus erythematosus), photosensitivity reactions, cutaneous vasculitis Erythema multiforme
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Weakness, muscle spasms (cramp in legs)
Renal and urinary disorders	Frequency unknown	Glycosuria, renal failure, interstitial nephritis
Reproductive system and breast disorders	Frequent	Erectile dysfunction

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General disorders and administrative site conditions	Frequency unknown	Fever
Investigations	Frequency unknown	Increase in triglycerides

a. Description of selected adverse reactions

Abnormal hepatic function / liver disorder

Most cases of abnormal hepatic function / liver disorder from post-marketing experience with telmisartan occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known (see section 5.1).

Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

PROFESSIONAL INFORMATION (APPROVED)

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Limited information is available for TESAR CO overdose in humans. The most prominent side-effects following overdose of telmisartan, as in TESAR CO, are bradycardia, hypotension and tachycardia. Overdose with hydrochlorothiazide, as in TESAR CO, is associated with dehydration and electrolyte depletion (hypokalaemia, hypochloraemia) resulting from excessive diuresis. The most common signs and symptoms of an overdose are somnolence and nausea.

Hypokalaemia may result in muscle spasm and/or accentuate cardiac dysrhythmias associated with the concomitant use of digoxin or certain anti-dysrhythmic medicines.

Management of overdose:

Treatment should be symptomatic and supportive, with monitoring of serum electrolytes, creatinine concentrations and renal function.

Place the patient in a supine position if hypotension occurs. Volume and salt replacements

must be given quickly.

Telmisartan, as in TESAR CO, is not removed by haemodialysis.

It is not known to what extent hydrochlorothiazide, as in TESAR CO, is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics

ATC code: C09DA07

Pharmacological classification: A 7.1.3 Other hypotensives.

TESAR CO consists of telmisartan (angiotensin II receptor antagonist) and hydrochlorothiazide (thiazide diuretic). These ingredients combined, provide an additive antihypertensive effect.

Mechanism of action

Telmisartan:

Telmisartan is a specific angiotensin II receptor (Type AT1) antagonist. It displaces angiotensin II 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 at the AT1 receptor. The binding is long-lasting. Plasma aldosterone levels are decreased by telmisartan.

Telmisartan does not inhibit human plasma renin or block ion channels. An 80 mg dose in

humans almost completely inhibits the angiotensin II evoked blood pressure increase.

The inhibitory effect of telmisartan is sustained over 24 hours and can still be measured up to 48 hours. The onset of antihypertensive activity occurs within 3 hours after administration of the first dose of telmisartan. After starting treatment, the maximum reduction in blood pressure is normally reached within 4 weeks and is maintained during long-term therapy.

The binding of telmisartan to AT1 receptors is long-lasting and the resulting antihypertensive effect persists over 24 hours after dosing. With respect to a time to recovery of baseline systolic blood pressure, there is a trend to a dose relationship. Data concerning diastolic blood pressure are inconsistent in this regard.

Telmisartan reduces both systolic and diastolic blood pressure in patients with hypertension, without affecting pulse rate.

Blood pressure gradually returns to pre-treatment values over a period of several days, upon abrupt cessation of treatment with telmisartan, without evidence of rebound hypertension.

The beneficial effects of telmisartan on cardiovascular morbidity and mortality are currently not known.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic. The mechanism of action of the antihypertensive effects of hydrochlorothiazide has not been elucidated.

Hydrochlorothiazide affects the distal renal tubular mechanism of electrolyte re-absorption and increases the excretion of chloride and sodium in equal amounts.

Hydrochlorothiazide increases aldosterone secretion, decreases plasma volume and increases plasma renin activity, 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 HCTZ, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6-12 hours.

5.2 Pharmacokinetic properties

Administration of telmisartan together with hydrochlorothiazide does not affect the pharmacokinetics of these molecules.

Absorption:

Telmisartan: Peak plasma concentrations are reached about 0,5 to 1,5 hours after an oral dose. Food slightly decreases the bioavailability of telmisartan. The reduction in the area under the plasma concentration-time curve (AUC0-∞) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose) when taken with food. Three hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Telmisartan does not accumulate significantly in plasma on repeated administration in healthy volunteers.

