APPROVED PROFESSIONAL INFORMATION: CO-MICARDIS

SCHEDULING STATUS: S_3

PROPRIETARY NAME AND DOSAGE FORM:

Co-Micardis® 40/12,5 mg tablets abcd
Co-Micardis® 80/12,5 mg tablets
Co-Micardis® 80/25 mg tablets

COMPOSITION:
CO-MICARDIS 40/12,5 mg: Each double layered tablet contains 40 mg telmisartan and 12,5 mg hydrochlorothiazide.
CO-MICARDIS 80/12,5 mg: Each double layered tablet contains 80 mg telmisartan and 12,5 mg hydrochlorothiazide.
CO-MICARDIS 80/25 mg: Each double layered tablet contains 80 mg telmisartan and 25 mg hydrochlorothiazide.
Inactive ingredients: lactose monohydrate, magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone, red iron oxide (or yellow iron oxide in the case of CO-MICARDIS 80/25 mg), sodium hydroxide, sodium starch glycolate and sorbitol.

Contains sugar (lactose and sorbitol).

PHARMACOLOGICAL CLASSIFICATION:
A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties:
CO-MICARDIS 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 AT_1) antagonist. It displaces angiotensin II from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds at the AT_1 receptor. The binding is long-lasting. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. In 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-MICARDIS, 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.

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-MICARDIS is taken with food, 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). 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 (C_{max} and AUC) with increasing doses. Telmisartan does not accumulate significantly in plasma on repeated administration in healthy volunteers.

Hydrochlorothiazide: Following oral administration of CO-MICARDIS 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.

INDICATIONS:
CO-MICARDIS 40/12,5 mg and 80/12,5 mg:
Treatment of mild to moderate hypertension. CO-MICARDIS is indicated in patients whose blood pressure has been stabilised at the same dosage of the individual components given together.

CO-MICARDIS 80/25 mg:
Treatment of essential hypertension in patients whose blood pressure is not adequately controlled on CO-MICARDIS 80/12,5 mg (80 mg telmisartan and 12,5 mg hydrochlorothiazide) or patients who have been previously stabilised
on the same dosage of the individual components of CO-MICARDSIS 80/25 mg (telmisartan 80 mg and hydrochlorothiazide 25 mg) given together.

CONTRAINDICATIONS:
- Hypersensitivity to any of the ingredients of CO-MICARDIS
- A history of angioedema related to previous therapy with angiotensin-converting enzyme (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)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **INTERACTIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**)
- Porphyria
- Thiazide diuretics in (fixed dose) combination (CO-MICARDIS) 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-MICARDIS may lead to toxic blood concentrations of lithium (see **INTERACTIONS**)
- Pregnancy and lactation (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION**)
- The concomitant use of CO-MICARDIS with aliskiren-containing products is contraindicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**)
- Biliary obstructive disorders
- Severe hepatic impairment, biliary cirrhosis and cholestasis
- 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-MICARDIS is contraindicated. Patients with fructose intolerance should not take CO-MICARDIS. Patients with galactosaemia should not take CO-MICARDIS. (See **WARNINGS AND SPECIAL PRECAUTIONS.)**
- Concomitant use of fluoroquinolones with Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance $\leq$ 30 mL/min) and in elderly patients.

WARNINGS AND SPECIAL PRECAUTIONS:

Pregnancy:

CO-MICARDIS should not be initiated during pregnancy.

Should a woman become pregnant while receiving CO-MICARDIS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see CONTRAINDICATIONS and PREGNANCY AND LACTATION). 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-MICARDIS should be stopped immediately and, if appropriate, alternative therapy should be started. **(**See **CONTRAINDICATIONS.)**

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 **CONTRAINDICATIONS**).

Renal impairment and kidney transplant:

CO-MICARDIS should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min) (see **CONTRAINDICATIONS**). Thiazide diuretic-associated uraemia may occur in patients with impaired renal function.
In patients with mild to moderate renal impairment, periodic monitoring of potassium, creatinine and uric acid levels is mandatory. There is no experience regarding the administration of CO-MICARDIS in patients with severe renal impairment or with a recent kidney transplant. **(**See **CONTRAINDICATIONS.)**

Intravascular volume depletion:

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers 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-MICARDIS and aliskiren is therefore contraindicated

(see **CONTRAINDICATIONS**). CO-MICARDIS should not be used concomitantly with aliskiren (see **CONTRAINDICATIONS**).

