

1. NAME OF THE MEDICINAL PRODUCT

MICARDIS PLUS 40/12.5 mg
MICARDIS PLUS 80/12.5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains:

[1,1'-biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6-bi-1H-benzimidazole]-1'-yl)methyl] (= telmisartan) 40 or 80 mg and hydrochlorothiazide 12.5 mg

3. PHARMACEUTICAL FORM

Tablet for oral use.

40/12.5mg: Oblong, white-red, biconvex two-layer tablets, possibly with red specks in the white layer. The white face is marked with "H4" and the Boehringer Ingelheim company symbol.

80/12.5mg: Oblong, white-red, biconvex two-layer tablets, possibly with red specks in the white layer. The white face is marked with "H8" and the Boehringer Ingelheim company symbol.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension.

As fixed dose combination MICARDIS PLUS is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone.

4.2 Posology and method of administration

Dosage

Adults

MICARDIS PLUS should be taken once daily. The dose of telmisartan could be up-titrated before switching to MICARDIS PLUS. Direct change from monotherapy to the fixed combinations may be considered.

- MICARDIS PLUS 40/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by MICARDIS 40 mg or hydrochlorothiazide.
- MICARDIS PLUS 80/12.5 mg may be administered in patients whose blood pressure is not adequately controlled by MICARDIS 80 mg or by MICARDIS PLUS 40/12.5 mg.

Sodium or volume depletion should be corrected before treatment commencement with MICARDIS PLUS.

The maximum antihypertensive effect is generally attained with MICARDIS PLUS 4 to 8 weeks after the start of treatment.

When necessary, MICARDIS PLUS may be administered with another antihypertensive drug.

In patients with severe hypertension treatment with telmisartan at doses up to 160 mg alone and in combination with hydrochlorothiazide 12.5 - 25 mg daily was well tolerated and effective.

Special populations

Geriatric patients

No dose adjustment is necessary for geriatric patients.

Paediatric patients

Safety and efficacy of MICARDIS PLUS have not been established in patients aged below 18 years. Use of MICARDIS PLUS is not recommended in children and adolescents.

Renal impairment

Due to the hydrochlorothiazide component, MICARDIS PLUS must not be used in 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 hemofiltration and is not dialyzable.

Hepatic impairment

In patients with mild to moderate hepatic impairment MICARDIS PLUS should be administered with caution. For telmisartan, the posology should not exceed 40mg once daily (see Contraindications). Thiazides should be used with caution in patients with impaired hepatic function.

Method of Administration

MICARDIS PLUS tablets are for once-daily oral administration and should be swallowed whole with liquid. MICARDIS PLUS 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 the active substances or, to any of the excipients, or to other sulphonamide-derived substances (hydrochlorothiazide is a sulphonamide-derived substance).
- Pregnancy
- Lactation
- Cholestasis and biliary obstructive disorders
- Severe hepatic impairment, coma hepaticum, hepatic precoma
- Severe renal impairment (creatinine clearance < 30 ml/min) or serum creatinine > 1.8 mg/100 ml), anuria, or acute glomerulonephritis
- Refractory hypokalaemia, hypercalcaemia
- Therapy-refractory hyponatraemia
- Hypovolaemia
- Symptomatic hyperuricaemia / gout
- The concomitant use of MICARDIS PLUS with aliskiren is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²)

In case of rare hereditary conditions that may be incompatible with an excipient of the product (see Special warnings and precautions), the use of the product is contraindicated.

4.4 Special warnings and precautions for use

Pregnancy:

Angiotensin II receptor blockers should not be initiated during pregnancy.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and if appropriate, alternative therapy should be started.

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. Such conditions, especially volume and/or sodium depletion, should be corrected before the administration of MICARDIS PLUS.

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

Hepatic impairment:

MICARDIS PLUS must not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since telmisartan is mostly eliminated in the bile. These patients can be expected to have reduced hepatic clearance for telmisartan.

