# Micardis® Plus

Boehringer Ingelheim

## Composition

1 tablet contains:

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| [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 |
| Hydrochlorothiazide | 12.5 mg |

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

or

1 tablet contains:

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|---|---|
| [1,1'-biphenyl]-2-carboxylic acid, 4'-[(1,4'dimethyl-2'-propyl[2,6-bi-1H-benzimidazole]-1'-yl)methyl] (= telmisartan) | 80 mg |
| Hydrochlorothiazide | 25 mg |

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

## Pharmacological properties

### Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists and diuretics, ATC code: C09DA07

Micardis Plus is a combination of an angiotensin II receptor antagonist, telmisartan, and a thiazide diuretic, hydrochlorothiazide. The combination of these ingredients has an additive antihypertensive effect, 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 $AT_1$) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the $AT_1$ receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the $AT_1$ receptor. Telmisartan selectively binds 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. After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4-8 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 trough to peak ratios consistently above 80% seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. 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 antihypertensive drugs such as amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, lisinopril, ramipril and valsartan).

In a double-blind controlled clinical trial (n=687 patients evaluated for efficacy) in non-responders to the 80 mg/12.5 mg combination, an incremental blood pressure lowering effect of the 80 mg/25 mg combination compared to continued treatment with the 80 mg/12.5 mg combination of 2.7/1.6 mm Hg (SBP/DBP) was demonstrated (difference in adjusted mean changes from baseline). In a follow-up trial with the 80 mg/25 mg combination, blood pressure was further decreased (resulting in an overall reduction of 11.5/9.9 mm Hg (SBP/DBP).

In a pooled analysis of two similar 8 week double-blind placebo-controlled clinical trials vs. valsartan/hydrochlorothiazide 160 mg/25 mg (n=2121 patients evaluated for efficacy) a significantly greater blood pressure lowering effect of 2.2/1.2 mm Hg (SBP/DBP) was demonstrated (difference in adjusted mean changes from baseline, respectively) in favour of telmisartan/hydrochlorothiazide 80 mg/25 mg combination.

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. 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.

The effects of Fixed Dose Combination of telmisartan/HCTZ on mortality and cardiovascular morbidity are currently unknown.

Hydrochlorothiazide: Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides 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.

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.

### Pharmacokinetics

Concomitant administration of hydrochlorothiazide and telmisartan has no effect on the pharmacokinetics of either drug substance in healthy subjects.

Absorption:

*Telmisartan:* Following oral administration peak concentrations of telmisartan are reached in 0.5–1.5 h after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42% and 58%, respectively. 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.

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:* 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:

*Telmisartan:* 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.

*Hydrochlorothiazide:* Hydrochlorothiazide is 68% protein bound in the plasma and its apparent volume of distribution is 0.8 ± 0.3 l/kg.

Biotransformation and elimination:

*Telmisartan:* Following either intravenous or oral administration of $^{14}$C-labelled telmisartan mo 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 onl metabolite that has been identified in humans. After a single dose of $^{14}$C-labelled telmisartan the glucuronide represents approximately 11% of the measured radioactivity in plasma.

The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan after oral administration is > 1500 ml/min.

Terminal elimination half-life was > 20 hours.

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

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

Gender:

Plasma concentrations of telmisartan are generally 2–3 times higher in females than in males. In clinical trials however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

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.

Patients with renal impairment: Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild to moderate renal impairment (creatinine clearance of 30–60 ml/min, mean about 50 ml/min) no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by haemodialysis. In patients with impaired renal function the rate of hydrochlorothiazide elimination is reduced. In a typical study in patients with a mean creatinine clearance of 90 ml/min the elimination half-life of hydrochlorothiazide was increased. In functionally anephric patients the elimination half-life is about 34 hours.

Patients with hepatic impairment: Pharmacokinetic studies in patients with hepatic impairmen showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is no changed in patients with hepatic impairment.

## 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.

Micardis Plus fixed dose combination (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on Micardis Plus 80 mg/12.5 mg (80 mg telmisartan/12.5 mg hydrochlorothiazide) or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

## Contraindications

Hypersensitivity to the active ingredient, to any of the excipients, or to other sulphonamide-derived substances (hydrochlorothiazide is a sulphonamide-derived substance); Second and third trimesters of pregnancy and lactation; Cholestasis and biliary obstructive disorders; Severe hepatic impairment; Severe renal impairment (creatinine clearance < 30 ml/min); Refractory hypokalaemia, hypercalcaemia.

