PRODUCT MONOGRAPH

Pr Micardis®

Telmisartan Tablets

40 mg and 80 mg

Angiotensin II AT1 Receptor Blocker

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[Pr]Micardis®

Telmisartan Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	tablet 40 mg , 80 mg	magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol

INDICATIONS AND CLINICAL USE

Treatment of Essential Hypertension
MICARDIS (telmisartan) is indicated for the treatment of mild to moderate essential hypertension.

MICARDIS may be used alone or in combination with thiazide diuretics.

The concurrent use with angiotensin converting enzyme inhibitors is not recommended.

Risk Reduction of Cardiovascular Morbidity
MICARDIS is indicated to reduce the risk of non-fatal stroke or non-fatal myocardial infarction in patients 55 years or older at high risk of developing major cardiovascular events who cannot tolerate an angiotensin converting enzyme inhibitor (ACEI).

High risk of cardiovascular events includes evidence of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or diabetes mellitus with evidence of end-organ damage. MICARDIS has been used with other required treatment such as other antihypertensives (including ACEI), antiplatelet or statins (see WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS and CLINICAL TRIALS section).

Geriatrics (> 65 years of age):
No dosing adjustment is necessary. It should be recognized, however, that greater sensitivity in some older individuals cannot be ruled out.

Pediatrics (< 18 years of age):
MICARDIS is not recommended for use in children below 18 years. The safety and efficacy of MICARDIS for use in children below 18 years have not been established.

CONTRAINDICATIONS

MICARDIS (telmisartan) is contraindicated in:

- Concomitant use of angiotensin receptor antagonists (ARBs) –including MICARDIS- with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2) is contraindicated (see WARNINGS and PRECAUTIONS, **Cardiovascular**, Dual Blockade of the Renin-Angiotensin System (RAS) and **Renal**, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs or aliskiren-containing drugs).
- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph
- Pregnant women (see WARNINGS AND PRECAUTIONS, Special Populations – Pregnant Women)
- Nursing women (see WARNINGS AND PRECAUTIONS, Special Populations – Nursing Women)
- Patients with the rare hereditary condition of fructose intolerance
    - Sorbitol: MICARDIS tablets contain 338 mg of sorbitol per maximum recommended daily dose.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

When used in pregnancy, angiotensin receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, MICARDIS should be discontinued as soon as possible (see WARNINGS AND PRECAUTIONS, Special Populations).

General

A case of rare but fatal angioedema occurred in a patient who had been medicated for about 6 months with telmisartan, the active component of MICARDIS. The Autopsy Report described evidence of edema of the laryngeal mucosa, with terminal respiratory and circulatory failure. This is in the context of approximately 5.2 million patient-years exposure to telmisartan annually.

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, MICARDIS should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is

involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 ml of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS - Post Marketing Adverse Drug Reactions).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be treated with MICARDIS (see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions - All Clinical Trials, Immune System, Not known: angioedema and ADVERSE REACTIONS - Post Market Adverse Drug Reactions).

Cardiovascular

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. These patients are at risk of decreased coronary perfusion resulting from a cardiac output that is limited by a fixed cardiac vascular obstruction.

Hypotension:
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with MICARDIS. Such conditions, especially volume and/or sodium depletion, should be corrected prior to administration of MICARDIS. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

Dual blockade of the Renin-Angiotensin System (RAS)
There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as MICARDIS, or of angiotensin-converting-enzyme inhibitors (ACEIs) with aliskiren increases the risk of hypotension, syncope, stroke, hyperkalemia and deterioration of renal function, including renal failure, in patients with diabetes mellitus (type 1 or type 2) and/or moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). Therefore, the use of MICARDIS in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including MICARDIS, with other agents blocking the RAS, such as ACEIs or aliskiren-containing drugs, is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Endocrine and Metabolism

Hyperkalemia:
Drugs such as MICARDIS that affect the renin-angiotensin-aldosterone system can cause

hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of drugs 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 a greater risk of an increase in serum potassium.

The use of a dual renin-angiotensin-aldosterone system (RAAS) blockade may lead to increased occurrence of hyperkalemia when given as add-on therapy in patients with controlled blood pressure.

Fertility

No Studies on fertility in humans have been performed. (see Part II: TOXICOLOGY, Reproduction).

Hepatic/Biliary/Pancreatic

Hepatic Impairment: As the majority of telmisartan is eliminated by biliary excretion, patients with cholestasis, biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan. Three to four fold increases in C_{max} and AUC were observed in patients with liver impairment as compared to healthy subjects. MICARDIS (telmisartan) should be used with caution in these patients (see DOSAGE AND ADMINISTRATION).

Neurologic

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.

Renal

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, dual blockade of the renin- angiotensin-aldosterone system (e.g. concomitant use of an ARB with an ACE-inhibitor or the direct renin-inhibitor aliskiren) and treatment with agents that inhibit this system have been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. There is no experience with long term use of MICARDIS (telmisartan) in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated. In susceptible patients, concomitant diuretic use may further increase the risk. Use of telmisartan should include appropriate assessment of renal function in these types of patients.

There is no experience regarding the administration of MICARDIS (telmisartan) in patients with a recent kidney transplant.

Renal Impairment
The use of ARBs – including MICARDIS – or of ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m^2). (See CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Special Populations

Pregnant Women:
Drugs that act directly on the renin-angiotensin-aldosterone system (RAAS) can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, MICARDIS (telmisartan) should be discontinued as soon as possible.

The use of angiotensin receptor (AT_1) blockers (ARBs) is not recommended during pregnancy and should not be initiated during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with ARB, similar risks may exist for this class of drugs. 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 antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs 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, hyperkalemia).

Infants with a history of in utero exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypotension and/or substituting for disordered renal function; however, limited experience with those procedures has not been associated with significant clinical benefit.

It is not known if telmisartan can be removed from the body by hemodialysis.

