APPROVED PROFESSIONAL INFORMATION - MICARDIS

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

Micardis® 40 mg abcd

Micardis® 80 mg

tablets

COMPOSITION:

MICARDIS 40 mg: Each tablet contains 40 mg telmisartan.

MICARDIS 80 mg: Each tablet contains 80 mg telmisartan.

Inactive ingredients: magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol.

Contains sugar (sorbitol).

PHARMACOLOGICAL CLASSIFICATION:

A 7.1.3 Vascular medicines – other hypotensives

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Telmisartan is a specific angiotensin II receptor (type AT_1) antagonist. It displaces angiotensin II 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 at the AT_1 receptor. The binding is long-lasting. Telmisartan does not inhibit human plasma renin or block ion channels.

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 administration of the first dose of telmisartan in hypertensive patients, onset of antihypertensive activity occurs 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 over 24 hours after dosing.
There is an apparent trend to a dose relationship with regard to a time to recovery of baseline systolic blood pressure. In this respect data concerning diastolic blood pressure are inconsistent.

In patients with hypertension, telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate.
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 proteinuria (including microalbuminuria and macroalbuminuria) in patients with hypertension and diabetic nephropathy.

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.

Pharmacokinetic properties:
Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %.
When MICARDIS is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). After 3 hours post 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 highly bound to plasma protein (> 99,5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 L.

Telmisartan is metabolised by conjugation to the glucuronide.
No pharmacological activity has been shown for the conjugate.
Telmisartan is characterised by biexponential decay 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.

Plasma concentrations were higher in females than in males, without relevant influence on efficacy.
After oral administration telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is < 2 % of dose.
Total plasma clearance (CL_{tot}) is high (approximately 900 mL/min) when compared with hepatic blood flow (about 1 500 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.

INDICATIONS:

Treatment of mild to moderate hypertension, either alone or in combination with hydrochlorothiazide.

Reduction of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease; the benefit of treatment is evident after at least 6 months of continued treatment.

CONTRAINDICATIONS:

- Hypersensitivity to any of the ingredients of MICARDIS
- A history of angioedema related to previous therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Bilateral renal artery stenosis
- Renal artery stenosis in patients with a single kidney
- Severe renal function impairment (creatinine clearance less than 30 mL/min)
- Aortic stenosis
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see **WARNINGS AND SPECIAL PRECAUTIONS**)
- Porphyria
- Lithium therapy: Concomitant administration with MICARDIS may lead to toxic blood concentrations of lithium (see **INTERACTIONS**)
- Pregnancy and lactation (see **WARNINGS AND SPECIAL PRECAUTIONS** and **PREGNANCY AND LACTATION**)
- Severe hepatic impairment
- Obstructive biliary disorders

- In case of rare hereditary conditions that may be incompatible with sorbitol, an excipient of the product, the use of MICARDIS is contraindicated (please refer to **WARNINGS AND SPECIAL PRECAUTIONS**)
- The concomitant use of MICARDIS with aliskiren-containing products is contraindicated (see **WARNINGS AND SPECIAL PRECAUTIONS** and **INTERACTIONS**)
- Concomitant use of fluoroquinolones with Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) is contraindicated in patients with moderate to severe renal impairment (Creatinine Clearance ≤ 30 mL/min) and in elderly patients.

WARNINGS AND SPECIAL PRECAUTIONS:

Pregnancy:

MICARDIS should not be initiated during pregnancy.

Should a woman become pregnant while receiving MICARDIS, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see CONTRAINDICATIONS and PREGNANCY AND LACTATION).

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 MICARDIS (see **CONTRAINDICATIONS**).

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 (see **CONTRAINDICATIONS**).

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

Dual blockade of the renin-angiotensin-aldosterone system (RAAS):

There is evidence that the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of MICARDIS and aliskiren is therefore contraindicated (see **CONTRAINDICATIONS**).
MICARDIS should not be used concomitantly with aliskiren (see **CONTRAINDICATIONS**).

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

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

Concomitant use of fluoroquinolones:

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients. (See **CONTRAINDICATIONS**.) Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

Primary aldosteronism:

Patients with primary aldosteronism generally will not respond to MICARDIS. Therefore, the use of MICARDIS is not recommended.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy:
See **CONTRAINDICATIONS**.

Hyperkalaemia:
During treatment with Micardis, 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 MICARDIS, 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 (see **CONTRAINDICATIONS**).

Hepatic impairment:
MICARDIS is mostly eliminated in the bile. Patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance (see **CONTRAINDICATIONS).** MICARDIS should be used only with caution in patients with mild to moderate hepatic impairment.

Sorbitol:
MICARDIS contains 338 mg of sorbitol per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Other:
Angiotensin receptor blockers, including MICARDIS, are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

Excessive reduction in blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

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 including MICARDIS.

INTERACTIONS:

MICARDIS may increase the hypotensive effect of other antihypertensive agents.

Co-administration of MICARDIS did not result in a clinically significant interaction with digoxin, warfarin, hydrochlorothiazide, glibenclamide, paracetamol, ibuprofen, simvastatin and amlodipine.

For digoxin a 20 % increase in median plasma digoxin trough concentration has been observed (in a single case a 39 %). Monitoring of plasma digoxin levels should be considered.

In one study the co-administration of MICARDIS 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. Increased serum levels have also been reported with MICARDIS. Careful monitoring of serum lithium levels is recommended during concomitant use.

Concomitant treatment with NSAIDs (including aspirin 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 MICARDIS 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 medicines like MICARDIS by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**).

Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see **CONTRAINDICATIONS**).

PREGNANCY AND LACTATION:
Safety in pregnancy and lactation has not been established (see **CONTRAINDICATIONS**). When pregnancy is planned or confirmed MICARDIS should be discontinued. Medicines affecting the renin-angiotensin system, such as MICARDIS, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
Women of childbearing age should ensure effective contraception.

DOSAGE AND DIRECTIONS FOR USE:
Adults:
Treatment of essential hypertension:
The recommended dose is 40 mg once daily.
In cases where the target blood pressure is not achieved, the MICARDIS dose can be increased to a maximum of 80 mg once daily. Alternatively, MICARDIS may be used in combination with a low dose thiazide diuretic such as hydrochlorothiazide

12,5 mg, which has been shown to have an additive blood pressure lowering effect with MICARDIS. When considering raising the dose, it must be borne in mind that the maximum antihypertensive effect is generally attained four to eight weeks after the start of treatment.

Reduction of cardiovascular morbidity and mortality:

The recommended dose is 80 mg once daily. It is not known whether doses lower than 80 mg of MICARDIS are effective in preventing cardiovascular morbidity and mortality.

When initiating MICARDIS therapy for the prevention of cardiovascular morbidity and mortality, monitoring of blood pressure is recommended and, if appropriate, adjustment of medications that lower blood pressure may be necessary.

The benefit of treatment is evident only after 6 months of continued treatment.

Renal impairment:

No dosage adjustment is required for patients with renal impairment, including those on haemodialysis. MICARDIS is not removed from blood by hemofiltration.

Hepatic impairment:

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

Elderly:

No dosing adjustment is necessary.

Children and adolescents up to 18 years:

The safety and efficacy of MICARDIS for use in children below 18 years have not been established.

SIDE EFFECTS:

The incidence of adverse events in controlled clinical trials was not dose related and showed no correlation with gender, age or race of the patients.

The following frequency classification is used:
very common ≥ 1/10; common ≥ 1/100 and < 1/10; uncommon ≥ 1/1 000 and < 1/100;
rare ≥ 1/10 000 and < 1/1 000; very rare < 1/10 000.

Infections and infestations:
Uncommon: urinary tract infections (including cystitis), upper respiratory tract infections

Blood and the lymphatic systemic disorders:
Uncommon: anaemia
Rare: thrombocytopenia

Immune system disorders:
Rare: hypersensitivity, angio-oedema (with fatal outcome)

Metabolism and nutrition disorders:
Uncommon: hyperkalaemia

Psychiatric disorders:
Uncommon: depression, insomnia
Rare: anxiety

Nervous system disorders:
Uncommon: syncope/fainting

Eye disorders:
Rare: visual disturbance

Ear and labyrinth disorders:

Uncommon: vertigo

Cardiac disorders:

Uncommon: bradycardia

Rare: tachycardia

Vascular disorders:

Uncommon: hypotension, orthostatic hypotension

Respiratory, thoracic and mediastinal disorders:

Common: cough

Uncommon: dyspnoea

Gastro-intestinal disorders:

Uncommon: abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting

Rare: dry mouth, stomach discomfort

Skin and subcutaneous tissue disorders:

Uncommon: increased sweating (hyperhidrosis), pruritus, rash

Rare: eczema, erythema, drug eruption, toxic skin eruption

Musculoskeletal, connective tissue and bone disorders:

Uncommon: back pain, muscle spasms (cramps in legs), myalgia

Rare: arthralgia, pain in extremity (leg pain)

Renal and urinary disorders:

Uncommon: renal impairment including acute renal failure

General disorders and administration site conditions:

Uncommon: chest pain, asthenia (weakness)

Rare: influenza-like symptoms

Investigations:

Uncommon: blood creatinine increased
Rare: haemoglobin decreased, blood uric acid increased, hepatic enzymes increased, blood creatine phosphokinase increased.

Post-marketing:
Side effects which have been spontaneously reported since the introduction of MICARDIS into the market.

Infections and infestations:
Sepsis including fatal outcome

Blood and the lymphatic systemic disorders:
Eosinophilia

Immune system disorders:
Anaphylactic reaction

Skin and subcutaneous tissue disorders:
Urticaria

Musculoskeletal, connective tissue and bone disorders:
Tendon pain (tendinitis like symptoms)

Metabolism and nutrition disorders:
Hypoglycaemia (in diabetic patients)

Hepato-biliary disorders:
Hepatic function abnormal/liver disorder

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
Limited information is available with regard to overdose in humans. The most prominent manifestations of MICARDIS overdose were hypotension and tachycardia; bradycardia also occurred. If symptomatic hypotension should occur,

supportive treatment should be instituted. MICARDIS is not removed by haemodialysis.

IDENTIFICATION :

MICARDIS 40 mg: White or off-white, oblong tablets; one face marked with 51H and the other with the Boehringer Company symbol.

MICARDIS 80 mg: White or off-white, oblong tablets; one face marked with 52H and the other with the Boehringer Company symbol.

PRESENTATION:

Blister packs of 28 tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Keep out of reach of children.
MICARDIS tablets should not be removed from their foil pack until required for administration in order to protect the product from moisture.

REGISTRATION NUMBERS:

MICARDIS 40 mg tablets: 33/7.1.3/0020
MICARDIS 80 mg tablets: 33/7.1.3/0021

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE:

Ingelheim Pharmaceuticals (Pty) Ltd
407 Pine Avenue
Randburg
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date of registration: 20 August 1999
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