PROFESSIONAL INFORMATION FOR CO-TELZA

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CO-TELZA 40/12,5 tablets.

CO-TELZA 80/12,5 tablets.

CO-TELZA 80/25 tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

CO-TELZA 80/25: Each tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.

CO-TELZA 40/12,5 contains sugar (lactose monohydrate, 310,80 mg and mannitol, 50 mg).

CO-TELZA 80/12,5 contains sugar (lactose monohydrate, 499,40 mg and mannitol, 50 mg).

CO-TELZA 80/25 contains sugar (lactose monohydrate, 486,70 mg and mannitol, 50 mg).

CO-TELZA 40/12,5 contains salt (sodium, 1,93 mg).

CO-TELZA 80/12,5 contains salt (sodium, 3,85 mg).

CO-TELZA 80/25 contains salt (sodium, 3,85 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CO-TELZA 40/12,5:

Biconvex, two-layered, capsule shaped uncoated tablets wherein, the hydrochlorothiazide layer is white to off white, debossed with ‘423’ and the telmisartan layer is mottled orange to reddish brown, without debossing. Hydrochlorothiazide layer may contain reddish brown specks.

CO-TELZA 80/12,5:

Biconvex, two-layered, capsule shaped uncoated tablets wherein, the hydrochlorothiazide layer is white to off white, debossed with ‘424’ and the telmisartan layer is mottled orange to reddish brown, without debossing. Hydrochlorothiazide layer may contain reddish brown specks.

CO-TELZA 80/25:

Biconvex, two-layered, capsule shaped uncoated tablets wherein, the hydrochlorothiazide layer is light yellow, debossed with ‘425’ and the telmisartan layer is mottled orange to reddish brown, without debossing. Hydrochlorothiazide layer may contain reddish brown specks.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CO-TELZA 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:

CO-TELZA 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 **CO-TELZA** 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, **CO-TELZA** may be administered with another antihypertensive medicine.

Special populations

Renal impairment:

Due to the hydrochlorothiazide component, **CO-TELZA** 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 to moderate hepatic impairment the dosage should not exceed **CO-TELZA 40/12,5 mg** once daily. **CO-TELZA** is not indicated in patients with severe hepatic impairment. Thiazides, as in **CO-TELZA**, 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 **CO-TELZA** in children and adolescents up to 18 years.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to telmisartan, hydrochlorothiazide or sulphonamide-derived medicines, or to any of the ingredients of **CO-TELZA**.
- 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.

- Addison's disease.
- Porphyria.
- Lithium toxicity may occur when **CO-TELZA** 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 section 4.4 and 4.6).

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking CO-TELZA, the treatment should 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 **CO-TELZA** 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 hypertension and renal insufficiency when patients with bilateral artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicines that affect the renin-angiotensin-aldosterone system (see section 4.3).

Renal artery stenosis:

CO-TELZA 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 impairment (creatinine clearance < 30 mL/min) should not take **CO-TELZA** (see section 4.3).

Uraemia, associated with hydrochlorothiazide, as in **CO-TELZA**, may occur in patients with renal impairment.

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

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

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 **CO-TELZA**.

The use of **CO-TELZA** is not recommended until this condition has been corrected.

Dual blockade of the renin-angiotensin-aldosterone system:

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

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

Treatment with other medicines that affect the renin-angiotensin-aldosterone system, including **CO-TELZA**, 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:

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

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy:

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

Hyperkalaemia:

Hyperkalaemia may occur during treatment with other medicines that affect the renin-angiotensin-aldosterone system, especially in the presence of heart failure or renal impairment. While this is not reported with telmisartan, as in **CO-TELZA**, adequate monitoring of serum potassium levels is recommended in patients at risk.

Co-administration of **CO-TELZA** 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 **CO-TELZA**, is mostly eliminated in the bile. Patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, **CO-TELZA** should not be given to these patients (see section 4.3). **CO-TELZA** should be used with caution in patients with progressive liver disease or mild to moderate hepatic impairment, since minor alterations or electrolyte balance and fluid may induce hepatic coma. There is no clinical experience with **CO-TELZA** in patients with hepatic impairment.

Metabolic and endocrine effects:

Treatment with **CO-TELZA** may impair glucose tolerance, therefore dose adjustment of antidiabetic medicines (including insulin) may be necessary. Latent diabetes mellitus may occur during **CO-TELZA** treatment. Increases in triglyceride and cholesterol levels have been associated with hydrochlorothiazide (as in **CO-TELZA**) therapy.

Hydrochlorothiazide, as in **CO-TELZA**, 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 **CO-TELZA**.

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 (AT_1) receptors by the telmisartan component of **CO-TELZA**, hyperkalaemia might occur. Frequent monitoring of serum potassium is recommended.