Preclinical studies with telmisartan do not indicate teratogenic effect, but have shown fetotoxicity. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses up to 45 mg/kg/day with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Significant levels of telmisartan

were present in rat milk and rat fetuses' blood during late gestation.

Nursing Women:
It is not known whether telmisartan is excreted in human milk but significant levels have been found in the milk of lactating rats. Because many drugs are excreted in human milk and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Diabetic Patients:

In diabetic patients with undiagnosed coronary artery disease (CAD) on blood pressure lowering therapy, the risk of fatal myocardial infarction and unexpected cardiovascular death may be increased. In patients with diabetes mellitus, CAD may be asymptomatic and therefore undiagnosed. These patients should undergo appropriate diagnostic evaluation, e.g. exercise stress testing, to detect and to treat CAD accordingly before initiating blood pressure lowering treatment with MICARDIS.

Pediatrics (< 18 years of age):
MICARDIS is not recommended for use in children below 18 years due to limited data on safety and efficacy.

Geriatrics (> 65 years of age):
Of the total number of patients receiving MICARDIS (telmisartan) in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were ≥75 years. No overall age related differences were seen in the adverse effect profile, but greater sensitivity in some older patients cannot be ruled out.

Monitoring and Laboratory Tests
For specific monitoring and laboratory tests, see WARNINGS AND PRECAUTIONS (Cardiovascular, Endocrine and Metabolism, Hepatic and Renal) and DRUG INTERACTIONS sections.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Side effects were reported in clinical trials with telmisartan in the indication hypertension or in

patients 50 years or older at high risk of cardiovascular events.

MICARDIS (telmisartan) has been evaluated for safety in 27 clinical trials involving 7968 patients treated for hypertension. Of these 7968 patients, 5788 patients were treated with MICARDIS monotherapy including 1058 patients treated for ≥1 year and 1395 patients treated in placebo-controlled trials.

In 3400 patients, discontinuation of therapy due to adverse events was required in 2.8% of MICARDIS patients and 6.1% of placebo patients.The following potentially serious adverse events have been reported rarely with telmisartan in controlled clinical trials: syncope and hypotension. In placebo-controlled trials, no serious adverse event was reported with a frequency of greater than 0.1% in MICARDIS-treated patients.

The safety profile of MICARDIS in patients treated for risk reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients. In this program, 11% of patients treated with telmisartan discontinued study medication due to adverse events. The most common adverse events that led to discontinuation were dizziness, hypotension and headache.

The adverse drug reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The listing also takes into account serious adverse events and adverse events leading to discontinuation reported in three clinical long-term studies including 21642 patients treated with telmisartan for prevention of cardiovascular morbidity and mortality for up to six years.

All Clinical Trials

The adverse drug events listed below have been accumulated from 27 clinical trials including 5788 hypertensive patients treated with telmisartan. Adverse events have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1000, <1/100); rare (≥1/10000, <1/1000); very rare (< 1/10000)

Body as a Whole, General:

Common: Chest pain, influenza-like symptoms, fatigue, conjunctivitis.
Uncommon: Hyperhidrosis, asthenia (weakness).

Blood and Lymphatic System:

Uncommon: Anaemia.
Rare: Thrombocytopenia.
Not known: Eosinophilia.

Cardiovascular System:

Common: Edema, palpitation.
Uncommon: Bradycardia, orthostatic hypotension, hypotension.
Rare: Tachycardia.

Central and Peripheral Nervous System:

Very Common: Headache.
Common: Dizziness, insomnia.
Uncommon: Vertigo.

Eye Disorders:

Rare: Visual disturbance.

Gastro-Intestinal System:

Common: Abdominal pain, diarrhoea, dyspepsia, nausea, constipation, gastritis.
Uncommon: Dry mouth, flatulence, vomiting.
Rare: Stomach discomfort.

Hepato-biliary Disorders:

Rare: 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

Immune System:

Rare: Hypersensitivity.
Not known: Anaphylactic reaction, angioedema.

Infections and Infestations:

Uncommon: Upper respiratory tract infections (including pharyngitis, sinusitis, bronchitis, rhinitis and coughing) and urinary tract infections (including cystitis).
Not known: Sepsis including fatal outcome.

Investigations:

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

Metabolism and Nutrition Disorders:

Uncommon: Hyperkalemia.
Rare: Hypoglycemia (in diabetic patients)

Musculo-Skeletal System:

Common: Arthralgia, muscle spasms (cramps in legs) or pain in extremity (leg pain), myalgia, arthritis, arthrosis.
Uncommon: Tendon pain (tendonitis like symptoms), back pain.

Nervous System:

Uncommon: Syncope (faint).

Psychiatric System:

Common: Anxiety, nervousness.
Uncommon: Depression.

Renal and Urinary System:

Uncommon: Renal impairment including acute renal failure.

Respiratory System:

Common: dyspnea.

Skin and Appendages System:

Common: Skin disorders like rash.
Uncommon: Pruritus.
Rare: Erythema, drug eruption, eczema, toxic skin eruption.
Not known: Urticaria.

Hemoglobin:

Infrequently, a decrease in hemoglobin has been observed which occurs more often during treatment with telmisartan than with placebo.