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

Concomitant use of fluoroquinolones:
Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See **CONTRAINDICATIONS**.) Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzyme (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-MICARDIS 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-MICARDIS), 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-MICARDIS.

Hepatic impairment:
Telmisartan is mostly eliminated in the bile. Patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, telmisartan should not be given to these patients – see **CONTRAINDICATIONS**. CO-MICARDIS 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-MICARDIS in patients with hepatic impairment.

Other metabolic disturbances:
Thiazide therapy, as in CO-MICARDIS, 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-MICARDIS therapy.
An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy, as in CO-MICARDIS.
Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy, as in CO-MICARDIS.

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

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) should 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-MICARDIS, hyperkalaemia might occur. Frequent monitoring of serum potassium is recommended.
Treatment with thiazide diuretics, as in CO-MICARDIS, has been associated with hyponatraemia and hypochloroaemic alkalosis.
Thiazides, as in CO-MICARDIS, 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-MICARDIS should be discontinued before carrying out tests for parathyroid function.
Thiazides, as in CO-MICARDIS, 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-MICARDIS, 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-MICARDIS.

Acute myopia and secondary angle-closure glaucoma:
Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of 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.

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

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

Sorbitol:
The maximum recommended daily dose of CO-MICARDIS contains 169 mg sorbitol in the 40/12,5 mg dose strength, or 338 mg sorbitol in the 80/12,5 mg and 80/25 mg dose strengths. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Lactose:
The maximum recommended daily dose of CO-MICARDIS contains 112 mg of lactose monohydrate in the 40/12,5 mg and 80/12,5 mg dose strengths, and 99 mg lactose monohydrate in the 80/25 mg dose strength. Patients with the rare hereditary condition of galactose intolerance e.g. galactosaemia should not take this medicine.

Effects on ability to drive and use machines:
No studies on the effect on the ability to drive and use machines have been performed. However, it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

INTERACTIONS:
Telmisartan, as in CO-MICARDIS, may increase the hypotensive effect of other antihypertensive agents.

Co-administration of telmisartan, as in CO-MICARDIS, 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-MICARDIS). Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with CO-MICARDIS. (See **CONTRAINDICATIONS**.)

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-MICARDIS, 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-MICARDIS, monitoring of potassium plasma levels is advised. (See **CONTRAINDICATIONS**.)

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

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-MICARDIS may have synergistic effects. Patients receiving NSAIDs and CO-MICARDIS should be adequately hydrated and be monitored for renal function at the beginning of, and during, combined treatment.
The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of CO-MICARDIS.

Fluoroquinolones:

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) 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 **CONTRAINDICATIONS**).

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

When administered concurrently, the following medicines may interact with thiazide diuretics (as in CO-MICARDIS):
Alcohol, barbiturates, or narcotics: potentiation of orthostatic hypotension may occur;
Antidiabetic medicines (oral agents and insulins): dosage adjustment of the antidiabetic medicine may be required;
Metformin: there is a risk of lactic acidosis when co-administered with hydrochlorothiazide (as in CO-MICARDIS);
Cholestyramine and colestipol resins: absorption of hydrochlorothiazide in CO-MICARDIS is impaired in the presence of anionic exchange resins;
Digoxin: thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digoxin-induced cardiac dysrhythmias;
Pressor amines (e.g. noradrenaline): the effect of pressor amines may be decreased;
Nondepolarizing skeletal muscle relaxants: the effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide as in CO-MICARDIS;
Treatment for gout: dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide, as in CO-MICARDIS, may raise the level of serum uric acid. Co-administration of thiazide, as in CO-MICARDIS, may increase the incidence of hypersensitivity reactions of allopurinol;
Calcium salts: thiazide diuretics, as in CO-MICARDIS, may increase serum calcium levels due to the decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly;
Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren: clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS)**.
Other interactions: the hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides, as in CO-MICARDIS. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics, as in CO-MICARDIS, by decreasing gastrointestinal motility and stomach emptying rate. Thiazides, as in CO-MICARDIS, may increase the risk of adverse effects caused by amantadine. Thiazides, as in CO-MICARDIS, may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
Concurrent hypovolaemia may induce acute renal failure.
Administration of thiazide diuretics, as in CO-MICARDIS, with vitamin D may potentiate a rise in serum calcium.