Hypochloraemic alkalosis and hyponatraemia:

Hypochloraemic alkalosis and hyponatraemia have been linked to treatment with hydrochlorothiazide, as in **CO-TELZA**.

Hypercalcaemia:

Hydrochlorothiazide, as in **CO-TELZA**, 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 **CO-TELZA** therapy before performing tests for parathyroid function.

Hypomagnesaemia:

Hydrochlorothiazide, as in **CO-TELZA** 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 **CO-TELZA**, 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 co-existent coronary artery disease (CAD), the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased when treated with blood pressure lowering medicines such as ARBs or ACE-inhibitors (such as **CO-TELZA**). In patients with diabetes mellitus, CAD may be asymptomatic and therefore undiagnosed. These patients should undergo appropriate diagnostic evaluation prior to initiation of treatment e.g., exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with **CO-TELZA**.

Acute Myopia and 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 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 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.

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 **CO-TELZA** 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 preventative 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.

CO-TELZA 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:

Telmisartan (as in **CO-TELZA**) 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.

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 **CO-TELZA**.

General:

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

Excipient warnings

Lactose:

CO-TELZA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **CO-TELZA**.

Sodium:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

The antihypertensive effect of telmisartan, as in **CO-TELZA**, may increase the hypotensive effects of other antihypertensive medicines.

Telmisartan, as in **CO-TELZA**, 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 **CO-TELZA**) 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 administration of lithium with telmisartan, as in **CO-TELZA.** Renal clearance is also decreased by hydrochlorothiazide, as in **CO-TELZA,** increasing the risk of lithium toxicity. Co-administration of lithium and **CO-TELZA** 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).

Medicines affecting potassium:

The potassium-depleting effect of hydrochlorothiazide, as in **CO-TELZA**, 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 **CO-TELZA**.

Equally, concomitant use of **CO-TELZA** and potassium-sparing diuretics, potassium supplements or salt substitutes containing potassium 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 **CO-TELZA**, and potassium plasma levels monitored (see section 4.3).

Dual 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 **CO-TELZA** is administered with medicines affected by serum potassium disturbances (e.g., digitalis glycosides, antidysrhythmics and medicines known to induce torsade's de pointes, such as dolasetron, erythromycin, clarithromycin, halofantrine, moxifloxacin, pimozide, chlorpromazine, ziprasidone and mizolastine).

Non-steroidal anti-inflammatory drugs (NSAIDS):

Concomitant use of NSAIDs, including aspirin, should be used with caution in patients taking telmisartan, as in **CO-TELZA**, 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 **CO-TELZA**. The co-administration of NSAIDs may reduce the diuretic, natriuretic and anti-hypertensive effects of hydrochlorothiazide, as in **CO-TELZA**. Patients taking NSAIDs and **CO-TELZA** should be sufficiently hydrated and be monitored for renal function at the beginning of, and during, combined treatment.

Additional information of CO-TELZA interaction:

The pharmacokinetics of telmisartan, as in **CO-TELZA**, are not affected by the hydrochlorothiazide in **CO-TELZA**.

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

Alcohol, barbiturates, narcotics:

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

Antidiabetic medicines (oral medicines and insulin):

- Treatment with hydrochlorothiazide, as in **CO-TELZA**, 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 **CO-TELZA** is co-administered with metformin.

Cholestyramine and colestipol resins:

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

Digoxin:

- Hypokalaemia or hypomagnesaemia, induced by hydrochlorothiazide, as in **CO-TELZA**, favours the onset of digoxin-induced cardiac dysrhythmias.

Pressor amines (e.g., noradrenaline):

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

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

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

Treatment for gout:

- Hydrochlorothiazide, as in **CO-TELZA**, may increase levels of serum uric acid, therefore dosage adjustment of uricosuric medicines may be necessary.

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

Calcium salts:

- Hydrochlorothiazide, as in **CO-TELZA**, 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 **CO-TELZA**. Anticholinergic medicines (e.g. biperiden, atropine) may increase the bioavailability of hydrochlorothiazide, as in **CO-TELZA**, by decreasing stomach emptying rate and gastrointestinal motility. Hydrochlorothiazide, as in **CO-TELZA**, may increase the risk of adverse effects caused by amantadine.

Hydrochlorothiazides, as in **CO-TELZA**, may reduce the renal excretion of cytotoxic medicines (e.g., methotrexate, cyclophosphamide) and increase their myelosuppressive effects.

Concurrent hypovolaemia may induce acute renal failure when taking **CO-TELZA**.

Administration of hydrochlorothiazide, as in **CO-TELZA**, with vitamin D may potentiate a rise in serum calcium.

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

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

Food does not affect the bioavailability of telmisartan, as in **CO-TELZA**.

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, **CO-TELZA** should be discontinued.

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

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

Should exposure to **CO-TELZA** have occurred during pregnancy, ultrasound check of renal function and skull is recommended.

