PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] Auro-Telmisartan HCTZ

Telmisartan/Hydrochlorothiazide Tablets, USP

Tablet, 80 mg/12.5 mg, and 80 mg/25 mg, Oral

Angiotensin II AT_1 Receptor Blocker/ Diuretic

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Auro-Telmisartan HCTZ (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated for:

- treatment of mild to moderate essential hypertension in patients in whom combination therapy with telmisartan and hydrochlorothiazide is considered appropriate.

Auro-Telmisartan HCTZ (80 mg telmisartan/25 mg hydrochlorothiazide) is indicated for:

- treatment of patients whose blood pressure is not adequately controlled by Auro-Telmisartan HCTZ 80 mg/12.5 mg or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.

These fixed-dose combinations are not indicated as initial therapy (see 4 DOSAGE AND ADMINISTRATION).

1.1 Pediatrics

- **Pediatrics (<18 years of age)***:* Based on the data submitted and reviewed by Health Canada, the safety and efficacy of telmisartan and hydrochlorothiazide tablets in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

Auro-Telmisartan HCTZ (telmisartan/hydrochlorothiazide) is contraindicated in:

- Concomitant use of angiotensin II receptor blockers (ARBs) –including the telmisartan component of Auro-Telmisartan HCTZ - 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual blockade of the Renin-Angiotensin System (RAS) and Renal, and 9.4 Drug-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 6 DOSAGE FORMS, STRENGTHS,

COMPOSITION AND PACKAGING section of the product monograph.

- Pregnant women (see 7.1.1 Pregnant Women).
- Breast-feeding women (see 7.1.2 Breast-feeding women).
- Patients with anuria due to the presence of hydrochlorothiazide.
- Patients with the rare hereditary condition of fructose intolerance (HFI).
    - Mannitol: Auro-Telmisartan HCTZ tablets contain 477.18 mg of mannitol per maximum recommended daily dose.
- Patients with rare hereditary problems of galactose intolerance, e.g., galactosaemia, the Lapp Lactase deficiency or glucose-galactose malabsorption.
    - Lactose: Auro-Telmisartan HCTZ tablets contain 29.60 mg of lactose monohydrate in the dose strengths of 80 mg/12.5 mg and 80 mg/25 mg.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
When used in pregnancy, angiotensin II receptor (AT_1) blockers (ARB) can cause injury or even death of the developing fetus. When pregnancy is detected, Auro-Telmisartan HCTZ should be discontinued as soon as possible (see 7.1 Special Populations).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Auro-Telmisartan HCTZ may be substituted in patients who have been stabilized on the individual telmisartan 80 mg and hydrochlorothiazide 12.5 mg components as described below.

4.2 Recommended Dose and Dosage Adjustment

- Auro-Telmisartan HCTZ (telmisartan/hydrochlorothiazide) is not for initial therapy.

- A patient whose blood pressure is not adequately controlled with telmisartan monotherapy 80 mg, may be switched to Auro-Telmisartan HCTZ, (telmisartan 80 mg/hydrochlorothiazide 12.5 mg) once daily.

- A patient whose blood pressure is not adequately controlled with Auro-Telmisartan HCTZ (telmisartan 80 mg/hydrochlorothiazide 12.5 mg), may be switched to Auro-Telmisartan HCTZ (telmisartan 80 mg/hydrochlorothiazide 25 mg) once daily.

Telmisartan Monotherapy

The recommended dose of telmisartan is 80 mg once daily. 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.
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.

Diuretic Treated Patients

In patients receiving diuretics, telmisartan therapy should be initiated with caution, since these patients may be volume depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of telmisartan to reduce the likelihood of hypotension (see 7 WARNINGS AND PRECAUTIONS, Hypotension). If this is not possible because of the patient's condition, telmisartan should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Considerations for Special Populations

Patients with Renal Impairment

The usual regimens of therapy with Auro-Telmisartan HCTZmay 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; in this instance, Auro-Telmisartan HCTZ is not recommended.

Patients with Hepatic Impairment

For patients with hepatic impairment, a starting dose of 40 mg of telmisartan is recommended. Auro-Telmisartan HCTZ is not recommended for patients with severe hepatic impairment.

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of telmisartan and hydrochlorothiazide tablets in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

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

Drug Discontinuation

If diagnosis of Acute Respiratory Distress Syndrome (ARDS) is suspected, Auro-Telmisartan HCTZ should be withdrawn and appropriate treatment given (see 7 WARNINGS AND PRECAUTIONS, Respiratory).

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued (see 7 WARNINGS AND PRECAUTIONS, Renal, Azotemia).

If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped (see 7 WARNINGS AND PRECAUTIONS, Skin).

In the event of significant hypercalcemia, Auro-Telmisartan HCTZ should be discontinued followed by assessment of parathyroid function (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hydrochlorothiazide).

If laryngeal stridor or angioedema of the face, extremities, lips, tongue, or glottis occurs, Auro-Telmisartan HCTZ should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears (see 7 WARNINGS AND PRECAUTIONS, Immune, Systemic Lupus Erythematosus).