Placebo-Controlled Trials

The overall incidence of adverse events reported with MICARDIS (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials. Adverse events occurring in ≥1% of 1395 hypertensive patients treated with MICARDIS monotherapy in placebo-controlled clinical trials, regardless of drug relationship, include the following:

Table 1: Adverse Events Occurring in > 1% of Hypertensive Patients Treated with MICARDIS Monotherapy

Adverse Event, by System	MICARDIS Total N = 1395 %	Placebo N = 583 %
Body as a Whole		
Back Pain	2.7	0.9
Chest Pain	1.3	1.2
Fatigue	3.2	3.3
Influenza-Like Symptoms	1.7	1.5
Pain	3.5	4.3
Central & Peripheral Nervous System		
Dizziness	3.6	4.6
Headache	8.0	15.6
Somnolence	0.4	1.0
Gastrointestinal System		
Diarrhea	2.6	1.0
Dyspepsia	1.6	1.2
Nausea	1.1	1.4

Adverse Event, by System	MICARDIS Total N = 1395 %	Placebo N = 583 %
Vomiting	0.4	1.0
Musculoskeletal System		
Myalgia	1.1	0.7
Respiratory System		
Coughing	1.6	1.7
Pharyngitis	1.1	0.3
Sinusitis	2.2	1.9
Upper Respiratory Tract Infection	6.5	4.6
Heart Rate and Rhythm Disorders		
ECG abnormal specific	0.2	1.0
Palpitation	0.6	1.0
Cardiovascular Disorders, General		
Hypertension	1.0	1.7
Oedema peripheral	1.0	1.2

The incidence of adverse events was not dose-related and did not correlate with the gender, age, or race of patients.

Less Common Clinical Trial Adverse Events (<1%)

In addition, the following adverse events, with no established causality, were reported at an incidence <1% in placebo-controlled clinical trials.

Autonomic Nervous System Disorders: sweating increased.

Body as a Whole: abdomen enlarged, allergy, cyst nos, fall, fever, leg pain, rigors, syncope.

Cardiovascular Disorders, General: hypotension, hypotension-postural, leg edema.

Central & Peripheral Nervous System Disorder: hypertonia, migraine-aggravated, muscle contraction-involuntary.

Gastrointestinal System Disorders: anorexia, appetite increased, flatulence, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry, abdominal pain.

Heart Rate & Rhythm Disorders: arrhythmia, tachycardia.

Metabolic & Nutritional Disorders: diabetes mellitus, hypokalaemia.

Musculoskeletal System Disorders: arthritis, arthritis aggravated, arthrosis, bursitis, fascitis plantar, tendinitis.

Myo Endo Pericardial & Valve Disorders: myocardial infarction.

Psychiatric Disorders: nervousness.

Red Blood Cell Disorders: anemia.

Reproductive Disorders, Female: vaginitis.

Resistance Mechanism Disorders: abscess, infection, bacterial, moniliasis genital, otitis media.

Respiratory System Disorders: bronchospasm, epistaxis, pneumonia, bronchitis.

Skin & Appendage Disorders: rash, skin dry.

Urinary System Disorders: Dysuria, hematuria, micturition disorder, urinary tract infection.

Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.

Vision Disorders: vision abnormal.

Abnormal Hematologic and Clinical Chemistry Findings

In placebo-controlled clinical trials involving 1041 patients treated with MICARDIS monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS.

Creatinine, Blood Urea Nitrogen:

Increases in BUN ($\geq$11.2 mg/dl) and creatinine ($\geq$0.5 mg/dl) were observed in 1.5% and 0.6% of MICARDIS-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with MICARDIS in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.

Hemoglobin, Hemotocrit:

Clinically significant changes in hemoglobin and hematocrit (<10g/dl and <30%, respectively) were rarely observed with MICARDIS treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.

Serum Uric Acid:

An increase in serum uric acid ($\geq$2.7 mg/dl) was reported in 1.7% of patients treated with MICARDIS and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (>10mEq/L) was observed in 2.3% of patients with MICARDIS, with 0.4% reported in patients at baseline. Increases in serum uric acid were primarily observed in patients who received MICARDIS in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.

Liver Function Tests:
Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5%, respectively of patients treated with MICARDIS compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Serum Potassium:
Marked laboratory changes in serum potassium (≥+/- 1.4 mEq/L) occurred rarely and with a lower frequency in MICARDIS-treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceeded 3 mEq/L) were found in 0.6% of MICARDIS-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.

Cholesterol:
In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time, in both cases cholesterol values reverted to baseline levels.

Serum elevations in cholesterol were reported as adverse events in 11 of 3445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

Post-Market Adverse Drug Reactions
Since the introduction of telmisartan in the market, cases of anxiety, dizziness, vision troubled, vertigo, abdominal distension, abdominal pain, retching, hyperhidrosis, arthralgia, myalgia, muscle spasm, back pain, asthenia, pain in extremity, fatigue, chest pain, blood creatinine increased, erythema, pruritus, syncope/faint, insomnia, depression, stomach discomfort, vomiting, hypotension (including orthostatic hypotension), bradycardia, tachycardia, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, hyperkalemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, and weakness have been reported. The frequency of these effects is unknown. As with other angiotensin II antagonists, rare cases of angioedema (with fatal outcome), pruritus, rash and urticaria have been reported.

Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

In addition, since the introduction of telmisartan in the market, cases with increased blood creatinine phosphokinase (CPK) have been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Table 2: Established or Potential Drug-Drug Interactions

Telmisartan	Effect	Clinical comment
Agents increasing serum potassium		Since the telmisartan reduces the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that telmisartan may have on serum potassium.
Digoxin	When telmisartan was co-administered with digoxin, mean increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed.	It is recommended that digoxin levels be monitored with appropriate dose adjustments when initiating, adjusting or discontinuing MICARDIS, to maintain appropriate plasma digoxin concentrations.
Diuretics	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with telmisartan.	The possibility of symptomatic hypotension with the use of telmisartan can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of telmisartan (see WARNINGS AND PRECAUTIONS – Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics.
Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs or aliskiren-containing drugs		Dual Blockade of the renin-angiotensin system with ARBs, ACEIs or aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment, and is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia. (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System).