There have been reports in the literature of haemolytic anaemia occurring with concomitant use with hydrochlorothiazide, as in CO-MICARDIS, and methyldopa.
Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

PREGNANCY AND LACTATION:
Pregnancy:
Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**).

When pregnancy is planned or confirmed CO-MICARDIS should be discontinued. Refer to **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS.**

Preclinical studies with telmisartan, as in CO-MICARDIS, do not indicate teratogenic effect, but have shown fetotoxicity.

Medicines affecting the renin-angiotensin system, such as CO-MICARDIS, 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-MICARDIS have occurred during pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken CO-MICARDIS should be closely observed for hypotension.

Thiazides, as in CO-MICARDIS, 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 thrombocytopenia and foetal, or neonatal, jaundice have been reported with maternal thiazide therapy.

Lactation:
CO-MICARDIS is contraindicated during lactation. It is not known whether telmisartan is excreted in human milk. Animal studies have shown excretion of telmisartan in breast milk. Thiazides appear in human milk and may inhibit lactation.

Fertility:
No studies on fertility in humans have been performed.
In preclinical studies, an effect of telmisartan and hydrochlorothiazide on male and female fertility was not observed.

DOSAGE AND DIRECTIONS FOR USE:
Adults:
CO-MICARDIS 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-MICARDIS 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-MICARDIS may be administered with another antihypertensive medicine.

Renal impairment:
Due to the hydrochlorothiazide component, CO-MICARDIS 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-MICARDIS 40/12,5 mg once daily. CO-MICARDIS is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

Elderly:
No dosage adjustment is necessary.

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

SIDE EFFECTS:
Fixed dose combination (CO-MICARDIS):

Adverse reactions reported in clinical trials with CO-MICARDIS (telmisartan plus hydrochlorothiazide) are shown below according to system organ class. Adverse reactions have been ranked under headings of frequency using the following convention:				
Very common (≥ 1/10)	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/100)**	**Rare (≥ 1/10 000, < 1/1 000)**	**Very rare (< 1/10 000)**
Infections and infestations:				
			bronchitis	
Metabolism and nutrition disorders:				
		hypokalaemia, hypoglycaemia	hyponatraemia, hyperuricaemia	
Psychiatric disorders:				
		anxiety	depression	
Nervous system disorders:				
	dizziness	syncope/fainting, paraesthesia	insomnia, sleep disturbances	
Eye disorders:				
			abnormal vision,	

			transient blurred vision	
Ear and labyrinth disorders:				
		vertigo		
Cardiac disorders:				
		tachycardia, cardiac dysrhythmias		
Vascular disorders:				
		hypotension, orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders:				
		dyspnoea	respiratory distress (including pneumonitis and pulmonary oedema)	
Gastrointestinal disorders:				
		diarrhoea, dry mouth, flatulence	abdominal pain, constipation, dyspepsia, vomitir	
Hepatobiliary disorders:				
			abnormal hepatic function/liver disorder	
Skin and subcutaneous tissue disorders:				
			angioedema (with fatal outcome), erythema, pruritus, rash, increased sweating, urticaria	
Musculoskeletal, connective tissue and bone disorders:				
		back pain, muscle spasm, myalgia	arthralgia, cramps in legs, leg pain	
Reproductive system and breast disorders:				
		impotence		
General disorders and administration site conditions:				
		chest pain	influenza-like symptoms,	

			pain	
Investigations:				
		increase in uric aci	increase in creatinine, increased blood creatine phosphokinase, increase in liver enzymes	

Post-marketing adverse reactions reported with CO-MICARDIS:	
Infections and infestations:	pharyngitis, sinusitis
Immune system disorders:	exacerbation or activation of systemic lupus erythematosus
Gastrointestinal disorders:	gastritis

Additional information on individual components
Undesirable effects previously reported with one of the individual components may be potential undesirable effects with CO-MICARDIS even if not observed in clinical trials with this product.