MICARDIS PLUS should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with MICARDIS PLUS in patients with hepatic impairment.

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.

Renal impairment and kidney transplant:

MICARDIS PLUS must not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) (see Contraindications).

There is no experience regarding the administration of MICARDIS PLUS in patients with severe renal impairment or with a recent kidney transplant. Experience with MICARDIS PLUS is modest in the patients with mild to moderate renal impairment, therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function.

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

Dual blockade of the renin-angiotensin-aldosterone system:

As a consequence of inhibiting the renin-angiotensin-aldosterone system changes in renal function (including acute renal failure) have been reported in susceptible individuals, especially if combining medicinal products that affect this system. Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor or the direct renin-inhibitor aliskiren to an angiotensin II receptor blocker) is not recommended and should therefore be limited to individually defined cases with close monitoring of renal function (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 medicinal products that affect this system has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure.

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 MICARDIS PLUS is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:

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

Metabolic and endocrine effects:

Thiazide therapy 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 thiazide therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy; however, at the 12.5 mg dose contained in MICARDIS PLUS, minimal or no effects were reported.

Hyperuricaemia may occur or frank gout may be precipitated in some patients receiving thiazide therapy.

Electrolyte imbalance:

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalaemia, hyponatraemia, and hypochloraemic alkalosis). Warning signs of fluid or electrolyte imbalance are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastro-intestinal disturbances such as nausea or vomiting.

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 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 (AT1) receptors by the telmisartan component of MICARDIS PLUS, hyperkalaemia might occur. Although clinically significant hyperkalaemia has not been documented with MICARDIS PLUS, risk factors for the development of hyperkalaemia include renal insufficiency and/or heart failure, and diabetes mellitus. Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes should be co-administered cautiously with MICARDIS PLUS.

Thiazides 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. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Sorbitol:

MICARDIS PLUS tablets 40/12.5 mg contains 169 mg sorbitol in each tablet. MICARDIS PLUS tablets 80/12.5 mg contains 338 mg sorbitol in each tablet.

Sorbitol is a source of fructose. MICARDIS PLUS tablets 80/12.5 mg is not recommended for use in patients with hereditary fructose intolerance (HFI).

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 MICARDIS PLUS.

Lactose:

MICARDIS PLUS tablets 40/12.5 mg contains 112 mg of lactose monohydrate in each tablet. MICARDIS PLUS tablets 80/12.5 mg contains 112 mg of lactose monohydrate in each tablet.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Ischaemic heart disease:

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

General:

Hypersensitivity reactions to HCTZ may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics, including HCTZ.

Cases of photosensitivity reactions have been reported with thiazide diuretics (see Adverse reactions). 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.

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, 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 drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of 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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry (see Adverse reactions). Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions.

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. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

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

4.5 Interaction with other medicinal products and other forms of interaction

Interactions linked to telmisartan

Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Co-administration of telmisartan 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 (39 % in a single case), 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 AUC₀₋₂₄ and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

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 blocker, including telmisartan. Furthermore, renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with MICARDIS PLUS. Lithium and MICARDIS PLUS should only be co-administered under medical supervision and serum lithium level monitoring is advisable during concomitant use.

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. ASA at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) is associated with the potential for acute renal

insufficiency in patients who are dehydrated. Compounds acting on the Renin-Angiotensin-System like telmisartan may have synergistic effects. Patients receiving NSAIDs and telmisartan should be adequately hydrated and be monitored for renal function at the beginning of combined treatment.

A reduced effect of antihypertensive drugs 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 thiazide diuretics in some patients.

Interactions linked to hydrochlorothiazide (HCTZ)

The antihypertensive effect of HCTZ can be potentiated by other diuretics, antihypertensive agents, guanethidine, methyl dopa, 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 agents, 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 agents (e.g. cyclophosphamide, fluorouracil, methotrexate) may lead to a reduction in the renal excretion of cytotoxic agents. Increased bone marrow toxicity (especially granulocytopenia) can be expected.

