Micardis® HCT

(telmisartan and hydrochlorothiazide)

Tablets, 40 mg/12.5 mg 80 mg/12.5 mg and 80 mg/25 mg

Boehringer Ingelheim

℞ only

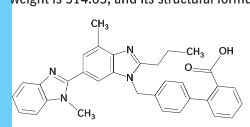
Prescribing Information

> **USE IN PREGNANCY**
> **When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus.** When pregnancy is detected, MICARDIS® HCT (telmisartan/hydrochlorothiazide) tablets should be discontinued as soon as possible (see **WARNINGS**, **Fetal/Neonatal Morbidity and Mortality**).

DESCRIPTION

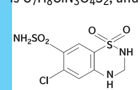
MICARDIS® HCT (telmisartan/hydrochlorothiazide) is a combination of telmisartan, an orally active angiotensin II antagonist acting on the AT_1 receptor subtype, and hydrochlorothiazide, a diuretic.

Telmisartan, a nonpeptide molecule, is chemically described as 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder with a molecular weight of 297.74. It is slightly soluble in water, and freely soluble in sodium hydroxide solution. Hydrochlorothiazide is chemically described as 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$, and its structural formula is:



MICARDIS HCT tablets are formulated for oral administration in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg, and 80 mg/25 mg telmisartan and hydrochlorothiazide, respectively. The tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, magnesium stearate, lactose monohydrate, microcrystalline cellulose, maize starch, sodium starch glycolate. As coloring agents, the 40 mg/12.5 mg and 80 mg/12.5 mg tablets contain iron oxide red, and the 80 mg/25 mg tablets contain iron oxide yellow. MICARDIS HCT tablets are hygroscopic and require protection from moisture.

CLINICAL PHARMACOLOGY

Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Telmisartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Telmisartan has much greater affinity (>3,000 fold) for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because telmisartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Telmisartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of telmisartan on blood pressure.

Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so coadministration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics.

The mechanism of the antihypertensive effect of thiazides is not fully understood.

Pharmacokinetics

General

Telmisartan

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration-time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg the bioavailability was 42% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half-life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations. Telmisartan has an accumulation index in plasma of 1.5 to 2.0 upon repeated once daily dosing.

Hydrochlorothiazide

When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours.

Metabolism and Elimination

Telmisartan

Following either intravenous or oral administration of ^{14}C-labeled telmisartan, most of the administered dose (>97%) was eliminated unchanged in feces via biliary excretion; only minute amounts were found in the urine (0.91% and 0.49% of total radioactivity, respectively).

Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; the glucuronide of the parent compound is the only metabolite that has been identified in human plasma and urine. After a single dose, the glucuronide represents approximately 11% of the measured radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Total plasma clearance of telmisartan is >800 mL/min. Terminal half-life and total clearance appear to be independent of dose.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated as unchanged drug within 24 hours.

Distribution

Telmisartan

Telmisartan is highly bound to plasma proteins (>99.5%), mainly albumin and α_1-acid glycoprotein. Plasma protein binding is constant over the concentration range achieved with recommended doses. The volume of distribution for telmisartan is approximately 500 liters, indicating additional tissue binding.

Hydrochlorothiazide

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Special Populations

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

Geriatric: 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 times higher in females than in males. In clinical trials, however, no significant increases in blood pressure response or in the incidence of orthostatic hypotension were found in women. No dosage adjustment is necessary.

Renal Insufficiency: Renal excretion does not contribute to the clearance of telmisartan. Based on modest experience in patients with mild-to-moderate renal impairment (creatinine clearance of 30-80 mL/min, mean clearance approximately 50 mL/min), no dosage adjustment is necessary in patients with decreased renal function. Telmisartan is not removed from blood by hemofiltration (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug Interactions: See **PRECAUTIONS**, **Drug Interactions**.

Pharmacodynamics

Telmisartan

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 plasma concentrations with approximately 40% inhibition persisting for 24 hours.

