Boehringer Ingelheim

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

CO-PRITOR® 40/12,5 mg
CO-PRITOR® 80/12,5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CO-PRITOR 40/12,5 mg: Each double layered tablet contains 40 mg telmisartan and 12,5 mg hydrochlorothiazide.
CO-PRITOR 80/12,5 mg: Each double layered tablet contains 80 mg telmisartan and 12,5 mg hydrochlorothiazide.

Contains sugar (112 mg lactose monohydrate per tablet) and sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

CO-PRITOR 40/12,5 mg: Oblong biconvex double layer tablets, first layer white to off-white, second layer red. Very small red particles from the second layer may be visible in the first layer. Boehringer Ingelheim Company symbol and “H4” engraved in the white layer. Diameter: 6,8 x 14,0 mm.

CO-PRITOR 80/12,5 mg: Oblong biconvex double layer tablets, first layer white to off-white, second layer red. Very small red particles from the second layer may be visible in the first layer. Boehringer Ingelheim Company symbol and “H8” engraved in the white layer. Diameter: 7,9 x 16,2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CO-PRITOR 40/12,5 mg and 80/12,5 mg

Treatment of mild to moderate essential hypertension. CO-PRITOR is indicated in adult 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-PRITOR should be taken once daily.
Two dosage strengths are provided: 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 changed to the appropriate combination dosage.

Sodium and/or volume depletion should be corrected before treatment commencement with CO-PRITOR.

When considering changing the patient's therapy with CO-PRITOR 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, CO-PRITOR may be administered with another antihypertensive medicine.

Special populations

Renal impairment

Due to the hydrochlorothiazide component, CO-PRITOR must not be used 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.
Telmisartan is not removed from blood by haemofiltration and is not dialysable.

Hepatic impairment

In patients with mild (Child-Pugh Class A) to moderate (Child-Pugh Class B) hepatic impairment CO-PRITOR should be administered with caution. For telmisartan, the dosage should not exceed 40 mg once daily (see section 4.3). Thiazides should be used with caution in patients with impaired hepatic function.

Geriatric patients

No dosage adjustment is necessary.

Paediatric patients

There are no data on the safety and efficacy of CO-PRITOR in patients aged below 18 years.
Use of CO-PRITOR is not recommended in children and adolescents.

Method of administration

CO-PRITOR tablets are for once-daily oral administration and should be swallowed whole with liquid. CO-PRITOR can be taken with or without food.

Handling instructions

Due to the hygroscopic property of the tablets they should be taken out of the sealed blister shortly before administration.

4.3 Contraindications

- Hypersensitivity to any of the active substances of CO-PRITOR or to any of the excipients listed in section 6.1.
- Hypersensitivity to other sulphonamide-derived substances
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs): These 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) or serum creatinine > 1,8 mg/100 mL), anuria, or acute glomerulonephritis
- 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 section 4.4 and 4.5)
- Porphyria
- Thiazide diuretics in (fixed dose) combination (CO-PRITOR) should not be given to patients with Addison's disease. This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines
- Lithium therapy: Concomitant administration with CO-PRITOR may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.4 and 4.6)
- The concomitant use of CO-PRITOR with aliskiren-containing products is contraindicated (see section 4.4 and 4.5)
- Biliary obstructive disorders
- Severe hepatic impairment, biliary cirrhosis, cholestasis, coma heparicum, hepatic precoma
- Therapy-refractory hyponatraemia
- Hypovolaemia
- Symptomatic hyperuricaemia/gout
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia
- In case of rare hereditary conditions that may be incompatible with an excipient of the product, the use of CO-PRITOR is contraindicated. Patients with fructose intolerance should not take CO-PRITOR. Patients with galactosaemia should not take CO-PRITOR. (See section 4.4)
- Concomitant use of fluoroquinolones with ACE inhibitors/Angiotensin receptor blockers is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance $\leq$ 30 mL/min) and in elderly patients.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Pregnancy

CO-PRITOR should not be initiated during pregnancy.

Should a woman become pregnant while receiving CO-PRITOR, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.4 and 4.6). Should a woman contemplate pregnancy, the doctor should consider alternative medication.

Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy.
When pregnancy is diagnosed, treatment with CO-PRITOR 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 renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-

angiotensin-aldosterone system (See section 4.3.)

Renal impairment and kidney transplant
CO-PRITOR must not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see section 4.3). 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 CO-PRITOR in patients with severe renal impairment or with a recent kidney transplant. (See section 4.3.)

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

Volume and/or sodium depleted patients
Symptomatic hypotension, especially after the first dose, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting.

Volume and/or sodium depletion, should be corrected before the administration of CO-PRITOR.
Cases of hyponatraemia accompanied by neurological symptoms (nausea, progressive disorientation, apathy) have been observed with the use of HCTZ.

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 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-PRITOR and aliskiren is therefore contraindicated (see section 4.3). CO-PRITOR should not be used concomitantly with aliskiren (see section 4.3).

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

Concomitant use of fluoroquinolones
Concomitant use of fluoroquinolones and 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 concomitantly.

Primary aldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of CO-PRITOR is not recommended.

Mitral valve stenosis
Special caution is indicated in patients suffering from mitral stenosis.

Hyperkalaemia
During treatment with other medicinal products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. While this is not documented with telmisartan (as in CO-PRITOR), adequate monitoring of serum potassium in patients at risk is recommended.
Based on experience with the use of other medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with CO-PRITOR.

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 must not be given to these patients (see section 4.3).
CO-PRITOR 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 CO-PRITOR in patients with hepatic impairment.
Other metabolic disturbances
Thiazide therapy, as in CO-PRITOR, may impair glucose tolerance. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required. Latent diabetes mellitus may become manifest during CO-PRITOR therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy, as in CO-PRITOR.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy, as in CO-PRITOR.

Electrolyte imbalance
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 be undertaken with caution. 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 ACTH. Conversely, due to the antagonism of the angiotensin II (AT_1) receptors by the telmisartan component of CO-PRITOR, hyperkalaemia might occur. Frequent monitoring of serum potassium is

recommended.

Treatment with thiazide diuretics, as in CO-PRITOR, has been associated with hyponatraemia and hypochloroaemic alkalosis.

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

Thiazides, as in CO-PRITOR, increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Warning signs or symptoms of fluid and electrolyte imbalance, 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.

Systemic lupus erythematosus
Thiazide diuretics, as in CO-PRITOR, have been reported to exacerbate 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 agents such as ARBs or ACE-inhibitors. In patients with diabetes mellitus CAD may be asymptomatic and therefore undiagnosed. Patients with diabetes mellitus should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating treatment with CO-PRITOR.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma
Hydrochlorothiazide, a sulfonamide, 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 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-PRITOR 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.
Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.
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 minimize the risk of skin cancer. CO-PRITOR 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).

Ischaemic heart disease
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 CO-PRITOR, may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Cases of photosensitivity reactions have been reported with use of thiazide diuretics (see Adverse reactions). In the event of a photosensitivity reaction occurring during treatment, discontinuation of the treatment is recommended. If resumption of the treatment is essential, areas exposed to the sun or to artificial UVA rays should be protected.

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, CO-PRITOR should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Sorbitol
The maximum recommended daily dose of CO-PRITOR contains 169 mg sorbitol in the 40/12,5 mg dose strength, or 338 mg sorbitol in the 80/12,5 mg dose strength. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Lactose
The maximum recommended daily dose of CO-PRITOR contains 112 mg of lactose monohydrate in the 40/12,5 mg and 80/12,5 mg dose strengths. Patients with the rare hereditary condition of galactose intolerance e.g. galactosaemia should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction
Interactions linked to telmisartan
Telmisartan, as in CO-PRITOR, may increase the hypotensive effect of other

antihypertensive agents.

Co-administration of telmisartan, as in CO-PRITOR, 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 39 %); 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.

Lithium
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists, including telmisartan (as in CO-PRITOR). Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with CO-PRITOR. (See section 4.3).

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 who are dehydrated. Compounds acting on the renin-angiotensin system like CO-PRITOR may have synergistic effects. Patients receiving NSAIDs and CO-PRITOR should be adequately hydrated and be monitored for renal function at the beginning of, and during, combined treatment.
A reduced effect of antihypertensive medicines like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.
The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of CO-PRITOR.