The bioavailability of thiazide diuretics may be increased by anticholinergic agents (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.

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 drugs 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 drugs are to be prescribed with MICARDIS PLUS, monitoring of potassium plasma levels is advised.

Conversely, based on the experience with the use of other drugs that blunt the renin-angiotensin system, concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. If these drugs are to be prescribed with MICARDIS PLUS, monitoring of potassium plasma levels is advised.

Periodic monitoring of serum potassium is recommended when MICARDIS PLUS is administered with drugs affected by serum potassium disturbances, e.g. digitalis glycosides, anti-arrhythmic agents and drugs known to induce torsades de pointes.

4.6 Fertility, pregnancy and lactation

Pregnancy

Telmisartan:

The use of angiotensin II receptor blocker is not recommended during the first trimester of pregnancy and should not be initiated during pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor blocker should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blocker therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy.

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

The use of angiotensin II receptor blocker is contraindicated during the second and third trimester of pregnancy.

Angiotensin II receptor blocker exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Should exposure to angiotensin II receptor blocker have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken angiotensin II receptor blocker should be closely observed for hypotension.

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

MICARDIS PLUS is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk. Non-clinical 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 ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery, it should be taken into account that dizziness, syncope or vertigo may occasionally 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 Adverse reactions

Summary of the safety profile

The overall incidence of adverse events reported with MICARDIS PLUS was comparable to those reported with telmisartan alone in randomised controlled trials involving 1471 patients receiving telmisartan plus hydrochlorothiazide (835) or telmisartan alone (636). There was no dose-relationship to undesirable effects and there was no correlation with gender, age or race of the patients.

Tabulated summary of adverse reactions

The following adverse reactions derived from the use of telmisartan/hydrochlorothiazide combination or the use of 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.

MedDRA System Organ Class terminology	Adverse reactions
Infections and infestations	bronchitis¹
	pharyngitis¹
	sinusitis¹
	upper respiratory tract infection²
	urinary tract infection²
	cystitis²
	sepsis (including fatal outcome)²
Neoplasms benign, malignant and unspecified (incl cysts and polys)	basal cell carcinoma³
	squamous cell carcinoma of skin³
	lip squamous cell carcinoma³
Blood and lymphatic system disorders	anaemia²
	thrombocytopenia^{2,3}
	thrombocytopenic purpura³
	eosinophilia²
	aplastic anaemia³
	haemolytic anaemia³
	bone marrow failure³
	leukopenia³
	agranulocytosis³
Immune system disorders	anaphylactic reaction²
	hypersensitivity^{2,3}
Metabolism and nutrition disorders	hypokalaemia^{1,3}
	hyponatraemia^{1,2,3}
	hyperuricaemia^{1,3}
	hyperkalaemia²
	hypoglycaemia (in diabetic patients)²
	hypovolaemia³
	electrolyte imbalance³
	decreased appetite³
	hyperglycaemia³
	hypomagnesaemia³
	hypercalcaemia³
	alkalosis hypochloraemic³
	hyperlipidaemia³
	diabetes mellitus inadequate control³
Psychiatric disorders	anxiety^{1,2}
	depression^{1,2,3}
	insomnia^{1,2}
	restlessness³
Nervous system disorders	dizziness^{1,3}
	syncope (faint)^{1,2}
	paraesthesia^{1,3}
	sleep disorder^{1,3}
	headache³
Eye disorders	visual impairment^{1,2,3}
	vision blurred¹
	acute myopia³
	acute angle-closure glaucoma³
	choroidal effusion³
Ear and labyrinth disorders	vertigo^{1,2}
Cardiac disorders	arrhythmia^{1,3}
	tachycardia^{1,2}
	bradycardia²
Vascular disorders	hypotension^{1,2}

