Micardis® Plus

Composition

1 tablet contains:

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

Excipients: **
povidone, meglumine, sodium hydroxide, sorbitol, magnesium stearate, microcristalline cellulose, ferric oxide red (E172), sodium starch glycolate, lactose monohydrate, maize starch

Sodium	MICARDIS PLUS tablets 40/12.5 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Sodium	MICARDIS PLUS tablets 80/12.5 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Indications

Treatment of essential hypertension.

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

Dosage and 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.

Special populations

Geriatric patients
No dose adjustment is necessary for geriatric patients [7,8].

Paediatric patients
Safety and efficacy of MICARDIS PLUS have not been established 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 [10] **and is not dialyzable** [11]**.**

Hepatic impairment
In patients with mild to moderate hepatic impairment **MICARDIS PLUS should be administered with caution. For telmisartan,** the posology should not exceed 40 mg once daily (see Contraindications)**.** Thiazides should be used with caution in patients with impaired hepatic function. [7,9]

Method of Administration

MICARDIS PLUS tablets are for once-daily **oral administration** and should be swallowed whole with liquid [12]. MICARDIS PLUS can be taken with or without food [12].

HANDLING INSTRUCTIONS

Due to the hygroscopic property of the tablets they should be taken out of the sealed blister shortly before administration [13–15].

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
- Choleastasis and biliary obstructive disorders
- Severe hepatic impairment, coma hepaticum, hepatic precoma
- Severe renal impairment (creatinine clearance < 30 mL/min), 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 m^2).

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.

Special Warnings and Precautions

Pregnancy:
Angiotensin II receptor blockers should not be initiated during pregnancy.
Unless continued angiotensin II receptor blockers 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 blockers 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.

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 [17]. 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 [10] **and is not dialyzable** [11].

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 [19] (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.

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:
The maximum recommended daily dose of MICARDIS PLUS contains 169 mg sorbitol in the dose strength 40/12.5 mg and 338 mg sorbitol in the dose strengths 80/12.5 mg and 80/25 mg.
Patients with the rare hereditary condition of fructose intolerance should not take this medicine.
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.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. 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.

Sodium:
MICARDIS PLUS tablets 40/12.5 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'. MICARDIS PLUS tablets 80/12.5 mg contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Ischaemic hearth 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 hydrochlorothiazide 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.

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 Reaction). 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.

Interactions

Interactions linked to telmisartan

Telmisartan may increase the hypotensive effect of other antihypertensive agents. Other interactions of clinical significance have not been identified.

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 Cmax 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 blockers, 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 (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 [42, 43].
The co-administration of NSAIDs may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics in some patients.

Interactions linked to hydrochlorothiazide (HCTZ)
When administered concurrently, the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur;
Antidiabetic drugs (oral agents and insulins): Dosage adjustment of the antidiabetic drug may be required;
Metformin: There is a risk of lactic acidosis when co-administered with hydrochlorothiazide;
Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;
Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favour the onset of digitalis-induced cardiac arrhythmias;
Pressor amines (e.g. noradrenaline): The effect of pressor amines may be decreased; Nondepolarizing skeletal muscle relaxants (e.g. tubocurarine): The effect of nondepolarizing skeletal muscle relaxants may be potentiated by hydrochlorothiazide;
Treatment for gout: Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Co-administration of thiazide may increase the incidence of hypersensitivity reactions of allopurinol;
Calcium salts: Thiazide diuretics 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;

Other interactions:
The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastro-intestinal motility and stomach emptying rate.
Thiazides may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

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.

Fertility, Pregnancy and Lactation

Pregnancy

Telmisartan:
The use of angiotensin II receptor blockers 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 blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

Unless continued angiotensin II receptor blockers 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 blockers is contraindicated during the second and third trimester of pregnancy.

Angiotensin II receptor blockers 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 blockers 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 blockers 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 not observed.

Driving and Using 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. [5]
If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Side Effects

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

Frequency categories:
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); not known (cannot be estimated from the available data).