Plasma concentration of angiotensin II and plasma renin activity (PRA) increased in a dose-dependent manner after single administration of telmisartan to healthy subjects and repeated administration to hypertensive patients. The once-daily administration of up to 80 mg telmisartan to healthy subjects did not influence plasma aldosterone concentrations. In multiple dose studies with hypertensive patients, there were no clinically significant changes in electrolytes (serum potassium or sodium), or in metabolic function (including serum levels of cholesterol, triglycerides, HDL, LDL, glucose, or uric acid).

In 30 hypertensive patients with normal renal function treated for 8 weeks with telmisartan 80 mg or telmisartan 80 mg in combination with hydrochlorothiazide 12.5 mg, there were no clinically significant changes from baseline in renal blood flow, glomerular filtration rate, filtration fraction, renovascular resistance, or creatinine clearance.

Hydrochlorothiazide

After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours.

Clinical Trials

Telmisartan

The antihypertensive effects of telmisartan have been demonstrated in six principal placebo-controlled clinical trials, studying a range of 20-160 mg; one of these examined the antihypertensive effects of telmisartan and hydrochlorothiazide in combination. The studies involved a total of 1773 patients with mild to moderate hypertension (diastolic blood pressure of 95-114 mmHg), 1031 of whom were treated with telmisartan. Following once daily administration of telmisartan, the magnitude of blood pressure reduction from baseline after placebo subtraction was approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Larger doses (up to 160 mg) did not appear to cause a further decrease in blood pressure.

Upon initiation of antihypertensive treatment with telmisartan, blood pressure was reduced after the first dose, with a maximal reduction by about 4 weeks. With cessation of treatment with telmisartan tablets, blood pressure gradually returned to baseline values over a period of several days to one week. During long-term studies (without placebo control) the effect of telmisartan appeared to be maintained for up to at least one year. The antihypertensive effect of telmisartan is not influenced by patient age, gender, weight or body mass index. Blood pressure response in black patients (usually a low-renin population) is noticeably less than that in Caucasian patients. This has been true for most, but not all, angiotensin II antagonists and ACE inhibitors.

The onset of antihypertensive activity occurs within 3 hours after administration of a single oral dose. At doses of 20, 40, and 80 mg, the antihypertensive effect of once daily administration of telmisartan is maintained for the full 24-hour dose interval. With automated ambulatory blood pressure monitoring and conventional blood pressure measurements, the 24-hour trough-to-peak ratio for 40-80 mg doses of telmisartan was 70-100% for both systolic and diastolic blood pressure. The incidence of symptomatic orthostasis after the first dose in all controlled trials was low (0.04%).

There were no changes in the heart rate of patients treated with telmisartan in controlled trials.

Telmisartan & Hydrochlorothiazide

In controlled clinical trials with over 2500 patients, 1017 patients were exposed to telmisartan (20 to 160 mg) and concomitant hydrochlorothiazide (6.25 to 25 mg). These trials included one factorial trial with combinations of telmisartan (20, 40, 80, 160 mg, or placebo) and hydrochlorothiazide (6.25, 12.5, 25 mg and placebo). Four other studies of at least six months duration allowed add-on of hydrochlorothiazide for patients who either were not adequately controlled on the randomized monotherapy dose or had not achieved adequate response after completing the up-titration of telmisartan.

The combination of telmisartan and hydrochlorothiazide resulted in additive placebo-adjusted decreases in systolic and diastolic blood pressure at trough of 16-21/9-11 mmHg for doses between 40/12.5 mg and 80/25 mg, compared to 9-13/7-8 mmHg for telmisartan 40 mg to 80 mg and 4/4 mmHg for hydrochlorothiazide 12.5 mg alone.

In active controlled studies, the addition of 12.5 mg hydrochlorothiazide to titrated doses of telmisartan in patients who did not achieve or maintain adequate response with telmisartan monotherapy further reduced systolic and diastolic blood pressure.

The antihypertensive effect was independent of age or gender.

There was essentially no change in heart rate in patients treated with the combination of telmisartan and hydrochlorothiazide in the placebo controlled trial.