MedDRA System Organ Class terminology	Adverse reactions
	orthostatic hypotension ^{1,2,3}
	vasculitis necrotising ³
Respiratory, thoracic and mediastinal disorders	dyspnoea ^{1,2}
	respiratory distress ^{1,3}
	pneumonitis ^{1,3}
	pulmonary oedema ^{1,3}
	acute respiratory distress syndrome ³
Gastrointestinal disorders	diarrhoea ^{1,2,3}
	dry mouth ^{1,2}
	flatulence ^{1,2}
	abdominal pain ^{1,2}
	constipation ^{1,3}
	dyspepsia ^{1,2}
	vomiting ^{1,2,3}
	gastritis ¹
	abdominal discomfort ^{2,3}
	pancreatitis ³
	nausea ³
Hepatobiliary disorders	abnormal hepatic function / liver disorder ^{1,2}
	Most cases of hepatic function abnormal/liver disorder from post-marketing experience with telmisartan occurred in patients in Japan, who are more likely to experience these adverse reactions.
	jaundice ³
	cholestasis ³
Skin and subcutaneous tissue disorders	angioedema (including fatal outcome) ^{1,2}
	erythema ^{1,2}
	pruritus ^{1,2}
	rash ^{1,2,3}
	hyperhidrosis ^{1,2}
	urticaria ^{1,2,3}
	eczema ²
	drug eruption ²
	toxic skin eruption ²
	toxic epidermal necrolysis ³
	lupus like syndrome ³
	cutaneous lupus erythematosus ³
	photosensitivity reaction ³
	erythema multiforme ³
Musculoskeletal and connective tissue disorders	back pain ^{1,2}
	muscle spasms (cramps in legs) ^{1,2,3}
	myalgia ^{1,2}
	arthralgia ^{1,2}
	pain in extremity (leg pain) ^{1,2}
	tendon pain (tendonitis like symptoms) ²
	systemic lupus erythematosus ¹
	Based on post-marketing experience
Renal and urinary disorders	renal impairment (including acute kidney injury) ^{2,3}
	glycosuria ³
Reproductive system and breast disorders	erectile dysfunction ^{1,3}
General disorders and administration site conditions	chest pain ^{1,2}
	influenza-like illness ^{1,2}
	pain ¹
	asthenia (weakness) ^{2, 3}
	pyrexia ³
Investigations	blood uric acid increased ^{1,2}

MedDRA System Organ Class terminology	Adverse reactions
	blood creatinine increased ^{1,2}
	hepatic enzyme increased ^{1,2}
	blood creatine phosphokinase increased ^{1,2}
	haemoglobin decreased ²

¹ Adverse reactions of FDC telmisartan + hydrochlorothiazide

² Adverse reactions of telmisartan as monotherapy

³ Adverse reactions of hydrochlorothiazide as monotherapy

Description of selected adverse reactions

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 4.5 and 5.1).

4.9 Overdose

Limited information is available for MICARDIS PLUS 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 arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.

Therapy

No specific information is available on the treatment of overdose with MICARDIS PLUS. The patient should be closely monitored, and the treatment should be symptomatic and supportive depending on the time since ingestion and the severity of the symptoms. Serum electrolytes and creatinine should be monitored frequently. 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

Pharmacotherapeutic group: Angiotensin II receptor blocker, plain (telmisartan), combination with Diuretics (hydrochlorothiazide)

ATC code: C09DA07

Mode of Action

MICARDIS PLUS is a combination of an angiotensin II receptor blocker, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone. MICARDIS PLUS once daily produces effective and smooth reductions in blood pressure across the therapeutic dose range.

Telmisartan:

Telmisartan is an orally effective and specific angiotensin II receptor (type AT1) blocker. Telmisartan displaces angiotensin II with very high affinity 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 the AT1 receptor. The binding is long lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

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.