In case of rare hereditary conditions that may be incompatible with an excipient of the product the use of the product is contraindicated (please refer to "special warnings and precautions").

## Special warnings and precautions

Hepatic impairment:

Micardis Plus should not be given to patients with cholestasis, biliary obstructive disorders or severe hepatic insufficiency since telmisartan is mostly eliminated with 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 should 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.

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

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 telmisartan 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.

– Hypokalaemia

Although hypokalaemia may develop with the use of thiazide diuretics, concurrent therapy with telmisartan may reduce diuretic-induced hypokalaemia. The risk of hypokalaemia is greatest in patients with cirrhosis of 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.

– Hyperkalaemia

Conversely, due to the antagonism of the angiotensin II ($AT_1$) 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.

– Hyponatraemia and hypochloraemic alkalosis

There is no evidence that Micardis Plus would reduce or prevent diuretic-induced hyponatraemia. Chloride deficit is generally mild and usually does not require treatment.

– Hypercalcaemia

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.

– Hypomagnesaemia

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.

Lactose:

The maximum recommended daily dose of Micardis Plus contains 112 mg of lactose monohydrate in the dose strengths 40/12.5 mg and 80/12.5 mg, and 99 mg lactose monohydrate in the dose strength 80/25 mg.
Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

Ethnic differences: As with all other angiotensin antagonists telmisartan is apparently less effective in lowering blood pressure in black patients than in non blacks, possibly because of higher prevalence of low renin states in the black hypertensive population.

Other: As with any antihypertensive agent, excessive reduction 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.

## Interactions

Interaction studies have only been performed in adults.
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Cases have also been reported with angiotensin II receptor antagonists, including Micardis Plus. Furthermore,renal clearance of lithium is reduced by thiazides so the risk of lithium toxicity could be increased with Micardis Plus. Co-administration of lithium and Micardis Plus should only be allowed under strict medical supervision and should not be recommended. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.

Medicinal products 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 the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. These medicinal products may potentiate the effect of hydrochlorothiazide on serum potassium (see *Special warnings and precautions*).

Medicinal products that may increase potassium levels or induce hyperkalaemia (e.g. ACE inhibitors, potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, cyclosporin or other medicinal products such as heparin sodium): If these medicinal products are to be prescribed with the hydrochlorothiazide-telmisartan combination, monitoring of potassium plasma levels is advised. Based on the experience with the use of other medicinal products that blunt the rennin-angiotensin-system, concomitant use of the above medicinal products may lead to increases in serum potassium (see *Special warnings and precautions*).

Medicinal products affected by serum potassium disturbances: Periodic monitoring of serum potassium and ECG is recommended when Micardis Plus is administered with drugs affected by serum potassium disturbances (e.g. digitalis glycosides, antiarrhythmics) and the following torsades de pointes inducing drugs (which include some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes. class Ia antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide); class III antiarrythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide); some antipsychotics:(e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol); others: (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV.)

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia favours the onset of digitalis-induced cardiac arrhythmias (see *Special warnings and precautions*).

Other antihypertensive agents: Telmisartan may increase the hypotensive effect of other antihypertensive agents.

Antidiabetic medicinal products (oral agents and insulin): Dosage adjustment of the antidiabetic medicinal products may be required (see *Special warnings and precautions*).

Metformin: There is a risk of lactic acidosis induced by possible functional renal failure when co-administered with hydrochlorothiazide;

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins;

Non-steroidal anti-inflammatory medicinal products: NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the diuretic, natriuretic and antihypertensive effects of thiazide diuretics and the antihypertensive effects of angiotensin II antagonists.
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of angiotensin II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

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;

Medicinal products used in the treatment for gout (eg. probenecid, sulfinpyrazone and allopurinol). Dosage adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be necessary. Coadministration 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;

Beta-blockers and diazoxide: 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 gastrointestinal motility and stomach emptying rate.

Amantadine: Thiazides may increase the risk of adverse effects caused by amantadine.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate): Thiazides may reduce the renal excretion of cytotoxic drugs and potentiate their myelosuppressive effects.

Based on their pharmacological properties it can be expected that the following medicinal product may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine.
Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics or antidepressants.