INDICATIONS AND USAGE

MICARDIS HCT (telmisartan/hydrochlorothiazide) is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

MICARDIS HCT (telmisartan/hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product.

Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Drugs 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 converting enzyme inhibitors. When pregnancy is detected, MICARDIS HCT (telmisartan/hydrochlorothiazide) tablets should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the 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, presumably resulting from decreased fetal renal function; 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 occurrences were due to exposure to the drug.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of MICARDIS HCT tablets as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, MICARDIS HCT tablets should be discontinued unless they are considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist 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 or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function.

A developmental toxicity study was performed in rats with telmisartan/hydrochlorothiazide doses of 3.2/1.0, 15/4.7, 50/15.6, and 0/15.6 mg/kg/day. Although the two higher dose combinations appeared to be more toxic (significant decrease in body weight gain) to the dams than either drug alone, there did not appear to be an increase in toxicity to the developing embryos.

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. In rabbits, embryolethality associated with maternal toxicity (reduced body weight gain and food consumption) was observed at 45 mg/kg/day [about 12 times the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis]. In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 15 mg/kg/day (about 1.9 times the MRHD on a mg/m^2 basis), administered during late gestation and lactation, were observed to produce adverse effects in neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Telmisartan has been shown to be present in rat fetuses during late gestation and in rat milk. The no observed effect doses for developmental toxicity in rats and rabbits, 5 and 15 mg/kg/day, respectively, are about 0.64 and 3.7 times, on a mg/m^2 basis, the maximum recommended human dose of telmisartan (80 mg/day).

Studies in which hydrochlorothiazide was administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg/kg/day, respectively, provided no evidence of harm to the fetus.

Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume-Depleted Patients

Initiation of antihypertensive therapy in patients whose renin-angiotensin system are activated such as patients who are intravascular volume- or sodium-depleted, e.g., in patients treated vigorously with diuretics, should only be approached cautiously. These conditions should be corrected prior to administration of MICARDIS HCT. Treatment should be started under close medical supervision (see **DOSAGE AND ADMINISTRATION**). If hypotension occurs, the patients should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide

Hepatic Impairment: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Hypersensitivity Reaction: Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

Systemic Lupus Erythematosus: Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction: Lithium generally should not be be given with thiazides (see **PRECAUTIONS**, **Drug Interactions**, ***Hydrochlorothiazide***, *Lithium*).

PRECAUTIONS

Serum Electrolytes

Telmisartan & Hydrochlorothiazide

In controlled trials using the telmisartan/hydrochlorothiazide combination treatment, no patient administered 40/12.5 mg, 80/12.5 mg or 80/25 mg had a decrease in potassium ≥1.4 mEq/L, and no patient experienced hyperkalemia. No discontinuations due to hypokalemia occurred during treatment with the telmisartan/hydrochlorothiazide combination. The absence of significant changes in serum potassium levels may be due to the opposing mechanisms of action of telmisartan and hydrochlorothiazide on potassium excretion on the kidney.

Hydrochlorothiazide

Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.

Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.

The antihypertensive effects of the drug may be enhanced in the post sympathectomy patient.

FRONT PANEL

If progressive renal impairment becomes evident consider withholding or discontinuing diuretic therapy.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function

Telmisartan

As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance. MICARDIS® HCT tablets should therefore be used with caution in these patients.

Impaired Renal Function

Telmisartan

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar results may be anticipated in patients treated with telmisartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of telmisartan in patients with unilateral or bilateral renal artery stenosis but an effect similar to that seen with ACE inhibitors should be anticipated.

Hydrochlorothiazide

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Symptomatic Hypotension: A patient receiving MICARDIS HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, MICARDIS HCT should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Potassium Supplements: A patient receiving MICARDIS HCT should be told not to use potassium supplements or salt substitutes that contain potassium without consulting the prescribing physician.

Drug Interactions

Telmisartan

Digoxin: When telmisartan was coadministered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Warfarin: 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 Drugs: Coadministration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

Hydrochlorothiazide

When administered concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics: Potentiation of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin): Dosage adjustment of the antidiabetic drug may be required.