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 section 4.3 and 4.4).

Fluoroquinolones
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).

Additional information on CO-PRITOR interaction
The pharmacokinetics of telmisartan are not affected by co-administration of hydrochlorothiazide.

Interactions linked to hydrochlorothiazide (HCTZ)
The antihypertensive effect of HCTZ can be potentiated by other diuretics, antihypertensive medicines, guanethidine, methyldopa, calcium antagonists, ACE inhibitors, ARBs, DRIs, beta-receptor blockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressants, vasodilators or by alcohol consumption.

Salicylates and other non-steroidal anti-inflammatory drugs (e.g. indomethacin) may reduce the antihypertensive and diuretic effect of HCTZ. In patients taking high-dose salicylates, the toxic effect of salicylates on the central nervous system may be potentiated. In patients developing hypovolaemia during treatment with HCTZ, concomitant administration of non-steroidal anti-inflammatory drugs may trigger acute renal failure.

Co-administration of thiazides (including hydrochlorothiazide) and allopurinol may possibly increase the frequency of hypersensitivity reactions to allopurinol. Co-administration of thiazides and amantadine may possibly increase the risk of amantadine-related adverse reactions.

There is an increased risk for the onset of hyperglycaemia with concomitant administration of HCTZ and beta-receptor blockers.

The effect of insulin or oral antidiabetics, uric acid-lowering medicines, as well as norepinephrine and epinephrine, may be attenuated with concomitant use of HCTZ. An adjustment of the insulin or oral antidiabetic dosage may therefore be required.

In concomitant treatment with cardiac glycosides, it must be remembered that myocardial sensitivity to cardiac glycosides will be increased by any hypokalaemia and/or hypomagnesaemia that develops during HCTZ therapy, thereby potentiating the effects and adverse effects of these cardiac glycosides.

Concomitant use of HCTZ and kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, carbenoxolone, penicillin G, salicylates, amphotericin B, antiarrhythmics or laxatives may lead to increased potassium loss.

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.

Concomitant use of natriuretic diuretics and antidepressants, antipsychotics or antiepileptics may lead to increased sodium loss.

Concomitant use of thiazide diuretics and cytotoxic medicines (e.g. cyclophosphamide, fluorouracil, methotrexate) may lead to a reduction in the renal excretion of cytotoxic medicines. Increased bone marrow toxicity (especially granulocytopenia) can be expected.

The bioavailability of thiazide diuretics may be increased by anticholinergic medicines (e.g. atropine, biperiden). This is probably due to a decrease in gastrointestinal motility and the gastric emptying rate. In contrast, prokinetic medicinal products such as cisapride may reduce the bioavailability of thiazide

diuretics.

Diuretics increase plasma lithium levels. As concomitant administration of HCTZ and lithium leads to potentiation of the cardio-and neurotoxic effects of lithium due to decreased lithium excretion, the lithium level must be monitored in patients receiving HCTZ and lithium. In patients in whom lithium has induced polyuria, diuretics can have a paradoxical antidiuretic effect.

The effect of curare-like muscle relaxants may be potentiated or prolonged by HCTZ. In cases where HCTZ cannot be discontinued before the use of curare-like muscle relaxants, the anaesthetist must be informed of the treatment with HCTZ.

Concomitant use of cholestyramine or colestipol reduces the absorption of HCTZ. However, the interaction may possibly be minimized by staggered dosing of hydrochlorothiazide and the resinate, so that hydrochlorothiazide is taken at least 4 hours before or 4-6 hours after administration of the resinate.

Concomitant use with vitamin D may reduce the excretion of calcium via the urine and potentiate the increase of calcium in serum.

When co-administered with calcium salts, hypercalcaemia may occur due to the increase in tubular calcium reuptake.

Concomitant use with ciclosporin may increase the risk of hyperuricaemia and gout-like complications.

Thiazides can increase the hyperglycaemic effect of diazoxide.

During concomitant use of methyldopa, there have been uncommon reports of haemolysis, caused by the formation of antibodies against hydrochlorothiazide.