When pregnancy is detected, Auro-Telmisartan HCTZ should be discontinued as soon as possible (see 7.1.1 Pregnant Women).

4.4 Administration

Auro-Telmisartan HCTZ may be administered with or without food, however it should be taken consistently with regard to food intake. Auro-Telmisartan HCTZ tablets are for once-daily oral administration and should be swallowed whole with liquid.

4.5 Missed Dose

If a dose is missed, patients should not take a double dose; patients should just carry on with the next dose at the usual time.

5 OVERDOSAGE

Limited information is available telmisartan and hydrochlorothiazide tablets with regard to overdose in humans. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacements given quickly. For the individual components of telmisartan and hydrochlorothiazide tablets , the following information is available:

Telmisartan

Based on limited data, the most prominent manifestations of overdose are hypotension, dizziness and tachycardia; bradycardia also occurred in this setting as a result of parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

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

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

Telmisartan is not removed by hemodialysis filtration and is not dialyzable. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 80 mg/12.5 mg and 80 mg/25 mg	Colloidal silicon dioxide, hydroxypropyl cellulose, lactose monohydrate, mannitol, meglumine, povidone, red ferric oxide (80 mg/12.5 mg), sodium hydroxide pellets, sodium stearyl fumarate & yellow ferric oxide (80 mg/25 mg).

Description & Packaging:
80 mg /12.5 mg:
White to off white and red coloured bi layered oblong shaped biconvex tablets debossed with “H” on one side and “72” on the other side. The white to off white layer may contain red specks. Available in Blister pack: 3 x 10 Tablets; HDPE Pack: 30’s, 100’s, 500’s & 1000’s Tablets.

80 mg/25 mg: White to off white and yellow coloured bi layered oblong shaped biconvex tablets debossed with “H” on one side and “76” on the other side. The white to off white layer may contain yellow specks. Available in Blister pack: 3 x 10 Tablets; HDPE Pack: 30’s, 100’s, 500’s & 1000’s Tablets.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin] after hydrochlorothiazide therapy was reported in some epidemiological studies. The risk may be higher with increasing cumulative use (see 8.5 Post Market Adverse Reactions). The photosensitizing action of hydrochlorothiazide may be a possible mechanism for NMSC (see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity – Hydrochlorothiazide).

Patients taking hydrochlorothiazide should be informed of the potential risk of NMSC. They should be advised to regularly check their skin for new lesions as well as changes to existing ones, and to promptly report any suspicious skin lesions. Patients should also be advised to limit exposure to sunlight, to avoid the use of indoor tanning equipment, and to use adequate protection (e.g., a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.

Alternatives to hydrochlorothiazide may be considered for patients who are at a particularly high risk for NMSC (e.g., light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.) (see 8.5 Post-Market Adverse Reactions).

Cardiovascular

Volume and/or sodium depleted patients

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 telmisartan. Such conditions, especially volume and/or sodium depletion, should be corrected prior to administration of telmisartan. In these patients, because of the potential fall in blood pressure, therapy with telmisartan should be initiated under close medical supervision.

Ischaemic heart disease

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.

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.

Dual blockade of the Renin-Angiotensin System (RAS)

There is evidence that co-administration of angiotensin II receptor blockers (ARBs), such as the telmisartan component of telmisartan and hydrochlorothiazide tablets , 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 Auro-Telmisartan HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ARBs, including the telmisartan component of Auro-Telmisartan HCTZ, 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.

Avoid the concomitant use of ACE inhibitors and ARBs in patients with diabetic nephropathy.

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes, and blood pressure.

Driving and Operating Machinery

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, syncope or vertigo may occasionally occur when taking antihypertensive therapy.

If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Endocrine and Metabolism

Electrolyte and Metabolic Imbalances

Telmisartan & Hydrochlorothiazide

In controlled trials using telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) in combination, there were no reports of hyperkalemia. Hypokalemia was reported in 1.4% of patients treated with the combination. No discontinuations due to hypokalemia occurred during treatment.

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 by the kidney.
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.

Hydrochlorothiazide

During thiazide diuretic therapy, periodic determinations of serum electrolytes to detect possible electrolyte imbalances should be performed at appropriate intervals. All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, particularly hyponatraemia, hypokalemia and alkalosis hypochloremic. Serum and urine electrolyte determinations are particularly important when the patient experiences excessive vomiting or receives parenteral fluids.

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 induce cardiac arrhythmia and may also sensitize or exacerbate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

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

Calcium excretion is decreased by thiazide diuretics which may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may also be evidence of hyperparathyroidism.

Thiazide diuretics have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia.

Hyperuricemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy.

Insulin requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy.

An increase in cholesterol and triglyceride levels has been associated with thiazide diuretic therapy.
Thiazide may decrease serum Protein Bound Iodine (PBI) levels without signs of thyroid disturbance.

<u>Diabetic Patients:</u>
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 Auro-Telmisartan HCTZ.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

As the predominant route of elimination of telmisartan is through biliary excretion, patients with cholestasis, biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan leading to increased systemic exposure. Auro-Telmisartan HCTZ should therefore be used with caution in these patients. Dosage reduction should be considered which would necessitate usage of the individual tablet formulations.