Other antihypertensive drugs: Additive effect or potentiation.

Cholestyramine and colestipol resins: Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43%, respectively.

Corticosteroids, ACTH: Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g., norepinephrine): Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine): Possible increased responsiveness to the muscle relaxant.

Lithium: Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with MICARDIS HCT.

Non-steroidal anti-inflammatory drugs: In some patients, the administration of a non-steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when MICARDIS HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Telmisartan & Hydrochlorothiazide

No carcinogenicity, mutagenicity, or fertility studies have been conducted with the combination of telmisartan and hydrochlorothiazide.

Telmisartan

There was no evidence of carcinogenicity when telmisartan was administered in the diet to mice and rats for up to 2 years. The highest doses administered to mice (1000 mg/kg/day) and rats (100 mg/kg/day) are, on a mg/m^2 basis, about 59 and 13 times, respectively, the maximum recommended human dose (MRHD) of telmisartan. These same doses have been shown to provide average systemic exposures to telmisartan >100 times and >25 times, respectively, the systemic exposure in humans receiving the MRHD (80 mg/day).

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

No drug-related effects on the reproductive performance of male and female rats were noted at 100 mg/kg/day (the highest dose administered), about 13 times, on a mg/m^2 basis, the MRHD of telmisartan. This dose in the rat resulted in an average systemic exposure (telmisartan AUC as determined on day 6 of pregnancy) at least 50 times the average systemic exposure in humans at the MRHD (80 mg/day).

Hydrochlorothiazide

Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic *in vitro* in the Ames mutagenicity assay of *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or *in vivo* in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained in the *in vitro* CHO Sister Chromatid Exchange (clastogenicity) assay, in the Mouse Lymphoma Cell (mutagenicity) assay, and in the *Aspergillus nidulans* non-disjunction assay.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and throughout gestation.

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters) (see **WARNINGS**, **Fetal/Neonatal Morbidity and Mortality**).

Nursing Mothers

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

In the controlled clinical trials (n=1017), approximately 20% of patients treated with telmisartan/hydrochlorothiazide were 65 years of age or older, and 5% were 75 years of age or older. No overall differences in effectiveness and safety of telmisartan/hydrochlorothiazide were observed in these patients compared to younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

MICARDIS HCT (telmisartan/hydrochlorothiazide) has been evaluated for safety in over 1700 patients, including 716 treated for over six months and 420 for over one year. In clinical trials with MICARDIS HCT, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with telmisartan and/or hydrochlorothiazide. The overall incidence of adverse events reported with the combination was comparable to placebo. Most adverse experiences were mild in intensity and transient in nature and did not require discontinuation of therapy.

Adverse events occurring at an incidence of 2% or more in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo, irrespective of their causal association, are presented in Table 1.

TABLE 1 Adverse Events Occurring in ≥ 2% of Telmisartan/Hydrochlorothiazide (HCTZ) Patients*

	Telm/HCTZ (N=414) (%)	Placebo (N=74) (%)	Telm (N=209) (%)	HCTZ (N=121) (%)
Body as a whole				
Fatigue	3	1	3	3
Influenza-like symptoms	2	1	2	3
Central/peripheral nervous system				
Dizziness	5	1	4	6
Gastrointestinal system				
Diarrhea	3	0	5	2
Nausea	2	0	1	2
Respiratory system disorder				
Sinusitis	4	3	3	6
Upper respiratory tract infection	8	7	7	10

* includes all doses of telmisartan (20-160 mg), hydrochlorothiazide (6.25-25 mg), and combinations thereof

The following adverse events were reported at a rate less than 2% in patients treated with telmisartan/hydrochlorothiazide and at a greater rate than in patients treated with placebo: back pain, dyspepsia, vomiting, tachycardia, hypokalemia, bronchitis, pharyngitis, rash, hypotension postural, abdominal pain.

Finally, the following adverse events were reported at a rate of 2% or greater in patients treated with telmisartan/hydrochlorothiazide, but were as, or more common in the placebo group: pain, headache, cough, urinary tract infection.

