MICARDIS® *

Composition

1 tablet contains 40 or 80 mg

[l,1'-biphenyl]-2-carboxylic acid, 4'-(l,4'dimethyl-2'-propyl[2,6-bi-1H-benzimidazole]-1'-yl)methyl] (= telmisartan)

Excipients: ** povidone, meglumine, sodium hydroxide, sorbitol, magnesium stearate

Indications

Treatment of essential hypertension.

Dosage and administration

Adults

The recommended dose is 40 mg once daily. Some patients may already benefit at a daily dose of 20 mg. in cases where the target blood pressure is not achieved, telmisartan dose can be increased to a maximum of 80 mg once daily. Alternatively, telmisartan may be used in combination with thiazide-type diuretics such as hydrochlorothiazide, which has been shown to have an additive blood pressure lowering effect with telmisartan. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four - eight weeks after the start of treatment.

MICARDIS® may be taken with or without food.

Renal impairment

No posology adjustment is required for patients with renal impairment, including those on haemodialysis.

Telmisartan is not removed from blood by hemofiltration.

Hepatic impairment

In patients with mild to moderate hepatic impairment the posology should not exceed 40 mg once daily.

Elderly

No dosing adjustment is necessary.

Children and adolescents

M1CARDIS® is not recommended for use in children below 18 years due to limited data on safety and efficacy.

Contraindications

- Hypersensitivity to the active ingredient or any of the excipients
- Second and third trimesters of pregnancy
- Lactation
- Biliary obstructive disorders
- Severe hepatic impairment

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

Special warnings and precautions

Pregnancy:

Angiotensin II receptor antagonists should not be initiated during pregnancy.

Unless continued angiotensin II receptor antagonist 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 antagonists should be stopped immediately, and if appropriate, alternative therapy should be started.

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:

When MICARDIS® is used in patients with impaired renal function, a periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of MICARDIS® in patients with a recent kidney transplant.

Intravascuiar 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, especially volume and/or sodium depletion, should be corrected before the administration of MICARDIS®.

Dual blockade of the renin-angnitensin-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 antagonist) is therefore not reccomended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

Other conditions with stimulation of the renin-angiotensin-aldosterone system:

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

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of MICARDIS® 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.

Hyperkalaemia:

During treatment with medicinal, products that affect the renin-angiotensin-aldosterone system hyperkalaemia may occur, especially in the presence of renal impairment and/or heart failure. Monitoring of serum potassium in patients at risk is recommended.

Based on experience with the use of medicinal products that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to an increase in serum potassium and should therefore be co-administered cautiously with MICARDIS®.

Hepatic impairment:

Telmisartan is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. MICARDIS® should be used with caution in these patients.

Sorbitol:

This product contains 338 mg of sorbitol per maximum recommended daily dose.

Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

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®.

Other:

As observed for angiotensin converting enzyme inhibitors, angiotensin receptor blockers including MICARDIS® are apparently less effective in lowering blood pressure in black people than in nonblacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

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.

Interactions

MICARDIS® 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 AUC_{0-24} and C_{max} of ramipril and ramiprilat. The clinical relevance of this observation is not known.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors.

Cases have also been reported with angiotensin II receptor antagonists including MICARDIS®. Therefore, 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 MICARDIS® 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.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia. The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics

Ace inhibitors, angiotensin II receptor antagonists, non steroidal antiinflammatory medicinal products (NSAIDs, including selective, COX-2 inhibitors), heparin, immunosupressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particular high in combination with potassium sparing-diuretics, and when combined with salt subsitutues containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents as lesser risk provided that precautions for use are strictly followed.

Diuretics (thiazide or loop diuretics):

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotensin when initiating therapy with telmisartan.

Potassium sparing diuretics or potassium supplements:

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spironolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Corticosteroids (systemic route):

Reduction of the antihypertensive effect.

Fertility, pregnancy and lactation

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

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

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

When used in pregnancy during the second and third trirnerters, drug that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, micardis tablets should be discontinued as soon as possible.

Drug that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin coverting enzyme inhibitors. When pregnancy is detected, Micardis tablets should be discountinued as soon as possible. The use of drug that act directly on the renin-angiotensin system during second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumbaly resulting from decreased fetal renal fiction: oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these accurrences were due to exposure to the drug.

Angiotensin II receptor antagonists 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).

Unless continued angiotensin II receptor antagonist 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.