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

Telmisartan does not accumulate significantly in plasma on repeated administration.

Hydrochlorothiazide: Peak plasma concentrations of hydrochlorothiazide are reached within 1 to 3 hours after oral administration. Hydrochlorothiazide has an absolute

bioavailability of about ± 60 %, based on cumulative renal excretion. When hydrochlorothiazide is taken with food, systemic availability has been reported to both increase and decrease when compared with a fasted state. However, these effects are small and have little clinical significance.

Distribution:

Telmisartan: Telmisartan is > 99,5 % bound to plasma proteins, mainly to albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (Vdss) is approximately 500 L which indicates additional tissue binding.

Hydrochlorothiazide: The plasma protein binding of hydrochlorothiazide is approximately 64 %. The apparent volume of distribution is approximately 0,8 ± 0,3 L/kg.

Biotransformation:

Telmisartan: Telmisartan undergoes conjugation to form an inactive acylglucuronide metabolite (approximately 11 % of the measured radioactivity in plasma after a single dose). The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Hydrochlorothiazide: Hydrochlorothiazide is not metabolised in man.

Elimination:

Telmisartan: After oral administration the total plasma clearance of telmisartan is > 1 500 mL/min). The terminal half-life of telmisartan is > 20 hours. Telmisartan is excreted almost entirely in the faeces via bile (> 97 %), mainly as the unchanged compound. The cumulative urinary excretion is < 1 % of the dose.

Hydrochlorothiazide: Hydrochlorothiazide is excreted almost completely unchanged in the urine. Approximately 60 % of an oral dose is eliminated in the urine within 48 hours. In

healthy patients' renal clearance is about 250 – 300 mL/min. The terminal half-life of hydrochlorothiazide is estimated to be around 10 – 15 hours, although the effects last longer.

Linearity/non-linearity:

Telmisartan: The pharmacokinetics of telmisartan, when administered orally, are non-linear with doses from 20 – 160 mg, with increasing doses showing a greater than proportional increase of plasma concentrations (Cmax and AUC). On repeated administration in healthy volunteers, telmisartan does not accumulate significantly in plasma.

Hydrochlorothiazide: Hydrochlorothiazide exhibits linear pharmacokinetics.

Pharmacokinetics in special patient groups

Elderly patients:

The pharmacokinetics of telmisartan do not differ between patients younger than 65 years of age and the elderly.

Gender:

Telmisartan: Although plasma concentrations of telmisartan are generally 2 – 3 times higher in women than in men, there is little influence on efficacy. However, in clinical trials, no significant increases in the incidence of orthostatic hypotension or in blood pressure response were found in females. No dosage adjustment is necessary.

Patients with renal impairment:

Telmisartan: Telmisartan is not removed from blood by haemodialysis. In patients with mildly decreased renal function, no dosage adjustment is required, nor in patients with mild to moderate renal impairment (creatinine clearance of 30 – 60 mL/min, mean about 50

mL/min). Renal excretion does not contribute to the clearance of telmisartan.

Hydrochlorothiazide: The rate of hydrochlorothiazide elimination is reduced in patients with impaired renal function. The elimination half-life of hydrochlorothiazide is increased in patients with a mean creatinine clearance of 90 ml/min. In those patients without functioning kidneys, the elimination half-life is about 34 hours.

Patients with hepatic impairment:

Telmisartan: Hepatic impairment results in an increase in absolute bioavailability of up to nearly 100 %. In patients with hepatic impairment the elimination half-life of telmisartan remains unchanged after a single dose.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Ferric oxide red (30E 172)

Ferric oxide yellow (10E 172)

Hypromellose

Lactose monohydrate

Mannitol

Magnesium stearate

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Meglumine

Microcrystalline cellulose

Povidone

Sodium hydroxide

Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

TESAR CO tablets are available in aluminium/aluminium blister strips of 28 or 30 tablets, packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

PROFESSIONAL INFORMATION (APPROVED)

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

TESAR CO 40/12,5 mg: A48/7.1.3/0106

TESAR CO 80/12,5 mg: A48/7.1.3/0107

9. DATE OF FIRST AUTHORISATION

April 2021

10. DATE OF REVISION OF THE TEXT

28 January 2025