Auro-Telmisartan HCTZ is not recommended for patients with severe hepatic impairment.

Thiazides 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 (see 4.2 Recommended Dose and Dosage Adjustment, Patients with Hepatic Impairment).

Immune

Hypersensitivity Reactions

Hypersensitivity reactions to the hydrochlorothiazide component of Auro-Telmisartan HCTZ may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus

Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

A case of rare but fatal angioedema occurred in a patient who had been medicated for about 6 months with telmisartan, one of the active components of telmisartan and hydrochlorothiazide tablets. 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.

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 8.5 Post Market Adverse Reactions).

Patients with a known hypersensitivity (anaphylaxis) or angioedema to ARBs should not be

treated with Auro-Telmisartan HCTZ (see 8.2 Clinical Trial Adverse Reactions-All Clinical Trials, Immune System, Unknown: angioedema and 8.5 Post Market Adverse Reactions).

Monitoring and Laboratory Tests

For specific monitoring and laboratory tests, see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Endocrine and Metabolism, Hepatic and Renal and 9 DRUG INTERACTIONS sections.

Ophthalmologic

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma
Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to week of a drug initiation. Untreated acute-angle glaucoma can lead to permanent vision loss. The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of sulfonamide or penicillin allergy.

Renal

Renal Impairment

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 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. In susceptible patients, concomitant diuretic use may further increase risk. Appropriate assessment of renal function should be conducted prior to use of Auro-Telmisartan HCTZ.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen were observed. Although there has been no long-term experience with telmisartan in this patient population, an effect similar to that observed with ACE inhibitors should be anticipated.

Due to the hydrochlorothiazide component, Auro-Telmisartan HCTZ is not recommended in

patients with severe renal impairment (creatinine clearance ≤ 30 mL/min).

Thiazide diuretics should be used with caution in patients with renal impairment.

There is no experience regarding the administration of telmisartan and hydrochlorothiazide tablets in patients with a recent kidney transplant.

The use of ARBs – including the telmisartan component of Auro-Telmisartan HCTZ – 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 2 CONTRAINDICATIONS and 9 DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Telmisartan is not removed from blood by hemofiltration and is not dialyzable.

Azotemia

Azotemia may be precipitated or increased by the hydrochlorothiazide component of Auro-Telmisartan HCTZ. Cumulative effects of the drug may develop in patients with impaired renal function since the primary route of excretion is through the urine.

Reproductive Health: Female and Male Potential

- **Fertility**

No studies on fertility in humans with the fixed dose combination or with the individual components have been performed (see 16 NON-CLINICAL TOXICOLOGY, Reproduction, and developmental toxicology).

Respiratory

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension.

Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake (see 4.2 Recommended Dose and Dosage Adjsutement, Drug Discontinuation).

Skin

Photosensitivity

Photosensitivity reactions have been reported with the use of thiazide diuretics.

7.1 Special Populations

7.1.1 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.

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

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

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.

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Hydrochlorothiazide crosses the placenta and appears in cord blood. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimester may compromise feto-placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance, fetal or neonatal jaundice and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational edema, gestational hypertension or

preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women.

Diuretics do not prevent development of toxemia (preeclampsia) of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

There has been no clinical experience with (telmisartan and hydrochlorothiazide) in pregnancy.

7.1.2 Breast-feeding

Auro-Telmisartan HCTZ is contraindicated during lactation since it is not known whether telmisartan is excreted in human milk but significant levels have been found in the milk of lactating rats.

Animal studies have shown excretion of telmisartan in breast milk. 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. Thiazide diuretics are excreted in human milk at low levels.

7.1.3 Pediatrics

Pediatrics (<18 years of age)*:*

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of telmisartan and hydrochlorothiazide tablets in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age):

In clinical trials (n=1725) of patients treated with the combination of telmisartan and hydrochlorothiazide, 348 (20.2%) were 65 to 74 years of age and 78 (4.5%) were 75 years of age or older. No overall differences in the safety or efficacy profiles were observed in elderly patients compared with younger patients. It should be recognized however, that greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Telmisartan and Hydrochlorothiazide Used in Combination

The overall incidence and pattern of adverse events reported with telmisartan and hydrochlorothiazide tablets (80 mg/25 mg) was comparable with telmisartan and hydrochlorothiazide tablets (80 mg /12.5 mg). A dose-relationship of undesirable effects was not established, and they showed no correlation with gender, age, or race of the patients.