Adverse events occurred at approximately the same rates in men and women, older and younger patients, and black and non-black patients.

In controlled trials (n=1017), 0.3% of patients treated with MICARDIS HCT 40/12.5 mg, 80/12.5 mg or 80/25 mg discontinued due to orthostatic hypotension, and the incidence of dizziness was 4%, 7%, and 1% respectively.

Telmisartan

Other adverse experiences that have been reported with telmisartan, without regard to causality, are listed below:

Autonomic Nervous System: impotence, increased sweating, flushing

Body as a Whole: allergy, fever, leg pain, malaise, chest pain

Cardiovascular: palpitation, dependent edema, angina pectoris, leg edema, abnormal ECG, hypertension, peripheral edema

CNS: insomnia, somnolence, migraine, vertigo, paresthesia, involuntary muscle contractions, hypoaesthesia

Gastrointestinal: flatulence, constipation, gastritis, dry mouth, hemorrhoids, gastroenteritis, enteritis, gastroesophageal reflux, toothache, non-specific gastrointestinal disorders

Metabolic: gout, hypercholesterolemia, diabetes mellitus

Musculoskeletal: arthritis, arthralgia, leg cramps, myalgia

Psychiatric: anxiety, depression, nervousness

Resistance Mechanism: infection, fungal infection, abscess, otitis media

Respiratory: asthma, rhinitis, dyspnea, epistaxis

Skin: dermatitis, eczema, pruritus

Urinary: micturition frequency, cystitis

Vascular: cerebrovascular disorder

Special Senses: abnormal vision, conjunctivitis, tinnitus, earache.

A single case of angioedema was reported (among a total of 3781 patients treated with telmisartan).

Hydrochlorothiazide

Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below:

Body as a whole: weakness

Digestive: pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation

Hematologic: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia

Hypersensitivity: purpura, photosensitivity, urticaria, necrotizing angiitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions

Metabolic: hyperglycemia, glycosuria, hyperuricemia

Musculoskeletal: muscle spasm

Nervous System/Psychiatric: restlessness

Renal: renal failure, renal dysfunction, interstitial nephritis

Skin: erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis

Special Senses: transient blurred vision, xanthopsia

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of MICARDIS tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to MICARDIS tablets. The most frequently spontaneously reported events include: headache, dizziness, asthenia, coughing, nausea, fatigue, weakness, edema, face edema, lower limb edema, angioneurotic edema, urticaria, hypersensitivity, sweating increased, erythema, chest pain, atrial fibrillation, congestive heart failure, myocardial infarction, blood pressure increased, hypertension aggravated, hypotension (including postural hypotension), hyperkalemia, syncope, dyspepsia, diarrhea, pain, urinary tract infection, erectile dysfunction, back pain, abdominal pain, muscle cramps (including leg cramps), myalgia, bradycardia, eosinophilia, thrombocytopenia, uric acid increased, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, anemia, and increased CPK.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers, including MICARDIS.

Clinical Laboratory Findings

In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS HCT tablets.

Hemoglobin and Hematocrit: Decreases in hemoglobin (≥ 2 g/dL) and hematocrit (≥ 9%) were observed in 1.2% and 0.6% of telmisartan/hydrochlorothiazide patients, respectively, in controlled trials. Changes in hemoglobin and hematocrit were not considered clinically significant and there were no discontinuations due to anemia.

Creatinine, Blood Urea Nitrogen (BUN): Increases in BUN (≥ 11.2 mg/dL) and serum creatinine (≥ 0.5 mg/dL) were observed in 2.8% and 1.4%, respectively, of patients with essential hypertension treated with MICARDIS HCT in controlled trials. No patient discontinued treatment with MICARDIS HCT due to an increase in BUN or creatinine.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. No telmisartan/hydrochlorothiazide treated patients discontinued therapy due to abnormal hepatic function.

Serum Electrolytes: See **PRECAUTIONS**.