MedDRA System Organ Class terminology	Adverse reactions	Frequencies
Infections and infestations	sepsis (including fatal outcome)	rare[2)]
	bronchitis	rare[1)]
	pharyngitis	rare[1)]
	sinusitis	rare[1)]
	upper respiratory tract infection	uncommon[2)]
	urinary tract infection	uncommon[2)]
	cystitis	uncommon[2)]
Neoplasms benign, malignant and unspecified (incl cysts and polys)	basal cell carcinoma	not known[3)]
	squamous cell carcinoma of skin	not known[3)]
	lip squamous cell carcinoma	not known[3)]
Blood and lymphatic system disorders	anaemia	uncommon[2)]
	thrombocytopenia	rare[2)], rare[3)]
	thrombocytopenic purpura	rare[3)]
	eosinophilia	rare[2)]
	aplastic anaemia	not known[3)]
	haemolytic anaemia	very rare[3)]
	myelosuppression	very rare[3)]
	leukopenia	very rare[3)]
	agranulocytosis	very rare[3)]
Immune system disorders	anaphylactic reaction	rare[2)]
	hypersensitivity	rare[2)]
Metabolism and nutrition disorders	hypokalaemia	uncommon[1)], very common[3)]
	hyponatraemia	rare[1)], rare[2)], common[3)]
	hyperuricaemia	rare[1)], common[3)]
	hyperkalaemia	uncommon[2)]
	hypoglycaemia (in diabetic patients)	rare[2)]
	decreased appetite	common[3)]
	hyperglycaemia	rare[3)]
	hypomagnesaemia	common[3)]
	hypercalcaemia	rare[3)]
	alkalosis hypochloraemic	very rare[3)]
	Glycosuria[3]	-
	diabetes mellitus inadequate control	rare[3)]
Psychiatric disorders	anxiety	uncommon[1)], rare[2)]
	depression	rare[1)], uncommon[2)], rare[3)]
	retlessness[3]	-
	insomnia	rare[1)], uncommon[2)]
Nervous system disorders	dizziness	common[1)], rare[3)]

Red font: Proposed addition from CCDS 0251-14 update; Blue font: Editorial and Rearrangement sentences; Yellow highlight: BPOM Proposed

MedDRA System Organ Class terminology	Adverse reactions	Frequencies
	syncope (faint)	uncommon[1], uncommon[2]
	paraesthesia	uncommon[1], rare[3]
	sleep disorder	rare[1], rare[3]
	headache	rare[3]
Eye disorders	visual impairment	rare[1], rare[2], rare[3]
	vision blurred	rare[1]
	angle closure glaucoma	not known[3]
	choroidal effusion	not known[3]
Ear and labyrinth disorders	vertigo	uncommon[1], uncommon[2]
Cardiac disorders	arrhythmia	uncommon[1], rare[3]
	tachycardia	uncommon[1], rare[2]
	bradycardia	uncommon[2]
Vascular disorders	hypotension	uncommon[1], uncommon[2]
	orthostatic hypotension	uncommon[1], uncommon[2], common[3]
	vasculitis necrotising	very rare[3]
Respiratory, thoracic and mediastinal disorders	dyspnoea	uncommon[1], uncommon[2]
	respiratory distress	rare[1], very rare[3]
	pneumonitis	rare[1], very rare[3]
	pulmonary oedema	rare[1], very rare[3]
Gastrointestinal disorders	diarrhoea	uncommon[1], uncommon[2], rare[3]
	dry mouth	uncommon[1], rare[2]
	flatulence	uncommon[1], uncommon[2]
	abdominal pain	rare[1], uncommon[2]
	constipation	rare[1], rare[3]
	dyspepsia	rare[1], uncommon[2]
	vomiting	rare[1], uncommon[2], common[3]
	gastritis	rare[1]
	abdominal discomfort	rare[2], not known[3]
	pancreatitis	very rare[3]
	nausea	common[3]
Hepatobiliary disorders	abnormal hepatic function / liver disorder 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	rare[1], rare[2]
	jaundice	rare[3]
	cholestasis	rare[3]
Skin and subcutaneous tissue disorders	angioedema (including fatal outcome)	rare[1], rare[2]
	erythema	rare[1], rare[2]
	pruritus	rare[1], uncommon[2]
	rash	rare[1], uncommon[2], common[3]
	hyperhidrosis	rare[1], uncommon[2]
	urticaria	rare[1], rare[2], common[3]
	eczema	rare[2]
	drug eruption	rare[2]
	toxic skin eruption	rare[2]
	toxic epidermal necrolysis	very rare[3]
	lupus-like syndrome	very rare[3]