## Pregnancy and lactation

Pregnancy: There are no adequate data on the use of telmisartan in pregnant women. Preclinical studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Animal studies do not indicate teratogenic effect, but have shown fetotoxicity. Therefore as a precautionary measure, Micardis Plus should preferably not be used during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy. In the second and third trimesters, substances that act directly on the renin-angiotensin-system can cause injury and even death in the developing foetus; therefore, Micardis Plus is contraindicated in the second and third trimesters of pregnancy. If pregnancy is diagnosed Micardis Plus should be discontinued as soon as possible. Thiazides cross the placental barrier and appear in cord blood. They may cause foetal electrolyte disturbances and possibly other reactions that have occurred in the adults. Cases of neonatal thrombocytopenia, of foetal or neonatal jaundice have been reported with maternal thiazide therapy.
Lactation: Micardis Plus is contraindicated during lactation since it is not known whether telmisartan excreted in human milk. Thiazides appear in human milk and may inhibit lactation.

## 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 or drowsiness may occasionally occur when taking antihypertensive therapy.

## Side effects

Fixed Dose Combination:
The overall incidence of adverse events reported with Micardis Plus was comparable to those reported with Micardis Plus 80 mg/25 mg and with Micardis Plus 80 mg/12.5 mg.
A dose-relationship of undesirable effects was not established and they showed no correlation with gender, age or race of the patients.

Adverse reactions reported in all clinical trials and occurring more frequently ($p \leq 0.05$) with telmisartan plus hydrochlorothiazide than with placebo are shown below according to system organ class. Adverse reactions known to occur with each component given singly but which have not been seen in clinical trials may occur during treatment with Micardis Plus.

Adverse reactions have been ranked under headings of frequency using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).
not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Common: Bronchitis, pharyngitis, sinusitis, upper respiratory tract infections, urinary tract infections

Immune system disorders
Uncommon: Hypersensitivity

Endocrine disorders
Uncommon: Diabetes mellitus inadequate control

Metabolism and nutrition disorders
Common: Hypercholesterolaemia, hypokalaemia.

Uncommon: Hyperuricaemia

Psychiatric disorders
Common: Anxiety

Nervous system disorders
Common: Dizziness

Ear and labyrinth disorders
Common: Vertigo

Gastrointestinal disorders
Common: Abdominal pain, diarrhoea, dyspepsia, gastritis

Skin and subcutaneous tissue disorders
Common: Eczema

Musculoskeletal and connective tissue disorders
Common: Arthralgia, osteoarthritis, back pain, muscle spasms or pain in extremity, myalgia

Reproductive system and breast disorders
Common: Erectile dysfunction

General disorders and administration site conditions
Common: Influenza-like illness, pain

As with other angiotensin II antagonists isolated cases of angioneurotic oedema, urticaria and other related reactions have been reported.

Laboratory findings
Changes in laboratory findings that were seen in clinical trials of telmisartan plus hydrochlorothiazide are included above (see Special warnings and precautions for use).

*Additional information on individual components*
Undesirable effects previously reported with one of the individual components may be potential undesirable effects with Micardis Plus, even if not observed in clinical trials with this product.

Telmisartan:
Undesirable effects occurred with similar frequency in placebo and telmisartan treated patients.
The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in placebo controlled trials. The following adverse drug reactions listed below have been accumulated from all clinical trials including 5788 hypertensive patients treated with telmisartan:
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Infections and infestations
Common: Symptoms of infection (e.g. urinary tract infection including cystitis), upper respiratory tract infection including pharyngitis and sinusitis

Psychiatric disorders
Uncommon: Anxiety

Eye disorders
Uncommon: Visual disturbance

Ear and labyrinth disorders
Uncommon: Vertigo

Gastrointestinal disorders
Common: Abdominal pain, diarrhoea, dyspepsia
Uncommon: Dry mouth, flatulence
Rare: Stomach discomfort

Skin and subcutaneous tissue disorders
Common: Eczema
Uncommon: Hyperhidrosis

Musculoskeletal and connective tissue disorders
Common: Arthralgia, back pain (e.g. sciatica), muscle spasms or pain in extremity, myalgia
Uncommon: Tendonitis

General disorders and administration site conditions
Common: Chest pain, influenza-like illness

In addition, since the introduction of telmisartan in the market, cases of erythema, pruritus, syncope, insomnia, depression, vomiting, hypotension (including orthostatic hypotension), bradycardia, tachycardia, hepatic function abnormal, liver disorder, renal impairment including acute renal failure (see Special warnings and precautions for use), hyperkalaemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, asthenia and drug ineffective have been reported. The frequency of these effects is unknown.

As with other angiotensin II antagonists isolated cases of angioneurotic oedema, urticaria and other related events have been reported.