OVERDOSAGE

Telmisartan

Limited data are available with regard to overdosage in humans. The most likely manifestations of overdosage with telmisartan would be hypotension, dizziness and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed in patients are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established. The oral LD_{50} of hydrochlorothiazide is greater than 10 g/kg in both mice and rats.

DOSAGE AND ADMINISTRATION

The usual starting dose of telmisartan is 40 mg once a day; blood pressure response is dose related over the range of 20-80 mg. Patients with depletion of intravascular volume should have the condition corrected or telmisartan tablets should be initiated under close medical supervision (see **WARNINGS**, **Hypotension in Volume Depleted Patients**). Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision (see **PRECAUTIONS**).

Hydrochlorothiazide is effective in doses of 12.5 mg to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy. The side effects (see **WARNINGS**) of telmisartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of telmisartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.

MICARDIS HCT (telmisartan/hydrochlorothiazide) tablets may be administered with other antihypertensive agents.

MICARDIS HCT tablets may be administered with or without food.

Replacement Therapy

The combination may be substituted for the titrated components.

Dose Titration by Clinical Effect

MICARDIS HCT is available as tablets containing either telmisartan 40 mg and hydrochlorothiazide 12.5 mg, or telmisartan 80 mg and hydrochlorothiazide 12.5 mg or 25 mg. A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg (see above) may be switched to MICARDIS HCT, telmisartan 80 mg/ hydrochlorothiazide 12.5 mg once daily, and finally titrated up to 160/25 mg, if necessary.

A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide may be switched to MICARDIS HCT (telmisartan 80 mg/hydrochlorothiazide 12.5 mg or telmisartan 80 mg/hydrochlorothiazide 25 mg) once daily. The clinical response to MICARDIS HCT should be subsequently evaluated and if blood pressure remains uncontrolled after 2-4 weeks of therapy, the dose may be titrated up to 160/25 mg, if necessary. Those patients controlled by 25 mg hydrochlorothiazide but who experience hypokalemia with this regimen, may be switched to MICARDIS HCT (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response.

Patients with Renal Impairment

The usual regimens of therapy with MICARDIS HCT may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so MICARDIS HCT is not recommended.

Patients with Hepatic Impairment

MICARDIS HCT is not recommended for patients with severe hepatic impairment. Patients with biliary obstructive disorders or hepatic insufficiency should have treatment started under close medical supervision using the 40/12.5 mg combination (see **PRECAUTIONS**).

HOW SUPPLIED

MICARDIS HCT (telmisartan/hydrochlorothiazide) is available in three strengths as biconvex two-layered, oblong-shaped, uncoated tablets in three combinations of 40 mg/12.5 mg, 80 mg/12.5 mg and 80 mg/25 mg telmisartan and hydrochlorothiazide, respectively. The hydrochlorothiazide layer is red in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets, and yellow in the 80 mg/25 mg tablets, and all are unmarked. The telmisartan layer for all three strengths is white, but may contain red specks in the 40 mg/12.5 mg and 80 mg/12.5 mg tablets and yellow specks in the 80 mg/25 mg tablets. The telmisartan layer is marked with the BOEHRINGER INGELHEIM logo and H4 for the 40 mg/12.5 mg dose strength, H8 for the 80 mg/12.5 mg dose strength and H9 for the 80 mg/25 mg dose strength.

Tablets are provided as follows:

MICARDIS HCT tablets 40 mg/12.5 mg are individually blister-sealed in cartons of 30 tablets as 3 x 10 cards (NDC 0597-0043-37).

MICARDIS HCT tablets 80 mg/12.5 mg are individually blister-sealed in cartons of 30 tablets as 3 x 10 cards (NDC 0597-0044-37).

MICARDIS HCT tablets 80 mg/25 mg are individually blister-sealed in cartons of 30 tablets as 3 x 10 cards (NDC 0597-0042-37).

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Tablets should not be removed from blisters until immediately before administration.

Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877 USA

Licensed from: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Micardis HCT Tablets are covered by U.S. Patent 5,591,762

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BACK PANEL