Telmisartan:

Additional side effects reported in clinical trials with telmisartan monotherapy (MICARDI in the indication hypertension or in patients 50 years or older at high risk of cardiovascular events were as follows:				
Very common (≥ 1/10)	**Common (≥ 1/100, < 1/10)**	**Uncommon (≥ 1/1 000, < 1/10**	**Rare (≥ 1/10 000, < 1/1 000)**	**Very rare (< 1/10 000)**
Infections and infestations:				
		urinary tract infections (including cystitis), upper respiratory tract infections		
Blood and the lymphatic system disorders:				
		anaemia	thrombocytopenia	
Immune system disorders:				
			hypersensitivity	
Metabolism and nutritional disorders:				
		hyperkalaemia	hypoglycaemia (in diabetic patients)	
Cardiac disorders:				

		bradycardia		
Gastrointestinal disorders:				
			stomach discomfort	
Skin and subcutaneous tissue disorders:				
			eczema, medicine eruption, toxic skin eruption	
Renal and urinary disorders:				
		renal impairment including acute renal failure		
General disorders and administration site conditions:				
		asthenia (weakness)		
Investigations:				
			decreased haemoglobin	

Post-marketing experience:

Hydrochlorothiazide: These side effects may be expected due to experience with hydrochlorothiazide as monotherapy:		
Frequent	**Less frequent**	**Frequencies are unknown**
Infections and infestations:		
		sialoadenitis
Blood and the lymphatic system disorders:		
	aplastic anaemia, haemolytic anaemia, bone marrow depression, leukopenia, neutropenia, agranulocytosis, thrombocytopenia	
Immune system disorders:		
	hypersensitivity, allergy, anaphylactic reactions	
Endocrine disorders:		
		loss of diabetic control
Metabolism and nutrition disorders:		
electrolyte imbalance, volum depletion		anorexia, loss of appetite, hypercholesterolaemia, hyperglycaemia
Psychiatric disorders:		
		restlessness
Nervous system disorders:		

		light-headedness
Eye disorders:		
		xanthopsia, acute myopia, acute angle-closure glaucoma
Vascular disorders:		
		necrotizing angiitis (vasculitis)
Gastrointestinal disorders:		
	pancreatitis, stomach upset	
Hepatobiliary disorders:		
	hepatocellular jaundice, cholestatic jaundice	
Skin and subcutaneous tissue disorders:		
	cutaneous lupus erythematosus like reactions (or reactivation of lupus erythematosus), photosensitivity reactions, cutaneous vasculitis, toxic epidermal necrolysis	
Musculoskeletal, connective tissue and bone disorders:		
		weakness
Renal and urinary disorders:		
		interstitial nephritis, renal dysfunction, glycosuria
General disorders and administration site conditions:		
		fever
Investigations:		
		increase in triglycerides

Telmisartan: Side effects which have been spontaneously reported since the introduction of telmisartan monotherapy into the market:	
Infections and infestations:	sepsis including fatal outcome
Blood and the lymphatic system disorders:	eosinophilia
Immune system disorders:	anaphylactic reaction
Musculoskeletal, connective tissue and bone disorders:	arthrosis, tendon pain (tendinitis like symptoms)

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Limited information is available for CO-MICARDIS with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia also occurred. Overdose with hydrochlorothiazide is associated with electrolyte

depletion (hypokalaemia, 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.

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

IDENTIFICATION:
CO-MICARDIS 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-MICARDIS 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.

CO-MICARDIS 80/25 mg: Oblong biconvex double layered tablets, first layer white, second layer yellow. Very small yellow particles from the second layer may be visible in the first layer. The white layer is marked with "H9" and the Boehringer Ingelheim company symbol.

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

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

REGISTRATION NUMBERS:
CO-MICARDIS 40/12,5 mg tablets: 35/7.1.3/0096
CO-MICARDIS 80/12,5 mg tablets: 35/7.1.3/0097
CO-MICARDIS 80/25 mg tablets: 42/7.1.3/0766

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Ingelheim Pharmaceuticals (Pty) Ltd
407 Pine Avenue
Randburg
South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:
Date of registration: 07 December 2001 (CO-MICARDIS 40/12,5 mg and 80/12,5 mg) and 25 November 2011 (CO-MICARDIS 80/25 mg).
Revised: 20 August 2019