Telmisartan	Effect	Clinical comment
Lithium salts	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor antagonists including MICARDIS.	Serum lithium level monitoring is advisable during concomitant use.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	Combinations of angiotensin-II antagonists (MICARDIS) and NSAIDs (including ASA and COX-2 inhibitors) might have an increased risk for acute renal failure and hyperkalemia. NSAIDs (including ASA and COX-2 inhibitors) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment, this may lead to acute renal failure.	Blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure. Monitoring of renal function at the beginning and during the course of the treatment should be recommended. Co-administration of MICARDIS did not result in a clinically significant interaction with ibuprofen.
Ramipril	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.
Warfarin	MICARDIS (telmisartan) administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).	
Other		Coadministration of MICARDIS also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, or hydrochlorothiazide.

Drug-Food Interactions
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) to approximately 19% (160 mg), and the reduction in C_{max} varies from approximately 26% (40 mg) to 56% (160 mg). However, three hours after administration, plasma concentrations are similar whether telmisartan is taken with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
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.

DOSAGE AND ADMINISTRATION

Dosing Considerations
The antihypertensive effect is present within 2 weeks and maximal reduction is generally attained after four weeks. If additional blood pressure reduction is required, a thiazide diuretic may be added.

MICARDIS should be taken consistently with or without food.

Recommended Dose and Dosage Adjustment

Treatment of Essential Hypertension:
The recommended dose of MICARDIS (telmisartan) is 80 mg once daily.

No initial dosing adjustment is necessary for elderly patients or for patients with renal impairment, but greater sensitivity in some older individuals cannot be ruled out. Markedly reduced telmisartan plasma levels were observed in patients on hemodialysis.

For patients with hepatic impairment a starting dose of 40 mg is recommended (see WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Risk Reduction of Cardiovascular Morbidity:
The recommended dose is 80 mg once daily in patients 55 years or older at high risk for a cardiovascular event. It is not known whether doses lower than 80 mg of MICARDIS are effective in preventing cardiovascular morbidity. It can be administered with other antihypertensive agents except an ACEI.

When initiating telmisartan therapy at this dose, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Missed Dose
MICARDIS should be taken at the same time each day, preferably in the morning. However, if a dose is missed during the day, the next dose should be continued at the usual time. Do not double dose.

OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most prominent manifestations of overdosage were hypotension and/or tachycardia; bradycardia also occurred. If symptomatic hypotension should occur, supportive treatment should be instituted.

Telmisartan is not removed by hemodialysis.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Telmisartan is an orally active angiotensin II AT_1 receptor antagonist. By selectively blocking the binding of angiotensin II to the AT_1 receptors telmisartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptors, and has essentially no affinity for the AT_2 receptors. AT_2 receptors have been found in many tissues, but to date they have not been associated with cardiovascular homeostasis. In vitro binding studies indicate that telmisartan has no relevant affinity for other receptors nor does it inhibit human plasma renin.

Telmisartan does not inhibit angiotensin converting enzyme, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it affect renin or other hormone receptors or ion channels involved in cardiovascular regulation of blood pressure and sodium homeostatis.

In hypertensive patients blockade of angiotensin II AT_1 receptors results in two to three fold increase in plasma renin and angiotensin II plasma concentrations. Long term effects of increased AT_2 receptor stimulation by angiotensin II are unknown.

Pharmacodynamics

Treatment of Essential Hypertension
In normal volunteers, a dose of telmisartan 80 mg inhibited the pressor response to an

intravenous infusion of angiotensin II by about 90% at peak with approximately 40% inhibition persisting for 24 hours.

In hypertensive patients with normal renal function, no clinically significant effects on renal plasma flow, filtration fraction, or glomerular filtration rate were observed. In multiple dose studies in hypertensive patients, telmisartan had no adverse effect on renal function as measured by serum creatinine or blood urea nitrogen.

The antihypertensive effects of telmisartan were demonstrated in 6 placebo-controlled clinical trials, in a total of 1773 patients, 1031 of whom were treated with MICARDIS (telmisartan). Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose and there was a gradual increase in the antihypertensive effect during continued treatment for $\leq$12 weeks, with most of the increase occurring during the first month. Onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. The antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. The magnitude of blood pressure reduction from baseline, after placebo subtraction, was on average (SBP/DBP) -11.3/-7.3 mmHg for MICARDIS 40 mg once daily, and -13.7/-8.1 mmHg for MICARDIS 80 mg once daily. Upon abrupt cessation of treatment with MICARDIS, blood pressure gradually returned to baseline values over a period of several days. During long term studies (without placebo control) the effect of telmisartan appeared to be maintained for $\geq$1 year.

For those patients treated with telmisartan 80 mg once daily who required additional blood pressure reduction, addition of a low dose of hydrochlorothiazide (12.5 mg) resulted in incremental blood pressure reductions of -9.4/-7.0 mmHg.

The antihypertensive effect of once-daily telmisartan (40-80 mg) was similar to that of once-daily amlodipine (5-10 mg), atenolol (50-100 mg), enalapril (5-20 mg) and lisinopril (10-40 mg).

There was essentially no change in heart rate in telmisartan-treated patients in controlled trials.

In clinical trials with post-dose in-clinic monitoring no excessive blood pressure lowering peak effect was observed even after the first dose, and the incidence of symptomatic orthostasis was very low (0.04%). With automated ambulatory blood pressure monitoring, the 24-hour trough-to-peak ratio for telmisartan was determined to be at least 80% for both systolic and diastolic blood pressure.

The antihypertensive effect of telmisartan is not influenced by patient age, weight or body mass index. Blood pressure in hypertensive black patients (usually a low renin population) is significantly reduced by telmisartan (compared to placebo), but less so than in non-black patients.

Diabetic Patients: Multiple exploratory post hoc analyses were carried out on the three cardiovascular (CV) outcome trials (ONTARGET, TRANSCEND and PRoFESS). In TRANSCEND and PRoFESS, an increased risk of unexpected CV death was seen with

telmisartan versus placebo in diabetics without previously diagnosed coronary artery disease (CAD) but not in those with a documented history of CAD. No such increased risk was demonstrated in ONTARGET for telmisartan versus ramipril in diabetes patients without previously diagnosed CAD.