Hydrochlorothiazide may reduce the response to adrenergic amines, such as norepinephrine.

Medicinal products 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, ACTH, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid and derivatives). If these medicines are to be prescribed with CO-PRITOR, 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, salt substitutes containing potassium or other medicines that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. If these medicines are to be prescribed with CO-PRITOR, monitoring of potassium plasma levels is advised. (See section 4.3.)

Medicinal products affected by serum potassium disturbances
Periodic monitoring of serum potassium is recommended when CO-PRITOR 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).

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety in pregnancy and lactation has not been established (see section 4.3).

When pregnancy is planned or confirmed CO-PRITOR should be discontinued. Refer to section 4.3 and 4.4.

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

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

Women of childbearing age should ensure effective contraception.

Should exposure to CO-PRITOR have occurred during pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken CO-PRITOR should be closely observed for hypotension.

Thiazides, as in CO-PRITOR, 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 thiazide therapy.

Breastfeeding
CO-PRITOR is contraindicated during lactation, since it is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk. Thiazides appear in human milk and may inhibit lactation.

Fertility
No studies on fertility in humans with the fixed dose combination or with the individual components have been performed.
In non-clinical studies, no effects of telmisartan and hydrochlorothiazide on male and female fertility were observed.

4.7 Effects on the ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, it should be taken into account that dizziness, syncope or vertigo may occur when taking antihypertensive therapy.
If patients experience these adverse events, they should avoid potentially hazardous

tasks such as driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

The following side effects derived from the use of the CO-PRITOR (telmisartan and hydrochlorothiazide combination) or the use of the monocomponents (telmisartan or hydrochlorothiazide) in clinical trials or from post-marketing experience are shown in the table below classified by MedDRA System organ class and MedDRA Preferred terms.

The following frequency classification is used:
very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100; rare ≥ 1/10 000 and < 1/1 000; very rare < 1/10 000; not known: cannot be estimated from the available data.

MedDRA preferred term:	Frequency for CO-PRITOR (telmisartan and hydrochlorothiazide fixed dose combination)	Frequency for telmisartan as monotherapy	Frequency for hydrochlorothiazide as monotherapy
Infections and infestations			
Sepsis (including fatal outcome)	-	Rare	-
Bronchitis	Rare	-	-
Pharyngitis	Rare	-	-
Sinusitis	Rare	-	-
Upper respiratory tract infection	-	Uncommon	-
Urinary tract infection	-	Uncommon	-
Cystitis	-	Uncommon	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of skin or lip)	-	-	Not known
Blood and lymphatic system disorders			
Anaemia	-	Uncommon	-
Thrombocytopenia	-	Rare	Rare
Thrombocytopenic purpura	-	-	Rare
Eosinophilia	-	Rare	-
Aplastic anaemia	-	-	Not known
Haemolytic anaemia	-	-	Very rare
Bone marrow failure	-	-	Very rare
Leukopenia	-	-	Very rare
Agranulocytosis	-	-	Very rare
Immune system disorders			

MedDRA preferred term:	Frequency for CO-PRITOR (telmisartan and hydrochlorothiazide fixed dose combination)	Frequency for telmisartan as monotherapy	Frequency for hydrochlorothiazide as monotherapy
Anaphylactic reaction	-	Rare	-
Hypersensitivity	-	Rare	Very rare
Metabolism and nutrition disorders			
Hypokalaemia	Uncommon	-	Very common
Hyponatraemia	Rare	Rare	Common
Hyperuricaemia	Rare	-	Common
Hyperkalaemia	-	Uncommon	-
Hypoglycaemia (in diabetic patients)	-	Rare	-
Decreased appetite	-	-	Common
Hyperglycaemia	-	-	Rare
Hypomagnesaemia	-	-	Common
Hypercalcaemia	-	-	Rare
Hypochloraemic alkalosis	-	-	Very rare
Hyperlipidaemia	-	-	Very common
Diabetes mellitus - inadequate control	-	-	Rare
Psychiatric disorders			
Anxiety	Uncommon	Rare	-
Depression	Rare	Uncommon	Rare
Insomnia	Rare	Uncommon	-
Nervous system disorders			
Dizziness	Common	-	Rare
Syncope (fainting)	Uncommon	Uncommon	-
Paraesthesia	Uncommon	-	Rare
Sleep disorder	Rare	-	Rare
Headache	-	-	Rare
Eye disorders			
Visual impairment	Rare	Rare	Rare
Blurred vision	Rare	-	-
Angle-closure glaucoma	-	-	Not known
Choroidal effusion	-	-	Not known
Ear and labyrinth disorders			
Vertigo	Uncommon	Uncommon	-
Cardiac disorders			
Dysrhythmia	Uncommon	-	Rare
Tachycardia	Uncommon	Rare	-
Bradycardia	-	Uncommon	-
Vascular disorders			
Hypotension	Uncommon	Uncommon	-