The combination of telmisartan and hydrochlorothiazide has been evaluated for safety in 1725 patients including 716 treated for over six months and 420 for over one year. In clinical trials with the individual components used in combination, no unexpected adverse events have been observed. Adverse experiences have been limited to those that have been previously reported with telmisartan and hydrochlorothiazide monotherapy. In general, treatment with the combination was well tolerated; most adverse experiences were mild and transient in nature and did not require discontinuation of therapy.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse events at an incidence of ≥1% in patients treated with 80 mg/12.5 mg telmisartan/hydrochlorothiazide combination, irrespective of their causal relationship, are presented in the following table. This table includes the results of two pivotal studies. One study, a factorial design, compared the use of various doses of telmisartan tablets and hydrochlorothiazide tablets in combination to telmisartan alone, hydrochlorothiazide alone and placebo. The other study compared the fixed dose combination 80 mg/12.5 mg of telmisartan/hydrochlorothiazide to telmisartan 80 mg alone

Table 2 - ADVERSE EVENTS OCCURRING IN ≥ 1% OF PATIENTS TREATED WITH 80 MG/12.5 MG TELMISARTAN/HYDROCHLOROTHIAZIDE IN PIVOTAL CLINICAL TRIALS

	Telmisartan/ HCTZ 80 mg/12.5 mg (n=320) %	Telmisartan 80 mg (n=322) %	HCTZ 12.5 mg (n=75) %	Placebo (n=74) %
Total with any adverse event	39.1	41.3	46.7	41.9
Autonomic nervous system Sweating increased	1.3	0.3	0	0
Body as a whole				
Back Pain	1.6	2.5	1.3	0
Fatigue	2.8	2.2	4.0	1.4
Influenza-Like Symptoms	1.6	1.2	2.7	1.4
Pain	2.2	2.2	4.0	6.8
Central & peripheral nervous system				
Dizziness	6.9	3.7	2.7	1.4
Headache	2.5	4.0	13.3	16.2
Gastro-intestinal system				
Abdominal Pain	1.6	0.9	0	0
Diarrhoea	4.1	1.6	0	0
Nausea	1.6	0.9	1.3	0
Respiratory system				
Pharyngitis	1.6	0.3	0	0
Upper Respiratory Tract infection	2.5	3.7	9.3	6.8

HCTZ = hydrochlorothiazide
Note: Telmisartan 80 mg open label treatment is not included in the Telmisartan 80 mg column

Additional adverse reactions reported in clinical trials with telmisartan plus hydrochlorothiazide are listed below according to system organ class:

Body as a Whole: Allergy, leg pain.

Central and Peripheral Nervous System: Vertigo.

Gastro-intestinal System: Dyspepsia, gastritis, gastro-intestinal disorder.

Metabolic and Nutritional System: Hypokalaemia, loss of diabetic control, hyperuricemia.

Musculo-Skeletal System: Myalgia, arthralgia.

Nervous System Disorders: Sleep disorder.

Psychiatric System: Anxiety.

Respiratory System: Bronchitis, sinusitis, respiratory distress, pneumonitis.

Reproductive system and breast disorders: erectile dysfunction.

Skin and Appendages System: Eczema, skin disorder.

Urinary System: Urinary tract infection.

In controlled trials with 1017 patients, 0.3% of patients treated with telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) used in combination discontinued due to hypotension.

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

Abnormal Hematologic and Clinical Chemistry Findings

In controlled trials, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of telmisartan and hydrochlorothiazide in combination.

Table 3 - Laboratory Parameter Results in Patients Treated with Telmisartan and Hydrochlorothiazide in Combination

Laboratory Parameter	% of Patients Treated with Telmisartan/ Hydrochlorothiazide	Clinical Comment
Increases in Blood Urea Nitrogen (BUN) (≥ 11.2 mg/dL)	2.8%	No patient discontinued treatment due to an increase in BUN.
Increases in Serum Creatinine (≥ 0.5 mg/dL)	1.4%	No patient discontinued treatment due to an increase in creatinine.
Decreases in Hemoglobin (≥ 2 g/dL)	1.2%	Changes in hemoglobin were not considered clinically significant and there were no discontinuations due to anemia.
Decreases in Hematocrit (≥ 9%)	0.6%	Changes in hematocrit were not considered clinically significant and there were no discontinuations due to anemia.

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

Serum Electrolytes: see 7 WARNINGS AND PRECAUTIONS.

Telmisartan

Additional 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.

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

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 ≥0.1% in telmisartan-treated patients.

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 illness, symptoms of infection (e.g., urinary tract infection, cystitis, fatigue, conjunctivitis)
Uncommon:	Hyperhidrosis, asthenia (weakness)

Blood and Lymphatic System:

Uncommon:	Anemia
Rare:	Thrombocytopenia
Unknown:	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: Abdominal 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, systemic lupus erythematosus*
*based on post-marketing experience.
Unknown**:** Anaphylactic reaction, angioedema

Infections and Infestations:

Uncommon: Upper respiratory tract infection. urinary tract infections Not known: Sepsis including fatal outcome

Investigations:

Uncommon: Blood creatinine increased
Rare: Blood uric acid increased, hepatic enzyme 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
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 kidney injury)

Respiratory System:

Common: Upper respiratory tract infection including pharyngitis and sinusitis, bronchitis, coughing, dyspnea, rhinitis

Skin and Appendages System:

Common: Skin disorders like rash
Uncommon: Pruritus
Rare: Erythema, drug eruption, eczema, toxic skin eruption
Unknown: Urticaria

Hemoglobin:

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

Clinical Trial Adverse Reactions Hydrochlorothiazide

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced, or therapy withdrawn.