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MedDRA System Organ Class terminology	Adverse reactions	Frequencies
	cutaneous lupus erythematosus	very rare[3)]
	photosensitivity reaction	rare[3)]
	erythema multiforme	not known[3)]
Musculoskeletal and connective tissue disorders	back pain	uncommon[1)], uncommon[2)]
	muscle spasm (cramps in legs)	uncommon[1)], uncommon[2)], not known[3)]
	myalgia	uncommon[1)], uncommon[2)]
	arthralgia	rare[1)], rare[2)],
	pain in extremity (leg pain)	rare[1)], rare[2)],
	tendon pain (tendonitis like symptoms)	rare[2)]
	systemic lupus erythematosus Based on post-marketing experience	rare[1)]
Renal and urinary disorders	renal impairment (including acute kidney injury)	uncommon[2)], not known[3)]
	glycosuria	not known [3)]
Reproductive system and breast disorders	erectile dysfunction	uncommon[1)], common[3)]
General disorders and administration site conditions	chest pain	uncommon[1)], uncommon[2)]
	influenza like illness	rare[1)], rare[2)],
	pain	rare[1)]
	asthenia (weakness)	uncommon[2)], not known[3)]
	pyrexia	not known[3)]
Investigations	blood uric acid increased	uncommon[1)], rare[2)]
	blood creatinine increased	rare[1)], uncommon[2)]
	hepatic enzyme increased	rare[1)], rare[2)]
	blood creatine phosphokinase increased	rare[1)], rare[2)]
	haemoglobin decreased	rare[1)], rare[2)]
	lipids increased	very common[3)]

[1] Adverse reactions of FDC telmisartan + hydrochlorothiazide
[2] Adverse reactions of telmisartan as monotherapy
[3] Adverse reactions of hydrochlorothiazide as monotherapy

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 [10] and is not dialyzable [11]. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Pharmacological properties

Pharmacotherapeutic group:
Angiontensin 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 AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long lasting.

Telmisartan does not show affinity for other receptors, including AT_2 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 hydrochlorothiazides, 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 [62] (in clinical trials comparing telmisartan to agents such as amlodipine [63,64], 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.

Clinical Trial

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

Pharmacokinetics

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 ^{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.

Elimination
Total plasma clearance (CLtot) 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, Cmax and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males without relevant influence on effocacy. 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 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.

Toxicology

In non-clinical safety studies performed with co-administration of telmisartan and hydrochlorothiazide in normotensive rats and dogs, doses producing exposure comparable to that in the clinical therapeutic range caused no additional findings not already observed with administration of either substance alone. There were no toxicological findings observed of relevance to human therapeutic use.
Toxicological findings also well known from non-clinical studies with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers were: a reduction of red cell parameters (erythrocytes, haemoglobin, haematocrit), changes of renal haemodynamics (increased blood urea nitrogen and creatinine), increased plasma renin activity, hypertrophy/hyperplasia of the juxtaglomerular cells and gastric mucosal injury.

Gastric lesions could be prevented/ameliorated by oral saline supplementation and group housing of animals. In dogs renal tubular dilation and atrophy were observed. These findings are considered to be due to the pharmacological activity of telmisartan.
No effects of telmisartan on male or female fertility were observed [142].

Telmisartan showed no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice. Studies with hydrochlorothiazide have shown equivocal evidence for a genotoxic or carcinogenic effect in some experimental models. However, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

There is no clear evidence of a teratogenic or embryotoxic potential for either telmisartan or hydrochlorothiazide administered as single entities or in combination. At toxic doses levels, however, non-clinical studies indicated some hazardous potential of telmisartan to fetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

Availabilty

Micardis PLUS 40/12.5 mg Box, 2 blister @ 10 Tablet	Reg No: DKI2055200110A1
Micardis PLUS 80/12.5 mg Box, 2 blister @ 10 Tablet	Reg No: DKI2055200110B1

Red font: Proposed addition from CCDS 0251-14 update; Blue font: Editorial and Rearrangement sentences; Yellow highlight: BPOM Proposed

Only on Doctor's Prescription.
Harus dengan Resep Dokter

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