MedDRA preferred term:	Frequency for CO-PRITOR (telmisartan and hydrochlorothiazide fixed dose combination)	Frequency for telmisartan as monotherapy	Frequency for hydrochlorothiazide as monotherapy
Orthostatic hypotension	Uncommon	Uncommon	Common
Necrotising vasculitis	-	-	Very rare
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Uncommon	Uncommon	-
Respiratory distress	Rare	-	Very rare
Pneumonitis	Rare	-	Very rare
Pulmonary oedema	Rare	-	Very rare
Acute respiratory distress syndrome	-	-	Very rare
Gastrointestinal disorders			
Diarrhoea	Uncommon	Uncommon	Common
Dry mouth	Uncommon	Rare	-
Flatulence	Uncommon	Uncommon	-
Abdominal pain	Rare	Uncommon	-
Constipation	Rare	-	Rare
Dyspepsia	Rare	Uncommon	-
Vomiting	Rare	Uncommon	Common
Gastritis	Rare	-	-
Abdominal discomfort	-	Rare	Rare
Pancreatitis	-	-	Very rare
Nausea	-	-	Common
Hepatobiliary disorders			
Abnormal hepatic function / liver disorder	Rare	Rare	-
Jaundice	-	-	Rare
Cholestasis	-	-	Rare
Skin and subcutaneous tissue disorders			
Angioedema (with fatal outcome)	Rare	Rare	-
Erythema	Rare	Rare	-
Pruritus	Rare	Uncommon	-
Rash	Rare	Uncommon	Common
Hyperhidrosis	Rare	Uncommon	-
Urticaria	Rare	Rare	Common
Eczema	-	Rare	-
Drug eruption	-	Rare	-
Toxic skin eruption	-	Rare	-
Toxic epidermal necrolysis	-	-	Very rare
Lupus-like syndrome	-	-	Very rare
Cutaneous lupus erythematosus	-	-	Very rare

MedDRA preferred term:	Frequency for CO-PRITOR (telmisartan and hydrochlorothiazide fixed dose combination)	Frequency for telmisartan as monotherapy	Frequency for hydrochlorothiazide as monotherapy
Photosensitivity reaction	-	-	Rare
Erythema multiforme	-	-	Not known
Musculoskeletal and connective tissue disorders			
Back pain	Uncommon	Uncommon	-
Muscle spasm (cramps in legs)	Uncommon	Uncommon	Not known
Myalgia	Uncommon	Uncommon	-
Arthralgia	Rare	Rare	-
Pain in extremity (leg pain)	Rare	Rare	-
Tendon pain (tendonitis like symptoms)	-	Rare	-
Systemic lupus erythematosus	Rare	-	-
Renal and urinary disorders			
Renal impairment (including acute kidney injury)	-	Uncommon	Not known (renal impairment), Uncommon (acute kidney injury)
Glycosuria	-	-	Rare
Reproductive system and breast disorders			
Erectile dysfunction	Uncommon	-	Common
General disorders and administration site conditions			
Chest pain	Uncommon	Uncommon	-
Influenza like illness	Rare	Rare	-
Pain	Rare	-	-
Asthenia (weakness)	-	Uncommon	Not known
Pyrexia	-	-	Not known
Investigations			
Blood uric acid increased	Uncommon	Rare	-
Blood creatinine increased	Rare	Uncommon	-
Hepatic enzyme increased	Rare	Rare	-
Blood creatine Phosphokinase increased	Rare	Rare	-
Haemoglobin decreased	Rare	Rare	-

Reporting of suspected adverse reactions
Reporting 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 the South African Health Products Regulatory Authority (SAHPRA) the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. Suspected adverse reactions can also be reported directly to the holder of the certificate of registration using the email address pv_local_south_africa@boehringer-ingelheim.com.