Hydrochlorothiazide:

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides effect 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. Presumably through blockade of the renin-angiotensin-aldosterone system, co-administration of telmisartan tends to reverse the potassium loss associated with these diuretics.

With hydrochlorothiazide, onset of diuresis occurs in 2 hours, and peak effect occurs at about 4 hours, while the action persists for approximately 6 - 12 hours; the antihypertensive effect lasts for up to 24 hours.

Pharmacodynamics

Telmisartan

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident 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 constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements. This is confirmed by through to peak ratios consistently above 80% seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies.

There is an apparent trend to a dose relationship to a time to recovery of baseline SBP. In this respect data concerning DBP are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The antihypertensive efficacy of telmisartan has been compared to agents representative of other classes of antihypertensive drugs (in clinical trials comparing telmisartan to agents such as amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan).

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.

Telmisartan treatment has been shown in clinical trials to be associated with statistically significant reductions in Left Ventricular Mass and Left Ventricular Mass Index in patients with hypertension and Left Ventricular Hypertrophy.

Telmisartan treatment has been shown in clinical trials (including comparators like losartan, ramipril and valsartan) to be associated with statistically significant reductions in proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Hydrochlorothiazide

Hydrochlorothiazide inhibits sodium reabsorption primarily in the distal tubule, whereby a maximum of about 15% of sodium filtered by the glomerulus may be excreted. The extent of chloride excretion is roughly equivalent to that of sodium excretion. Potassium excretion is also increased by hydrochlorothiazide and is essentially determined by potassium secretion in the distal tubule and collecting duct (increased sodium and potassium ion exchange). Bicarbonate excretion may be increased by high hydrochlorothiazide doses as a result of carbonic anhydrase inhibition, resulting in urine alkalinisation.

The saluretic/diuretic effect of hydrochlorothiazide is not significantly affected by acidosis or alkalosis.

Initially, the glomerular filtration rate is slightly reduced.

During long-term therapy with hydrochlorothiazide, calcium excretion via the kidneys is reduced, which may result in hypercalcaemia.

In hypertensive patients, hydrochlorothiazide has an antihypertensive effect. However, the mechanism has yet to be sufficiently clarified. It has been argued, for instance, that the effect of thiazide diuretics in terms of reducing vascular tone is due to a decrease in sodium concentration in the vascular wall and, hence, due to reduced responsiveness to norepinephrine.

In patients with chronic renal impairment (creatinine clearance less than 30 mL/min and/or serum creatinine above 1.8 mg/100 mL), hydrochlorothiazide has virtually no effect.

In patients with renal and ADH-sensitive diabetes insipidus, hydrochlorothiazide has an antidiuretic effect.

Clinical Trials

Prevention of cardiovascular morbidity and mortality

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which represents a broad cross-section of cardiovascular high risk patients.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years. The population studied was 73% male, 74% Caucasian, 14% Asian and 43% were 65 years of age or older. Hypertension was present in nearly 83% of randomized patients: 69% of patients had a history of hypertension at randomization and an additional 14% had actual blood pressure readings above 140/90 mm Hg. At baseline, the total percentage of patients with a medical history of diabetes was 38% and an additional 3% presented with elevated fasting plasma glucose levels. Baseline therapy included acetylsalicylic acid (76%), statins (62%), beta-blockers (57%), calcium channel blockers (34%), nitrates (29%) and diuretics (28%).

The primary endpoint was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure.

Adherence to treatment was better for telmisartan than for ramipril or the combination of telmisartan and ramipril, although the study population had been pre-screened for tolerance to treatment with an ACE-inhibitor. The analysis of adverse events leading to permanent treatment discontinuation and of serious adverse events showed that cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Telmisartan had similar efficacy to ramipril in reducing the primary endpoint. The incidence of the primary endpoint was similar in the telmisartan (16.7%), ramipril (16.5%) and telmisartan plus ramipril combination (16.3%) arms. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5% CI 0.93 - 1.10,

p (non-inferiority) = 0.0019). The treatment effect was found to persist following corrections for differences in systolic blood pressure at baseline and over time. There was no difference in the primary endpoint based on age, gender, race, baseline therapies or underlying disease.

