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 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 is comparable to that of agents representative of other classes of antihypertensive drugs (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, losartan, and lisinopril). 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.

### 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

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### MICARDIS Plus

**Boehringer**

**Composition**
1 tablet contains telmisartan 40 or 80 mg
Hydrochlorothiazide 12.5 mg
Excipients: povidone, meglumine, sodium hydroxide, sorbitol, magnesium stearate, microcrystalline cellulose, iron oxide red, sodium starch glycolate, lactose monohydrate, maize starch

**Pharmacological properties**
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 antagonist (type AT1) antagonist. 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. 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
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.

**Pharmacokinetics**

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

**Absorption:**

Telmisartan: Following oral administration peak concentrations of telmisartan are reached in 0.5 – 1.5 hours after dosing. The absolute bioavailability of telmisartan at 40 mg and 160 mg was 42% and 58%, respectively. 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 64% protein bound in the plasma and its apparent volume of distribution is 0.8 ± 0.3 l/kg.

**Biotransformation and elimination:**

Telmisartan: 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.

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 impairment showed an increase in absolute bioavailability up to nearly 100%. The elimination half-life is not 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.

**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; Choleastasis and biliary obstructive disorders; Severe hepatic impairment; Severe renal impairment (creatinine clearance <30 ml/min); Refractory hypokalaemia, hypercalcaemia.

**Special warnings and precautions**

Hepatic impairment: Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive
disorders or severe hepatic insufficiency can be expected to have reduced clearance. Therefore, MICARDIS Plus should not be given to these patients. 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: Experience with MICARDIS Plus is modest and therefore periodic monitoring of potassium, creatinine and uric acid serum levels is recommended. MICARDIS Plus should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min). Thiazide diuretic-associated azotaemia may occur in patients with impaired renal function. There is no experience regarding the administration of MICARDIS Plus in patients with a recent kidney transplant.

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. Increase in cholesterol and triglyceride levels have 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 gastrointestinal 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.

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. 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: A recommended daily dose of MICARDIS Plus 40/12.5 mg tablets contains 169 mg sorbitol. MICARDIS Plus is therefore unsuitable for patients with hereditary fructose intolerance. 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
Lithium: Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. In addition, renal clearance of lithium is reduced by thiazides as a consequence the risk of lithium toxicity may 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, carbeneoxolone, 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 reninangiotensin 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 antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide); class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide); some antipsychotics: (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sulthiame, amisulpride, tiapride, pimozone, haloperidol, droperidol); others: (e.g. bepridil, cisapride, diphenamid, erythromycin IV, halofantrin, mizolastin, pentamidine, sparfloxacin, terfenadine, vincamine IV).
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.

Pregnancy and lactation
There are no adequate data on the use of telmisartan in pregnant women. Preclinical studies do not indicate teratogenic effect, but have shown fetotoxicity. Therefore as a precautionary measure, telmisartan 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, telmisartan is contraindicated in the second and third trimesters of pregnancy. If pregnancy is diagnosed telmisartan 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. Telmisartan is contraindicated during lactation since it is not known whether it is 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 must be borne in mind 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 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. Adverse reactions reported in all clinical trials and occurring more frequently (p ≤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.

Infections and infestations: Bronchitis, pharyngitis, sinusitis, upper respiratory tract infections, urinary tract infections;
Immune system disorders: Allergy;
Endocrine disorders: Loss of diabetic control;
Metabolism and nutrition disorders:
Hypercholesterolaemia, hyperuricaemia, hypokalaemia
Psychiatric disorders: Anxiety; Nervous system disorders: Dizziness
Ear and labyrinth disorders: Vertigo
Gastro-intestinal disorders: Abdominal pain, diarrhoea, dry mouth, dyspepsia, flatulence, gastrointestinal disorders
Skin and subcutaneous tissue disorders: Eczema, skin disorders;
Musculoskeletal, connective tissue and bone disorders: Arthralgia, arthrosis, back pain, leg pain, myalgia

Reproductive system and breast disorders: Impotence
General disorders and administration site conditions: Influenza-like symptoms, pain
As with other angiotensin II antagonists isolated cases of angio-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.
Additional information on individual components: Undesirable effects previously reported with one of the individual components are potential undesirable effects with MICARDIS Plus, even if not observed thus far in clinical trials.

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 comparable to placebo (43.9%) in placebo controlled trials. The adverse drug reactions listed below have been accumulated from all clinical trials including 5788 hypertensive patients treated with telmisartan:
Infections and infestations: Symptoms of infection (e.g. urinary tract infections including cystitis), upper respiratory tract infections including pharyngitis and sinusitis
Psychiatric disorders: Anxiety
Eye disorders: Abnormal vision;
Ear and labyrinth disorders: Vertigo
Gastro-intestinal disorders: Abdominal pain, diarrhoea, dry mouth, dyspepsia, flatulence, gastrointestinal disorders
Skin and subcutaneous tissue disorders: Skin disorders like eczema, sweating increased;
Musculoskeletal, connective tissue and bone disorders: Arthralgia, back pain (e.g. sciatica), cramps in legs or leg pain, myalgia, tendinitis like symptoms.
General disorders and administration site conditions: Chest pain, influenza-like symptoms. In addition, since the introduction of telmisartan in the market, cases of erythema, pruritus, faintness, insomnia, depression, vomiting, hypotension, bradycardia,
Musculoskeletal, connective tissue and bone disorders: Muscle spasm, weakness
Renal and urinary disorders: Interstitial nephritis, renal dysfunction
General disorders and administration site conditions: Fever
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. 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. 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. MICARDIS Plus may be taken with or without food.
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 40/12.5mg once daily. Miacardis 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 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. The most likely manifestations of telmisartan overdose are expected to be hypotension and tachycardia; bradycardia might 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 arrhythmias associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic drugs. No data are available for telmisartan 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.

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

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