These findings in diabetics with added cardiovascular risk, could be related to a pre-existing but asymptomatic or silent CAD. Diabetics with undiagnosed and therefore untreated CAD may be at increased risk when lowering blood pressure too far, e.g. when initiating antihypertensive therapy, due to a further reduction of perfusion in an already narrowed coronary artery.

Risk Reduction of Cardiovascular Morbidity
See CLINICAL TRIALS section.

Pharmacokinetics

Absorption: Following oral administration, telmisartan is well absorbed, with a mean absolute bioavailability of about 50%. Mean peak concentrations of telmisartan are reached in 0.5-1 hour after dosing.

The pharmacokinetic profile is characterized by greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses >40 mg. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours, and does not accumulate in plasma upon repeated once-daily dosing.

Metabolism: Telmisartan is metabolized by conjugation with glucuronic acid to form an acylglucuronide of telmisartan. This glucuronide is the only metabolite which has been identified in human plasma and urine. Following both oral dosing and intravenous administration of radiolabeled telmisartan, the parent compound represented approximately 85% and the glucuronide approximately 11% of total radioactivity in plasma. No pharmacological activity has been shown for the glucuronide conjugate.

The CYP 450 isoenzymes are not responsible for telmisartan metabolism.

Excretion: Total plasma clearance of telmisartan is > 800 mL/min. Half-life and total clearance appear to be independent of dose. Biliary excretion is the main route of elimination of telmisartan and its metabolite. Following intravenous and oral administration of C^{14} labelled telmisartan 0.91% and 0.49% of administered dose were found in the urine as glucuronide, respectively. Most of the oral and intravenous dose, >97%, was excreted in feces as the parent compound.

Women have a lower telmisartan clearance and have a greater systolic blood pressure response at trough than men.

Distribution: Telmisartan is >99.5% bound to plasma protein, mainly albumin and a1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with

therapeutic doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding sites.

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) to approximately 19% (160 mg), and the reduction in C_{max} varies from approximately 26% (40 mg) to 56% (160 mg). However, three hours after administration, plasma concentrations are similar whether telmisartan is taken with or without food.

Special Populations and Conditions

Pediatrics:
Telmisartan pharmacokinetics have not been investigated in patients <18 years of age.

Geriatrics:
The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years. (see DOSAGE AND ADMINISTRATION)

Gender:
Plasma concentrations of telmisartan are generally 2-3 fold higher in females than in males. No dosage adjustment is necessary.

Hepatic Insufficiency:
In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100%. A lower starting dose should be considered. (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency:
Renal excretion of telmisartan is negligible. No dosage adjustment is necessary in patients with renal insufficiency. In patients on hemodialysis both Cmax and AUC of telmisartan were markedly reduced as compared to healthy volunteers. Telmisartan is not removed by hemodialysis. (see WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION)

Genetic Polymorphism:
No studies were conducted to evaluate the influence of genetic polymorphisms on the pharmacokinetics or pharmacodynamics of telmisartan.

STORAGE AND STABILITY

MICARDIS tablets are hygroscopic and require protection from moisture. Tablets are packaged in blisters and should be stored at room temperature, 15-30°C (59-86°F). Tablets should not be removed from blisters until immediately prior to administration.

DOSAGE FORMS, COMPOSITION AND PACKAGING

MICARDIS is available as white, oblong-shaped, uncoated tablets containing telmisartan 40 mg or 80 mg. Tablets are marked with the Boehringer Ingelheim logo on one side, and on the other side, either 51H or 52H for the 40 mg and 80 mg strengths, respectively.

The non-medical ingredients also contained with each table are as follows: magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol.

MICARDIS Tablets 40 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.

MICARDIS Tablets 80 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

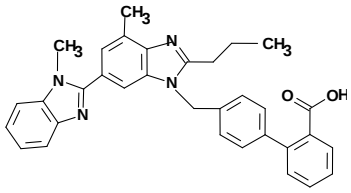
Drug Substance

Proper name: Telmisartan

Chemical name: [1,1'-Biphenyl]-2-carboxylic acid,4'-[(1,4'- dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-(CAS)[1]

Molecular formula and molecular mass: $C_{33}H_{30}N_4O_2$, 514.63

Structural formula:



Physicochemical properties:

Description:
Telmisartan is a white to off-white, odorless crystalline powder. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except HCL), and soluble in strong base.

Polymorphism:
Exhibits two different polymorphic modifications, Form A (thermodynamically more stable) and Form B, and a third pseudo polymorphic form.

Melting Point: 269 ± 1°C (polymorphic Form A)
183 ± 1°C (polymorphic Form B)

Apparent partition coefficient: $\log_{papp} = 3.2$

CLINICAL TRIALS

Study demographics and trial design

Table 3: Summary of patient demographics for clinical trials in specific indication

Study	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 40 mg, 80 mg, 120 mg (40 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 4 weeks	207	51.8 (30-68)	62% male/ 38% female
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 20 mg, 40 mg, 80 mg, 120 mg (40 mg + 80 mg), 160 mg (80 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 4 weeks	274	52.3 (28-72)	69% male/ 31% female
Randomized, Double blind, Placebo-controlled in mild to moderate essential hypertensive patients	Treatment doses: 40 mg, 80 mg, 120 mg, 160 mg (80 mg + 80 mg) once daily Route of Administration: Oral Duration of treatment: 12 weeks	440	54.1 (21-83)	64% male/ 36% female
TRANSCEND: Randomized, Double blind, Placebo controlled in $\geq$ 55 year old patients at high risk for cardiovascular events and intolerant to ACEI	Treatment doses: telmisartan 80 mg and placebo once daily Route of Administration: Oral Duration of treatment: 4.75 years	5,926	66.9	57% male/ 43% female