*Laboratory findings*
Infrequently, a haemoglobin decrease or a blood uric acid increase has been observed which occur more often during treatment with telmisartan than with placebo. Increase in creatinine or hepatic enzyme increase have been observed during treatment with telmisartan but these changes in laboratory findings occurred with a frequency similar to or lower than placebo .In addition since the introduction of telmisartan in the market, cases with blood creatine phosphokinase increased (CPK) have been reported.

Hydrochlorothiazide:
Hydrochlorothiazide may cause or exacerbate hypovolaemia which could lead to electrolyte imbalance (see Special warnings and precautions for use ).
Adverse events of unknown frequency reported with the use of hydrochlorothiazide alone include:

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|---|---|
| Infections and infestations | Sialoadenitis |
| Blood and lymphatic system disorders | Anaemia (including aplastic anaemia), haemolytic anaemia, bone marrow depression, leukopenia, neutropenia, agranulocytosis, thrombocytopenia |
| Immune system disorders | Anaphylactic reactions |
| Metabolism and nutrition disorders | Anorexia, decreased appetite |
| Psychiatric disorders | Depression, restlessness |
| Nervous system disorders | Dizziness, paraesthesia, sleep disorder |
| Eye disorders | Vision blurred, xanthopsia |
| Ear and labyrinth disorder | Vertigo |
| Cardiac disorders | Arrhythmia |
| Vascular disorders | Orthostatic hypotension, vasculitis necrotizing |
| Respiratory, thoracic and mediastinal disorders | Respiratory distress, pneumonitis and pulmonar oedema |
| Gastrointestinal disorders | Constipation, pancreatitis, diarrhoea, stomach discomfort |
| Hepatobiliary disorders | Jaundice (jaundice hepatocellular or cholestatic jaundice) |
| Skin and subcutaneous tissue disorders | Cutaneous lupus erythematosus, cutaneous vasculitis, photosensitivity reactions, rash, urticaria, toxic epidermal necrolysis |
| Musculoskeletal and connective tissue disorders | Asthenia, muscle spasm |
| Renal and urinary disorders | Nephritis interstitial, renal impairment |
| General disorders and administration site conditions | Pyrexia |

*Laboratory findings*
Hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides.

Dosage and administration

- Adults: Micardis Plus should be taken once daily with liquid, with or without food in patients whose blood pressure is not adequately controlled by telmisartan alone. 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. Micardis Plus 80/25 mg may be administered in patients whose blood pressure is not adequately controlled by Micardis Plus 80/12.5 mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.
  The maximum antihypertensive effect is generally attained with Micardis Plus 4–8 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.

Renal impairment: Due to the hydrochlorothiazide component, Micardis Plus should not be used by patients with severe renal dysfunction (creatinine clearance < 30 ml/min). Loop diuretics are preferred to thiazides in this population. Experience in patients with mild to moderate renal impairment is modest but has not suggested adverse renal effects and dose adjustment is not considered necessary. Periodic monitoring of renal function is advised.

Hepatic impairment: In patients with mild to moderate hepatic impairment the posology should not exceed Micardis Plus 40/12.5 mg once daily. Micardis Plus is not indicated in patients with severe hepatic impairment. Thiazides should be used with caution in patients with impaired hepatic function.

Elderly: No dosage adjustment is necessary .

Children and adolescents: Safety and efficacy of Micardis Plus have not been established in children and in adolescents up to 18 years.

Overdose:
No data are available. Limited information is available for Micardis Plus with regard to overdose in humans.
Telmisartan is not removed by haemodialysis. The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

Symptoms: The most likely manifestations of telmisartan overdose are hypotension and tachycardia; bradycardia can also occur. 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 arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs.
Treatment: 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 Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and/or gastric lavage. Activated charcoal may be useful in the treatment of overdose. 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.

Storage instructions: Store in a safe place below 30 °C

Availability: Tablets of 40/12.5 mg , 80/12.5 mg and 80/25 mg

Date of package insert: January 2008 (SPC)

Manufactured by
Boehringer Ingelheim Pharma GmbH & Co. KG,
for Boehringer Ingelheim International GmbH,
Ingelheim am Rhein,
Germany

This is a medicament
Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament
The doctors and the pharmacist are experts in medicine, its benefits and risks.
Do not by yourself interrupt the period of treatment prescribed for you.
Do not repeat the same prescription without consulting your doctor.

**Keep medicament out of reach of children!**

Council of Arab Health Ministers – Union of Arab Pharmacists