Cardiovascular: Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics)

Central nervous system: Dizziness, vertigo, paresthesia, headache, xanthopsia

Gastrointestinal system: Anorexia, gastric irritation, nausea, vomiting, cramps, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia

Hypersensitivity: Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions

Other: Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision

Placebo-Controlled Trials-Telmisartan Monotherapy

The overall incidence of adverse events reported with telmisartan (41.4%) was usually comparable to placebo (43.9%) in controlled clinical trials.

Adverse events occurring in ≥1% of 1395 hypertensive patients treated with telmisartan *monotherapy* in placebo-controlled clinical trials, regardless of drug relationship, include the following:

Table 4 - Adverse Events Occurring in ≥1% of 1395 Hypertensive Patients Treated with Telmisartan Monotherapy

Adverse Event, by System	Telmisartan 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
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.

8.3 Less Common Clinical Trial Adverse Reactions

In addition, the following adverse events, with no established causality, were reported at an incidence <1% in placebo-controlled clinical trials with telmisartan monotherapy as well as telmisartan/hydrochlorothiazide combination therapy:

Clinical trial telmisartan monotherapy

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, constipation

Heart Rate & Rhythm Disorders: arrhythmia, tachycardia

Metabolic & Nutritional Disorders: diabetes mellitus, hypokalaemia

Musculoskeletal System Disorders: arthritis, arthritis aggravated, bursitis, fascitis plantar, tendon pain

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, dyspnea

Skin & Appendage Disorders: rash, skin dry, angioedema (rare)

Urinary System Disorders: dysuria, hematuria, micturition disorder, urinary tract infection, cystitis

Vascular (Extracardiac) Disorders: cerebrovascular disorder, purpura.

Vision Disorders: vision abnormal.

Respiratory: rhinitis, dyspnea

Special senses: conjunctivitis

Clinical Trials with Telmisartan and Hydrochlorothiazide Combination Therapy

Gastrointestinal: constipation

Respiratory: dyspnea

Skin and Subcutaneous Tissue Disorders: angioedema (rare)

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

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

Table 5 - Laboratory Parameter Results in Placebo-Controlled Clinical Trials Involving 1041 Patients Treated with Telmisartan Monotherapy

Laboratory Parameter	% of Placebo Patients	% of Patients Treated with Telmisartan	Clinical Comment
Increases in ALT > 3 times the upper limit of normal	1.7%	0.5%	No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
Increases in AST > 3 times the upper limit of normal	0.8%	0.1%	No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.

Laboratory Parameter	% of Placebo Patients	% of Patients Treated with Telmisartan	Clinical Comment
Increases in Blood Urea Nitrogen (BUN) ≥ 11.2 mg/dl	0.3%	1.5%	These increases occurred primarily with telmisartan in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in blood urea nitrogen and creatinine.
Increases in Creatinine ≥ 0.5 mg/dl	0.3%	0.6%	These increases occurred primarily with telmisartan in combination with hydrochlorothiazide. One telmisartan treated patient discontinued therapy due to increases in blood urea nitrogen and creatinine.
Increases in Serum Potassium (≥ 1.4 mEq/L	0.6%	0.3%	Clinically significant changes in potassium (that exceeded 3 mEq/L) were found in 0.6% of telmisartan- treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.
Decreases in Serum Potassium (> 1.4 mEq/L	0.3%	0.1%	Clinically significant changes in potassium (that exceeded 3 mEq/L) were found in 0.6% of telmisartan- treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo- treated patients were 0.6% and 0.8%.
Increases in Serum Uric Acid > 2.7 mg/dl	0.0%	1.7%	Clinically significant hyperuricemia (>10mEq/L) was observed in 2.3% of patients with telmisartan, with 0.4% reported in patients at baseline. Increases in serum uric acid were primarily observed in patients who received telmisartan in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia

Hemoglobin, Hemotocrit

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

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.

8.5 Post-Market Adverse Reactions

Telmisartan

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 kidney injury), hyperkalemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, hyponatraemia and weakness have been reported. The frequency of these effects is unknown. As with other angiotensin II blockers, rare cases of angioedema (including 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.

Hydrochlorothiazide

Adverse experiences that have been reported with hydrochlorothiazide alone without regard to causality are listed below:

Blood and Lymphatic System: aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia (sometimes with purpura) bone marrow depression

Body as a Whole: fever, asthenia (weakness)

Cardiovascular: orthostatic hypotension, cardiac arrhythmias

Central and Peripheral Nervous System: dizziness, vertigo, paraesthesia, restlessness, nervousness

Eye Disorders: transient blurred vision, xanthopsia, (acute myopia, acute angle-closure

glaucoma, and choroidal effusion; *frequency unknown*)
Gastrointestinal Disorders: pancreatitis, sialadenitis, gastric irritation, anorexia, nausea, vomiting, diarrhea, constipation, abdominal discomfort

Hepatobiliary Disorders: jaundice (cholestatis intrahepatic).