Telmisartan was also found to be similarly effective to ramipril in several pre-specified secondary endpoints, including a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo. The hazard ratio of telmisartan vs. ramipril for this endpoint in ONTARGET was 0.99 (97.5% CI 0.90 - 1.08, p (non-inferiority) = 0.0004).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

Epidemiological studies have shown that long-term treatment with hydrochlorothiazide reduces the risk of cardiovascular mortality and morbidity.

The effects of fixed dose combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.5).

5.2 Pharmacokinetics properties

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

Telmisartan

Absorption

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. Food slightly reduces the bioavailability of telmisartan with a reduction in the area under the plasma concentration time curve (AUC) of about 6% with the 40 mg tablet and about 19% after a 160 mg dose. By 3 hours after administration plasma concentrations are similar whether telmisartan is taken fasting or with food. The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy.

Distribution

Telmisartan is highly bound to plasma proteins (> 99.5%) mainly albumin and alpha1-acid glycoprotein. The apparent volume of distribution for telmisartan is approximately 500 litres indicating additional tissue binding.

Biotransformation

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 ¹⁴C-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.

Elimination

Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min compared with hepatic blood flow (about 1500 mL/min). Terminal elimination half-life was > 20 hours.

Linearity

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.

Hydrochlorothiazide

Absorption

Following oral administration of MICARDIS PLUS 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%.

Distribution

Hydrochlorothiazide is 64% protein bound in the plasma and its apparent volume of distribution is 0.8 ± 0.3 l/kg.

Biotransformation

Hydrochlorothiazide is not metabolised in man and is excreted almost entirely as unchanged drug in urine.

Elimination

About 60% of the oral dose are eliminated as unchanged drug within 48 hours. Renal clearance is about 250 – 300 mL/min. The terminal elimination half-life of hydrochlorothiazide is 10 – 15 hours.

PK in specific populations

Gender differences

Gender differences in plasma concentrations of telmisartan were observed, C_{max} and AUC being approximately 3- and 2-fold higher in females compared to males without relevant influence on efficacy. There was a trend towards higher plasma concentrations of hydrochlorothiazide in female than in male subjects. This is not considered to be of clinical relevance.

Geriatric patients

Pharmacokinetics of telmisartan do not differ between the younger and geriatric patients.

Renal impairment

Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment. 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.

Hepatic impairment

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Maize starch
Meglumine
Microcrystalline cellulose
Povidone (K25)
Red iron oxide
Sodium hydroxide
Sodium starch glycollate (type A)
Sorbitol (E420)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to packaging for information on shelf-life

6.4 Special Precautions for storage

Store below 30°C.
Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Tablets of 40/12.5mg and 80/12.5mg:
One Alu/Alu Blister contains 10 tablets. One box contain 30 tablets.

6.6 Special precautions for disposal and other handling

Micardis Plus should be kept in the sealed blister due to the hygroscopic property of the tablets. Tablets should be taken out of the blister shortly before administration.

7. MARKETING AUTHORISATION HOLDER / MANUFACTURER

Manufactured by:
Boehringer Ingelheim Hellas Single Member S.A.
Koropi Attiki, 19441, Greece.

Packed & released by:
Boehringer Ingelheim Shanghai Pharmaceuticals Co. Ltd.
China (Shanghai) Pilot Free Trade Zone, China.

For:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein
Germany

8. MARKETING AUTHORISATION NUMBER(S)

MAL20034439AZ – Micardis Plus tablet 40/12.5 mg
MAL20034440AZ – Micardis Plus tablet 80/12.5 mg

9. DATE OF REVISION OF THE TEXT

25 Aug 2023

Store in a safe place out of the reach of children!
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