* median age
T = telmisartan

Study results

Table 4: Results of studies

<table>
<tr><th>Endpoint(s)</th><th>Efficacy Results</th></tr>
<tr><td>Change from baseline in supine DBP at trough (24 hours post dosing) at last double-blind visit.</td><td>
<u>Intent-to-Treat Supine Blood Pressure Results</u>
<table>
<tr><td></td><td></td><td><u>Adjusted Mean Changes from Baseline (mmHg)</u></td><td></td></tr>
<tr><td><u>Treatment</u></td><td><u>N</u></td><td><u>Systolic</u></td><td><u>Diastolic</u></td></tr>
<tr><td>Placebo</td><td>43</td><td>+3.5</td><td>-1.5</td></tr>
<tr><td>Telmisartan 40 mg</td><td>40</td><td>-10.0****</td><td>-7.9***</td></tr>
<tr><td>Telmisartan 80 mg</td><td>41</td><td>-15.5****</td><td>-8.7***</td></tr>
<tr><td>Telmisartan 120 mg</td><td>41</td><td>-12.5****</td><td>-9.8****</td></tr>
</table>
***: $p \leq 0.001$ vs. Placebo
****: $p \leq 0.0001$ vs. Placebo
</td></tr>
<tr><td>Change from baseline in supine DBP at trough (24-hours post-dosing) at the last observation during the double-blind phase</td><td>
<u>Intent-to-Treat Analysis of the Change from Baseline in Supine Blood Pressure</u>
<table>
<tr><td></td><td></td><td><u>Adjusted[1] Mean Change (S.E.) (mmHg)</u></td><td></td></tr>
<tr><td><u>Treatment</u></td><td><u>N</u></td><td><u>Diastolic</u></td><td><u>Systolic</u></td></tr>
<tr><td></td><td></td><td>(baseline = 102.4)</td><td>(baseline = 151.2)</td></tr>
<tr><td>Placebo</td><td>46</td><td>-0.4 (1.2)</td><td>3.2 (1.9)</td></tr>
<tr><td>Telmisartan 20 mg</td><td>47</td><td>-6.9 (1.1)****</td><td>-3.3 (1.8)*</td></tr>
<tr><td>Telmisartan 40 mg</td><td>47</td><td>-8.6 (1.2)****</td><td>-7.8 (1.9)****</td></tr>
<tr><td>Telmisartan 80 mg</td><td>44</td><td>-10.5 (1.2)****</td><td>-9.8 (1.9)****</td></tr>
<tr><td>Telmisartan 120 mg</td><td>45</td><td>-8.9 (1.2)****</td><td>-9.1 (1.9)****</td></tr>
<tr><td>Telmisartan 160 mg</td><td>44</td><td>-9.4 (1.2)****</td><td>-11.7 (2.0)****</td></tr>
</table>
[1] Based on a model with the effects of baseline blood pressure, center, treatment and treatment-by-center interaction.
Legend for treatment comparison with placebo:
*: $p < 0.05$ (two-sided test)
****: $p < 0.0001$
</td></tr>
</table>

<table>
<tr><th>Endpoint(s)</th><th>Efficacy Results</th></tr>
<tr><td>Change from baseline in supine DBP and SBP at trough (24 hours post-dosing) at the last observation during the double-blind phase.</td><td><u>Intent-to-Treat Analysis of the Change from Baseline in Supine Blood Pressure at Trough</u>

<u>Adjusted[1] Mean Changes (S.E.) (mmHg)</u>

<u>Treatment</u> | <u>N</u> | <u>Diastolic</u> (baseline = 100.4) | <u>Systolic</u> (baseline = 153.9)
Placebo | 74 | -1.8 (0.9) | +0.8 (1.6)
Telmisartan 40 mg | 72 | -9.3 (0.9)**** | -11.6 (1.6)****
Telmisartan 80 mg | 71 | -9.7 (0.9)**** | -11.8 (1.6)****
Telmisartan 120 mg | 72 | -8.8 (0.9)**** | -10.0 (1.5)****
Telmisartan 160 mg | 73 | -8.6 (0.9)**** | -11.9 (1.5)****

[1] Based on a model with the effects of baseline blood pressure, center, treatment and treatment-by-center interaction

****: p < 0.0001

Note: Significance of the treatment-by-center interaction was 0.5789 and 0.1557 for diastolic and systolic, respectively.</td></tr>
<tr><td>Primary: Composite of cardiovascular death, myocardial infarction, stroke or hospitalization for congestive heart failure

Secondary: First three components of primary endpoint</td><td>No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).</td></tr>
</table>

BP = blood pressure
DBP = diastolic blood pressure
SBP = systolic blood pressure

<u>TRANSCEND Study</u>

TRANSCEND randomized in a double-blind fashion 5,926 patients to telmisartan 80 mg once daily or placebo after a 3-4-week run-in period on placebo and then telmisartan [9]. Patients were ≥55 years, and at high risk of a CV event as indicated by coronary artery (prior MI, stable or unstable angina, prior PTCA or CABG) or peripheral arterial disease (prior limb bypass or angioplasty, claudication, artery stenosis), prior stroke or TIA or high risk diabetics. All patients had a *known intolerance to ACE inhibitors*. The patient population studied was 57% male, 62% Caucasian, 60% were ≥65 years and were followed-up for a median period of 56 months. Patients also received acetylsalicylic acid (75%), statins (56%), beta-blockers (59%), calcium-channel blockers (41%), nitrates (34%) and diuretics (33%). Approximately 83% and 76% of the patients were considered as adherent to the medication at 2 and 4 years, respectively. The *primary endpoint* was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for congestive heart failure. The *secondary endpoint* was a composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The results summarized in Table 5 indicate that telmisartan may reduce the risk of non-fatal MI or non-fatal stroke but not of total or cardiovascular mortality and may be considered in patients who cannot tolerate an ACE inhibitor.