Hypersensitivity: purpura

Immune System Disorders: anaphylactic reactions

Laboratory Findings: Metabolic: hyperglycaemia, glucosuria, hyperuricaemia

Metabolism and Nutrition Disorders: volume depletion, decreased appetite, hypomagnesemia, hypercalcemia, alkalosis hypochloraemic, hyperglycemia, glycosuria, electrolyte imbalances (including hyponatraemia and hypokalaemia), hypercholesterolemia

Musculoskeletal: muscle spasm, cramps in legs

Nervous System Disorders: headache, light-headedness

Non-melanoma skin cancer: Some pharmacoepidemiological studies have suggested a higher risk of squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) of the skin with increasing use of hydrochlorothiazide. A systematic review and meta-analysis undertaken by Health Canada suggested, with important uncertainty, that the use of hydrochlorothiazide for several years (>3 years) could lead to:

- 122 additional cases (95% CI, from 112 to 133 additional cases) of SCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 3 observational studies);

- 31 additional cases (95% CI, from 24 to 37 additional cases) of BCC per 1000 treated patients compared with non-use of hydrochlorothiazide (meta-analysis of 2 observational studies).

Renal: renal failure, renal dysfunction, interstitial nephritis

Respiratory Disorders: respiratory distress, pneumonitis, pneumonia, acute respiratory distress syndrome (ARDS)*; frequency very rare*

Skin and Subcutaneous Tissue Disorders: rash, urticaria, erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, photosensitivity reaction, lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Vascular disorders: necrotising angiitis (vasculitis)

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
Concomitant use of angiotensin II receptor blockers (ARBs) –including the telmisartan component of Auro-Telmisartan HCTZ - 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 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Dual blockade of the Renin-Angiotensin System (RAS) and Renal, and 9.4 Drug-Drug Interactions, Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs or aliskiren-containing drugs).

9.2 Drug Interactions Overview

Telmisartan

Cytochrome P450: Telmisartan is not metabolized by the cytochrome P450 (CYP) isoenzymes; as such, it is not expected that a pharmacokinetic interaction of telmisartan with drugs which inhibit or induce CYP isozymes will occur.

Hydrochlorothiazide

Cytochrome P450: Hydrochlorothiazide is not metabolized by humans; as such, no pharmacokinetic interaction with agents known to inhibit or induce CYP isozymes or other enzymes systems is expected.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 - Established or Potential Drug-Drug Interactions with Telmisartan

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Agents increasing serum potassium	T	Telmisartan component of telmisartan/hydrochlorothiazide 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	CT	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 Auro-Telmisartan HCTZ, to maintain appropriate plasma digoxin concentrations.
Dual Blockade of the Renin-Angiotensin System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	CT	The treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	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 (see 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System).
Lithium Salts	C, T	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with	Serum lithium level monitoring is advisable during concomitant use.
		angiotensin converting enzyme inhibitors. Rare cases have also been reported with angiotensin II receptor blockers including telmisartan.	

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	T, CT	Combinations of angiotensin-II blockers (telmisartan) 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 blockers exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment, this may lead to acute renal failure. A reduced effect of antihypertensive drugs like telmisartan by inhibition of vasodilating prostaglandins has been reported during combined treatment with NSAIDs.	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 telmisartan did not result in a clinically significant interaction with ibuprofen.
Ramipril	CT	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	CT	Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration.	The decrease in the mean warfarin trough plasma concentration did not result in a change in the International Normalized Ratio (INR).

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Table 7 - Established or Potential Drug-Drug Interactions with Hydrochlorothiazide

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Alcohol, barbiturates and narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor of serum potassium level.
Anti-diabetic drugs (e.g., oral hypoglycemic agents and insulin)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control.Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g., guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACEI, ARB, and direct renin inhibitors.	Review of national and international guidelines for the management of antihypertensive combination therapy is recommended.
Antineoplastic drugs, including cyclophosphamid e and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematological status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
β-adrenergic receptor blocking agents propranolol, metoprolol, sotalol, or acebutolol	C	Hydrochlorothiazide may reduce the response to adrenergic amines, such as norepinephrine.	No significant pharmacokinetic interactions were noted when these agents were administered concomitantly, separately or in fixed combination.
Bile acid sequestrants, e.g., cholestyramine and colestipol resins	CT	Bile acid sequestrants bind thiazide diuretics in the gut and impair gastrointestinal absorption by 43-85%. Administration of thiazide 4 hours after a bile acid sequestrant reduced absorption of hydrochlorothiazide by 30-35%.	Give thiazide 2-4 hours before or 6 hours after the bile acid sequestrant. Maintain a consistent sequence of administration. Monitor blood pressure, and increase dose of thiazide, if necessary.