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

Hydrochlorothiazide as contained in **CO-TELZA**, cross 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 thrombocytopaenia and foetal, or neonatal, jaundice have been reported with maternal thiazide therapy.

Breastfeeding:

CO-TELZA 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 **CO-TELZA**, is excreted in human milk. Hydrochlorothiazide appears in human milk and may inhibit lactation.

Fertility:

No studies on fertility in humans have been performed. In preclinical 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

The effect of **CO-TELZA** on the ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Tabulated list of adverse reactions:

Fixed-dose combination CO-TELZA:

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 erythematous*
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
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*

Hepato-biliary 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 and connective tissue 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 uric acid, increase in creatinine, increased blood creatinine phosphokinase, increase in liver enzymes

***** Post-marketing side effects reported with **CO-TELZA**.

Telmisartan monotherapy:

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	Anaemia, thrombocytopenia

	Frequency unknown	Eosinophilia*
Immune system disorders	Less frequent Frequency unknown	Hypersensitivity Anaphylactic reaction*
Nervous system disorders	Less frequent	Somnolence
Metabolism and nutrition disorders	Less frequent	Hyperkalaemia, hypoglycaemia (in diabetic patients)
Cardiac disorders	Less frequent	Bradycardia
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Cough Interstitial lung disease
Gastrointestinal disorders	Less frequent	Stomach discomfort, taste disturbance, taste loss
Skin and subcutaneous tissue disorders	Less frequent	Eczema, drug eruption, toxic skin eruption
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	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
Investigations	Less frequent	Haemoglobin decreased

Hydrochlorothiazide monotherapy (Post-marketing experience):

System Organ Class:	Frequency:	Side effects:

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	Frequent Frequency unknown	Electrolyte imbalance, volume depletion Anorexia, loss of appetite, hypercholesterolaemia, hyperglycaemia
Psychiatric disorders	Frequency unknown	Restlessness
Nervous system disorders	Less frequent Frequency unknown	Headache Light-headedness
Eye disorders	Frequency unknown	Yellow vision (xanthopsia), acute myopia, acute angle-closure glaucoma

Vascular disorders	Frequency unknown	Necrotising angitis (vasculitis)
Gastrointestinal disorders	Frequent Less frequent	Nausea Upset stomach, pancreatitis
Hepato-biliary disorders	Less frequent	Jaundice hepatocellular, jaundice cholestatic
Skin and subcutaneous tissue disorders	Less frequent	Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions (or reactivation of cutaneous lupus erythematosus), photosensitivity reactions, cutaneous vasculitis
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Weakness
Renal and urinary disorders	Frequency unknown	Glycosuria, renal failure, interstitial nephritis
General disorders and administrative site conditions	Frequency unknown	Fever
Investigations	Frequency unknown	Increase in triglycerides

Description of selected adverse reactions:

Hepatic function abnormal/ liver disorder:

Most cases of hepatic function abnormal/ 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:

Reported suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/ risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**,found online under SAHPRA's publications: www.sahpra.org.za

4.9 Overdose

Signs and symptoms:

Limited information is available for **CO-TELZA** overdose in humans. The most prominent side effects following overdose of telmisartan, as in **CO-TELZA**, are bradycardia, hypotension and tachycardia. Overdose with hydrochlorothiazide,as in **CO-TELZA**, 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 **CO-TELZA**, is not removed by haemodialysis.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC Code: C09CA07.

Pharmacological classification: A 7.1.3 Vascular medicines – Other hypotensives.

CO-TELZA 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 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. An 80 mg dose in humans almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and is still measurable 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- long-term therapy. The binding of telmisartan to AT_1 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 the antihypertensive effect of hydrochlorothiazide has not been elucidated. Hydrochlorothiazide affects the 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, without increasing the renal excretion of potassium and bicarbonate.

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 ($AUC_{0-\infty}$) 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.

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 (V_{dss}) 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 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 (C_{max} 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 dose 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Hypromellose

Lactose monohydrate

Magnesium stearate

Mannitol

Meglumine

Povidone K 25

Silica colloidal anhydrous

Sodium hydroxide

Sodium stearyl fumarate

Talc.

Contains the following colourants:

Iron oxide red (in **CO-TELZA 40/12,5; 80/12,5** and **80/25**) and iron oxide yellow (in **CO-TELZA 80/25**).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Silver aluminium/aluminium blister strips containing 10 or 15 tablets each, packed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

13 Pasita Street

Rosen Heights

Rosen Park

Bellville

7530

South Africa

8. REGISTRATION NUMBERS

CO-TELZA 40/12,5: 51/7.1.3/0181

CO-TELZA 80/12,5: 51/7.1.3/0182

CO-TELZA 80/25: 51/7.1.3/0183

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 23 February 2021