Table 5. Primary and secondary composite endpoints and components of these endpoints for the full-analysis-set (intent-to-treat). Outcomes are for the first event.

OUTCOME	Telmisartan N = 2954 No. of events (%)	Placebo N = 2972 No. of events (%)	Hazard Ratio (95% CI)	p-value
Primary endpoint*	465 (15.7%)	504 (17.0%)	0.92 (0.81, 1.05)	0.216
Secondary endpoint**	384 (13.0%)	440 (14.8%)	0.87 (0.76, 1.00)	0.048
Individual components of the primary/secondary endpoint***				
Cardiovascular mortality	227 (7.7%)	223 (7.5%)	1.03 (0.85, 1.24)	0.776
Non-fatal MI	114 (3.9%)	145 (4.9 %)	0.79 (0.62, 1.01)	0.057
Non-fatal stroke	112 (3.8%)	136 (4.6%)	0.83 (0.64, 1.06)	0.137
Hospitalization for CHF	134 (4.5%)	129 (4.3%)	1.05 (0.82, 1.34)	0.694
Total mortality	364 (12.3%)	349 (11.7%)	1.05 (0.91, 1.22)	0.491

*Composite of CV death, myocardial infarction, stroke, or hospitalization for heart failure
**Composite of CV death, myocardial infarction, or stroke
*** For individual components of the composite endpoints, all events, regardless whether or not they were the first event, were considered. Therefore, they are more than first events considered for the primary or secondary composite endpoint

DETAILED PHARMACOLOGY

In *in vitro* studies, telmisartan displaced ^{125}I-angiotensin II from its binding site at the AT_1 receptor with an inhibitor constant (Ki) of 3.7 nM.

In isolated strips of rabbit aorta, telmisartan exerted potent angiotensin II antagonism: the calculated dissociation constant was K_B $3.3 \bullet 10^{-10}$M.

In vivo results showed that telmisartan was a potent and long acting antagonist of the functional response to exogenously administered angiotensin II in rats, rabbits and dogs after both intravenous and oral administration. Telmisartan showed dose dependent and long lasting (>24h) antihypertensive effects after single or repeated oral administration in various rodent models of experimental hypertension.

TOXICOLOGY

Acute Toxicity:

In acute oral toxicity studies no deaths and no changes occurred in rats or dogs at 2000 mg/kg, the highest oral dose tested. The i.v. LD_{50} in rats was 150-200 mg/kg in males and 200-250 mg/kg in females.

Chronic Toxicity

Chronic oral toxicity of telmisartan was evaluated in studies following administration of doses ≤500 mg/kg for ≤26 weeks in rats, and ≤1 year in dogs. Chronic intravenous toxicity was evaluated in studies of ≤4 weeks at doses ≤20 mg/kg in rats and ≤50 mg/kg in dogs.

Repeated dose administration of telmisartan resulted in marked and long lasting hypotension, hyperplasia of juxtaglomerular apparatus and lesions of the gastrointestinal tract. Further effects were reduced body weight gain, heart weight and red blood cell indices, increased potassium and AST and ALT, the latter in the absence of morphological evidence of toxicity. No effect doses were not identified for decreased erythroid indices, increased BUN and juxtaglomerular hypertrophy/hyperplasia in rats and dogs.

Reproduction

In studies on fertility and reproductive performance in male and female rats no effect on mating performance, reproductive organs, or fertility in either sex, or on litter parameters was observed with telmisartan doses of 5-100 mg/kg. No teratogenic or embryotoxic potential in rats was observed at doses ≤50 mg/kg administered from day 7 through day 16 of pregnancy. However, at toxic dose levels, non-clinical studies indicated some hazardous potential of telmisartan to fetal development (increased number of late resorptions in rabbits) and to the postnatal development of the offspring: lower body weight, delayed eye opening, and higher mortality.

Telmisartan was detectable in the placenta, fetus and amniotic fluid of rats after single oral doses of 1 mg/kg.

Mutagenicity

Telmisartan was not mutagenic at a concentration range of 10 to 2500 ug/plate in the bacterial reverse mutation assay, with or without metabolic activation. No potential for chromosomal damage was found in the mouse micronucleus test at a dose range of 250 to 1000 mg/kg. No forward mutations at the HPRT locus in V79 cells were induced at a concentration range of 10 to 100 ug/ml, with or without metabolic activation. No chromosomal aberrations were induced in human peripheral lymphocytes *in vitro* at concentrations ≤100 ug/ml without metabolic activation and concentrations ≤200 ug/ml with metabolic activation.

Carcinogenicity

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg and in rats at 3, 15 and 100 mg/kg. Drug administration did not affect survival time in either study and also tumor mortality was not increased. Incidence and time to appearance of palpable masses showed no treatment influence in mice and rats. No

increases were observed in overall tumor incidence, incidence of benign and malignant tumors or tumor multiplicity.

Gastrointestinal Tract

Gastric and/or duodenal mucosal erosions and ulcers were seen in rats given ≥4 mg/kg orally or ≥2 mg/kg i.v. and in dogs given ≥40 mg/kg orally. Most lesions were small, focal or multifocal in distribution and limited to the mucosa and submucosa. Ulcers and erosions healed rapidly after drug withdrawal.

Urinary Tract and Electrolytes

Hypertrophy of the juxtaglomerular apparatus and increased granularity of renin-producing cells of the juxtaglomerular apparatus, afferent arterioles and interlobular arteries of the kidney were observed in rats at doses of ≥1 mg/kg and in dogs at ≥5 mg/kg. In rats and dogs subjected to long term treatment with telmisartan, plasma renin activity returned to normal levels after 26 to 52 weeks of treatment. Reversible slight to mild increases in serum potassium levels occurred in rats at oral doses of ≥4 mg/kg. In dogs, non-progressive increases in serum potassium levels were noted at 50 and 500 mg/kg in the 52 week oral study. Minimal to mild, reversible increases in blood urea nitrogen and creatinine were evident at oral doses of ≥4 mg/kg in rats and ≥5 mg/kg in dogs.