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Calcium and vitamin D supplements	C	Thiazides decrease renal excretion of calcium and increase calcium release from bone.	Monitor serum calcium, especially with concomitant use of high doses of calcium supplements. Dose reduction or withdrawal of calcium and/or vitamin D supplements may be necessary.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatraemia. Concomitant use with thiazide diuretics may potentiate hyponatraemia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotrop ic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia may occur.	Monitor serum potassium, and adjust medications, as required.
Digoxin	CT	Thiazide-induced electrolyte disturbances, e.g., hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or thiazide, as required.
Drugs that alter GI motility, i.e., anticholinergic agents, such as atropine and prokinetic agents, such as metoclopramide, domperidone	CT, T	Bioavailability of thiazide diuretcs may be increased by anticholinergic agents due to a decrease in gastrointestinal motility and gastric emptying. Conversely, prokinetic drugs may decrease the bioavailability of thiazide diuretics.	Dose adjustment of thiazide may be required.
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RCS	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Lithium	CT	Thiazide diuretics reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of thiazide diuretics with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor lithium levels closely.
Non-steroidal Anti-Inflammatory drugs (NSAIDs including ASA and COX-2 inhibitors)	CT	The co-administration of a non-steroidal anti- inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. The potential for acute renal insufficiency in patients who are dehydrated may be enhanced. NSAID-related retention of sodium and water antagonises the diuretic and antihypertensive effects of thiazides. NSAID-induced inhibition of renal prostaglandins leading to decreases of renal blood flow, along with thiazide- induced decreases in GFR may lead to acute renal failure. Patients with heart failure may be at particular risk.	Patients receiving NSAIDs and Auro-Telmisartan HCTZ should be adequately hydrated and be monitored for renal function at the beginning of the combined treatment. Monitoring of renal function at the beginning and during the course of the treatment is recommended as well as regular hydration of the patient. Therefore, when Auro-Telmisartan HCTZ and NSAIDs are used concomitantly, the patient should be observed closely to determine whether the desired effect of the diuretic is obtained. If combination use is necessary, also monitor serum potassium and blood pressure closely. Dose adjustments may be required.
Pressor amines (e.g., norepinephrine)	CT	Decreased response to pressor amines may occur.	The effect is considered not sufficient to preclude their concurrent use.
Selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, escitalopram, sertraline)	T, C	Concomitant use with thiazide diuretics may potentiate hyponatraemia.	Monitor serum sodium levels. Use with caution.

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Skeletal muscle relaxants of the curare family e.g., tubocurare	C	Thiazide drugs may increase the responsiveness of some skeletal muscle relaxants, such as curare derivatives.	In cases where HCTZ cannot be discontinued before the use of curare-like muscle relaxants, the anaesthetist must be informed of the treatment with HCTZ.
Topiramate	CT	Additive hypokalemia. Possible thiazide-induced increase in topiramate serum concentrations.	Monitor serum potassium and topiramate levels. Use potassium supplements, or adjust topiramate dose as necessary.

Legend: C = Case Study; RCS = Retrospective Cohort Study; CT = Clinical Trial; T = Theoretical

9.5 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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Auro-Telmisartan HCTZ (telmisartan/hydrochlorothiazide) is a combination of telmisartan a selective angiotensin II receptor blocker, plain (telmisartan), in combination with hydrochlorothiazide, a thiazide diuretic.

Telmisartan

Telmisartan is an orally active, AT1 selective angiotensin II receptor blocker. By selectively blocking the binding of angiotensin II to the AT1 receptors, telmisartan inhibits the vasoconstrictor and aldosterone-secreting effects of angiotensin II. Telmisartan blocks AT1

receptors and has essentially no affinity for the AT2 receptors. AT2 receptors have been found in many tissues; to date, they have not been found to be associated with cardiovascular homeostasis.

Telmisartan does not inhibit angiotensin converting enzyme (ACE, 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 homeostasis.

In hypertensive patients, antagonism of angiotensin II AT1 receptors results in two to three-fold increases in plasma renin and angiotensin II plasma concentrations. Long term effects of increased AT2 receptor stimulation by angiotensin II are unknown.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic which affects the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in the distal tubule, thus promoting water excretion. 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 latter effects of the renin-aldosterone link are mediated by angiotensin II; as such, co-administration of an angiotensin II AT1 receptor blocker may prevent the potassium loss associated with thiazide diuretics. The precise mechanism of the antihypertensive effect of thiazides however, is not fully understood.

10.2 Pharmacodynamics

Telmisartan

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 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 ≤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 telmisartan 40 mg once daily, and -13.7/-8.1 mmHg for telmisartan 80 mg once daily. Upon abrupt cessation of treatment with telmisartan, 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 ≥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.

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 is significantly reduced by telmisartan (compared to placebo), but less so than in non-black patients.

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.

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.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and an antihypertensive agent. After oral administration of hydrochlorothiazide, diuresis begins within 2 hours, peaks in about 4 hours and lasts 6 to 12 hours.

Hydrochlorothiazide affects the renal tubular mechanism of electrolyte reabsorption, increasing excretion of sodium and chloride in approximately equivalent amounts and reduces the rate of formation of solute-free water. Natriuresis causes a secondary loss of potassium and

bicarbonate.

In hypertensive patients, hydrochlorothiazide has an antihypertensive effect. However, the mechanism has yet to be sufficiently clarified. Hydrochlorothiazide has no effect on normal blood pressure.

Telmisartan and Hydrochlorothiazide Combination

In a placebo-controlled clinical study, the combination of telmisartan and hydrochlorothiazide resulted in decreases in trough systolic blood pressure (SBP) and diastolic blood pressure (DBP) which were greater than the decreases induced by either agent administered as monotherapy.