Should exposure to angiotensin II receptor antagonists 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 antagonists should be closely observed for hypotension.

MICARDIS® is contraindicated during lactation since it is not known whether it is excreted in human milk. Non-clinical studies have shown excretion of telmisartan in breast milk.

Fertility:

No studies on fertility in humans have been performed.

In non-clinical studies, an effect of MICARDIS® on male and female fertility was not observed.

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

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials. The incidence of adverse events was not dose related and showed no correlation with gender, age or race of the patients.

The adverse drug reactions listed below have been accumulated from controlled clinical trials including 5788 hypertensive patients treated with telmisartan:

Infections and infestations:

Urinary tract infections (including cystitis), upper respiratory tract infections, sepsis including fatal outcome

Blood and lymphatic system disorders:

Anaemia, eosinophilia, thrombocytopenia

Immune system disorders:

Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:

Hyperkalaemia, hypoglycaemia (in diabetic patients)

Psychiatric disorders:

Insomnia, depression, anxiety

Nervous system disorders:

Syncope (faint)

Eye disorders:
Visual disturbance

Ear and labyrinth disorders :
Vertigo

Cardiac disorders:
Bradycardia, tachycardia

Vascular disorders:
Hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:
Dyspnoea

Gastro-intestinal disorders:
Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth, stomach discomfort

Hepatobiliary disorders:
Hepatic function abnormal / 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.

Skin and subcutaneous tissue disorders:
Pruritus, hyperhidrosis, rash, angioedema (with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption

Musculoskeletal connective tissue and bone disorders:
Back pain, muscle spasms (cramps in legs), myalgia, arthralgia, pain in extremity (leg pain), tendon pain (tendinitis like symptoms)

Renal and urinary disorders:
Renal impairment including acute renal failure (see also under Special precautions and warnings)

General disorders and administration site conditions:
Chest pain, asthenia (weakness), influenza-like illness

Investigations:

Blood creatinine increased, haemoglobin decreased, blood uric acid increased, hepatic enzymes increased, blood creatine phosphokinase (CPK) increased.

Overdose

Limited information is available with regard to overdose in humans. The most prominent manifestations of telmisartan overdose were hypotension and tachycardia, bradycardia also occured. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by haemodialysis.

Pharmacological properties

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 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.

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 antihypertensive drugs such as amlodipine, atenolol, enalapril, hydrochlorothiazide [62,63], losarían, lisinopril, ramipril and valsarían.

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pretreatment 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 micro albuminuria and macro albuminuria) 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.

Pharmacokinetics

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50%.

When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC) of telmisartan varies from approximately 6% (40 mg dose) to approximately 19% (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.

Gender differences in plasma concentrations were observed, C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males without relevant influence on efficacy.

Telmisartan is largely bound to plasma protein (> 99.5%), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{ss}) is approximately 500 L.

Telmisartan is metabolised by conjugation to the glucoronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Telmisartan is characterised by biexponentialdecay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, area

under the plasma concentration-time curve (AUC) increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan.

After oral (and intravenous) administration telmisartan is nearly exclusively excreted with the feces, exclusively as unchanged compound. Cumulative urinary excretion is < 2% of dose. Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min compared with hepatic blood flow (about 1500 mL/min).

Elderly patients

The pharmacokinetics of telmisartan do not differ between younger and elderly patients.

Patients with 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.

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.

Toxicology

In non-clinical safety studies doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit) and changes in renal hhaemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs renal tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically mediated side effects, known from non-clinical studies with both angiotensin converting enzyme inhibitors and angiotensin II antagonists, were prevented by oral saline supplementation.

In both species increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of ACE-inhibitors and other angiotensin II antagonists, do not appear to have clinical significance.

No clear evidence of a teratogenic effect was observed; 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, higher mortality.

There was no evidence of mutagenicity and relevant clastogenic activity in in vitro studies and no evidence of carcinogenicity in rats and mice.

Availability

Tablets 40 mg
Box,contains 2 alu blisters of 10 tablets

Tablet 80 mg
Box, contains 2 alu blisters of 10 tablets

Storage Conditions:

Store in the original package in order to protect from moisture.

Store below 30°C, in a safe place, out of the reach of children.

Shelf-life: 48 months

Only on doctor's prescription

Harus dengan resep dokter.

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.KG
Ingelheim am Rhein, Germany
For:
Boehringer Ingelheim International Gmbh
Ingelheim am Rhein, Germany

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