4.9 Overdose
Limited information is available for CO-PRITOR with regard to overdose in humans.

Symptoms
The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred. Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and dehydration resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence.
Hypokalaemia may result in muscle spasm and/or accentuate cardiac dysrhythmias associated with the concomitant use of digoxin or certain anti-dysrhythmic medicines.

Therapy
No specific information is available on the treatment of overdosage with CO-PRITOR. The patient should be closely monitored, and the treatment should be symptomatic and supportive depending on the time since ingestion and the severity of the symptoms. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. Telmisartan is not removed by haemofiltration and is not dialyzable. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A 7.1.3 Vascular medicines – other hypotensives

CO-PRITOR 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 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. In man, an

80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.
After administration of the first dose of CO-PRITOR, onset of antihypertensive activity occurs within 3 hours. The maximum reduction in blood pressure is generally attained 4 weeks after the start of treatment and is sustained during long-term therapy.
The antihypertensive effect persists over 24 hours after dosing.
There is an apparent trend to a dose relationship with regard to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.

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.
Beneficial effects of telmisartan on mortality and cardiovascular morbidity are currently unknown.

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.

5.2 Pharmacokinetic properties

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

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

When CO-PRITOR is taken with food, 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). After 3 hours post administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The pharmacokinetics of orally administered telmisartan are non-linear over doses from 20 – 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated administration in healthy volunteers.

Hydrochlorothiazide: Following oral administration of CO-PRITOR peak concentrations of hydrochlorothiazide are reached in approximately 1,0 – 3,0 hours

after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60 %.
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 mean steady state apparent volume of distribution (V_{dss}) is approximately 500 L indicating additional tissue binding.

Hydrochlorothiazide: Hydrochlorothiazide is 64 % protein bound in the plasma and its apparent volume of distribution is 0,8 ± 0,3 L/kg.

Biotransformation and elimination
Telmisartan: Following either intravenous or oral administration of ^{14}C-labelled telmisartan, most of the administered dose (> 97 %) was eliminated in faeces via biliary excretion. Only minute amounts were found in urine.
Telmisartan is metabolised by conjugation to form a pharmacologically inactive acylglucuronide. The glucuronide of the parent compound is the only metabolite that has been identified in humans.
After a single dose of ^{14}C-labelled telmisartan the glucuronide represents approximately 11 % of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan. Total plasma clearance of telmisartan after oral administration is > 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 – 300 mL/min in healthy volunteers. The terminal pharmaceutical elimination half-life of hydrochlorothiazide is 10 – 15 hours, although the biological effects last longer.

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

Gender
Telmisartan: Plasma concentrations of telmisartan are generally 2 – 3 times higher in females than in males without relevant influence on efficacy. 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.

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 – 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 after a single dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose
Povidone
Red iron oxide
Sodium hydroxide
Sodium starch glycolate
Sorbitol.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C. Keep out of reach of children.
CO-PRITOR tablets should not be removed from their foil pack until required for administration in order to protect the product from moisture.

6.5 Nature and contents of container

Carton containing 28 tablets packed in aluminium blister strips of 7 tablets per strip.

6.6 Special precautions for disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ingelheim Pharmaceuticals (Pty) Ltd
Suite 1, Building 4, 2nd Floor
Waterfall Corporate Campus
74 Waterfall Drive
Midrand
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8. REGISTRATION NUMBERS

CO-PRITOR 40/12,5 mg tablets: 35/7.1.3/0347
CO-PRITOR 40/12,5 mg tablets: 35/7.1.3/0348

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 20 September 2002

10. DATE OF REVISION OF THE TEXT

24 June 2025

NAMIBIA Reg. No.	
CO-PRITOR 40/12,5 mg: 10/7.1.3/0271	NS2
CO-PRITOR 80/12,5 mg: 10/7.1.3/0272	