Hematology

Slight to mild reversible reductions of red blood cell count, hematocrit, and/or hemoglobin were observed after repeated oral dosing with telmisartan ≥50 mg/kg in the rat and ≥5 mg/kg in the dog.

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PART III: CONSUMER INFORMATION

[Pr]Micardis®
(Telmisartan) **Tablets**

Read this carefully before you start taking MICARDIS and each time you get a refill. This leaflet is a summary and will not tell you everything about MICARDIS. Talk to your doctor, nurse, or pharmacist about your medical condition and treatment and ask if there is any new information about MICARDIS.

ABOUT THIS MEDICATION

What the medication is used for:

- To treat high blood pressure
- To reduce the risk of non-fatal heart attack or non-fatal stroke

What it does:
MICARDIS is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in **"-SARTAN".**

This medicine does not cure your disease. It helps to control it. Therefore, it is important to continue taking MICARDIS regularly even if you feel fine.

When it should not be used:
Do not take MICARDIS if you:

- Are allergic to telmisartan or to any non-medicinal ingredient in the formulation.
- Have experienced an allergic reaction with swelling of the face, lips, tongue, throat, or sudden difficulty breathing or swallowing to any ARB. Be sure to tell your doctor, nurse, or pharmacist that this happened to you.
- Are pregnant or intend to become pregnant. Taking MICARDIS during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. It is possible that MICARDIS passes into breast milk.
- Are allergic to some sugars (fructose and/or sorbitol intolerant).
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.

What the medicinal ingredient is:
Telmisartan

What the non-medicinal ingredients are:
Magnesium stearate, meglumine, povidone, sodium hydroxide and sorbitol

What dosage forms it comes in:
Tablets: 40 mg and 80 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions - Pregnancy
MICARDIS should not be used during pregnancy. If you discover that you are pregnant while taking MICARDIS, stop the medication and please contact your doctor, nurse, or pharmacist as soon as possible.

Before you use MICARDIS talk to your doctor or pharmacist if you:

- Have experienced an allergic reaction to any drug used to lower blood pressure.
- Have narrowing of a heart valve, diabetes, liver or kidney disease, heart or blood vessel disease.
- Are dehydrated or if you suffer from excessive vomiting, diarrhea, or sweating.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with MICARDIS is not recommended.
- Are taking an angiotensin-converting-enzyme inhibitor (ACEI).
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of "water pill" that makes your body keep potassium).
- Are on a low salt diet.
- Are on dialysis.
- Are less than 18 years old.
- Have been told by your doctor that you have an intolerance to some sugars.

Before you perform tasks which require special attention (driving a car or operating dangerous machinery), wait until you know how you respond to MICARDIS. Dizziness, lightheadedness, or fainting can especially occur after the first dose and when the dose is increased.

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MICARDIS:

- Blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products (e.g. Rasilez), or angiotension-converting-enzyme inhibitors (ACEI).
- Lithium, used to treat mood disorder.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) used to reduce pain and swelling. Examples include acetylsalicylic acid (ASA), celecoxib, naproxen and ibuprofen.
- Digoxin to treat many heart conditions.
- Warfarin, used to prevent blood clots (blood thinner).

PROPER USE OF THIS MEDICATION

Take MICARDIS exactly as prescribed. It is recommended to take your dose at about the same time everyday with or without food, but it should be taken the same way each day.
Do not stop taking your medication before informing your doctor, nurse, or pharmacist.

Usual adult dose:
The recommended dose of MICARDIS is 80 mg once daily. Your doctor may prescribe 40 mg once daily if you have liver disease.

Overdose:

If you think you have taken too much MICARDIS contact your doctor, nurse, pharmacist, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you have forgotten to take your dose during the day, carry on with the next one at the usual time. Do not double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- back or leg pain, muscle cramps, joint pain, muscle spasms
- headache, anxiety
- diarrhea, constipation, nausea, vomiting, upset stomach, abdominal pain, flatulence
- dry mouth
- rash, eczema, skin eruptions
- drowsiness, insomnia, fatigue
- visual disturbances
- upper respiratory infection

If any of these affects you severely, tell your doctor, nurse or pharmacist.

MICARDIS can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Very Common	**Chest pain**		√	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness	√		
	Shortness of breath	√		
Uncommon	**Depression:** Low mood, loss of interest in activities, change in appetite and sleep patterns	√		
	Kidney Disorder: Change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
	Increased levels of potassium in the blood: Irregular heartbeats, muscle weakness and generally feeling unwell		√	
	Urinary Tract Infections (Cystitis): Frequent or painful urination, feeling unwell		√	
Rare	**Liver disorder:** Yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
	Low blood sugar: Shaky, irregular heartbeat, sweating, hunger, dizziness **(in diabetic patients)**		√	
Unknown	**Allergic Reaction:** Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing (potentially with fatal outcome)			√
	Sepsis (blood poisoning): Chills, confusion, fever or low body temperature, shakiness, irregular heartbeat (including fatal outcome)			√
	Rhabdomyolysis : Muscle pain that you cannot explain, muscle tenderness or weakness or dark brown urine		√	

This is not a complete list of side effects. For any unexpected effects while taking MICARDIS, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

MICARDIS tablets should be stored at room temperature (15°C - 30°C). Tablets should not be removed from blisters until immediately prior to administration. Avoid excessive heat and moisture.

Keep out of reach and sight of children and pets.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 0701E
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.boehringer-ingelheim.ca or by contacting the sponsor, Boehringer Ingelheim (Canada) Ltd., at: 1-800-263-5103 ext. 84633

Please check our website to see if more up-to-date information has been posted.

This leaflet was prepared by Boehringer Ingelheim (Canada) Ltd.

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