In a controlled clinical trial directly comparing telmisartan and hydrochlorothiazide tablets with telmisartan (80mg) monotherapy, trough SBP and DBP reductions observed with telmisartan and hydrochlorothiazide tablets were significantly greater than with telmisartan alone.

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

The antihypertensive effect of telmisartan/hydrochlorothiazide (80 mg/12.5 mg) was independent of age or gender. The overall response to the combination was similar for black and non-black patients.

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

10.3 Pharmacokinetics

There are no pharmacokinetic interactions between telmisartan and hydrochlorothiazide as the pharmacokinetic parameters of the individual components are unchanged by their co-administration as telmisartan and hydrochlorothiazide tablets. The results of a randomized, crossover study demonstrated that the bioavailabilities of telmisartan and hydrochlorothiazide were the same, whether administered as the fixed-dose combination or as the single entity formulations.

Table 8 - Single Dose Pharmacokinetics in Normotensive Subjects (10 Male and 10 Female Caucasian Subjects, 18 to 45 years of age). Given are arithmetic means (%CV).

Drug	Therapy	C_{max} (ng/mL)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)	Clearance (CL/f) (mL/min.)	Volume of Distribution (Vz/f) (L)
Telmisartan: monotherapy	A	246 (%CV 69.4)	22.2 (%CV 30)	1439 (%CV 94)	1650 (%CV 62)	2908 (%CV 60)
Telmisartan: combination therapy	B	266 (%CV 103)	24.4 (%CV 33)	1467 (%CV 94)	1565 (%CV 63)	3091 (%CV 63)
Hydrochlorothiazide: combination therapy	A	75.3 (%CV 26)	11.4 (%CV 43)	580.4 (%CV 27)	380 (%CV 23)	363.8 (%CV 43)
Hydrochlorothiazide: monotherapy	B	75.7 (%CV 22)	11.5 (%CV 36)	563.9 (%CV 20)	384 (%CV 20)	380.4 (%CV 40)

Telmisartan

Absorption: Following oral administration, telmisartan is well absorbed with a mean absolute bioavailability of about 50%. Mean peak plasma concentrations (C_{max}) of telmisartan are reached in 0.5 -1 hour after dosing. The pharmacokinetic profile is characterized by greater than proportional increases in plasma concentrations (C_{max} and AUC) with increasing doses >40 mg. Telmisartan shows bi-exponential decay kinetics with terminal elimination half life of approximately 24 hours and does not accumulate in plasma upon repeated once daily administration. Food slightly reduces the bioavailability of telmisartan.

Distribution: Telmisartan is extensively bound to plasma proteins (> 99.5%) at concentrations achieved at the recommended dosage. The apparent volume of distribution is approximately 500 L, suggesting extensive tissue binding sites.

Metabolism: Telmisartan is metabolized by conjugation to form a pharmacologically inactive acylglucuronide; this is the only metabolite that has been detected in human plasma and urine. Following both oral dosing and intravenous administration of radiolabelled telmisartan, the parent compound represented approximately 85%, and the glucuronide approximately 11% of total radioactivity in plasma. The cytochrome P450 isoenzymes are not involved in the metabolism of telmisartan.

Elimination: Total plasma clearance of telmisartan is > 800 mL/min. Biliary excretion is the predominant route of elimination of telmisartan and its metabolite.

Hydrochlorothiazide

Absorption: Following oral administration, peak concentrations of hydrochlorothiazide were reached approximately 2.0 hours after dosing. Based on cumulative renal excretion of hydrochlorothiazide the absolute bioavailability was about 60% to 70%.

Distribution: Hydrochlorothiazide is 40% protein bound in the plasma and its apparent volume of distribution is 2 to 5 L/kg.

Elimination: Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. The plasma-half life has been observed to vary between 5.6 and 14.8 hours when the plasma levels can be followed for up to 24 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours. Hydrochlorothiazide crosses the placenta but not the blood-brain barrier and is excreted in breast milk.

Special Populations and Conditions

Telmisartan
Pediatrics: Telmisartan pharmacokinetics have not been investigated in patients < 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics: The pharmacokinetics of telmisartan does not differ between elderly patients and those younger than 65 years of age.

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

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

Hepatic Insufficiency: In patients with hepatic insufficiency, plasma concentrations of telmisartan are increased, and absolute bioavailability approaches 100% (see 7 WARNINGS AND PRECAUTIONS and 4 DOSAGE AND ADMINISTRATION). Reduction of the dose of telmisartan should be considered which would necessitate usage of the individual tablet formulations.

Renal Insufficiency:
Lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient subjects and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Drug Interaction - Telmisartan and Hydrochlorothiazide

A randomized, 3-way crossover study was conducted in 14 healthy subjects to investigate the potential for a pharmacokinetic interaction between telmisartan and hydrochlorothiazide when administered concomitantly. Oral doses of either hydrochlorothiazide alone (25 mg, qd x 7), telmisartan alone (160 mg, qd x 7) or both drugs at the respective doses in combination, daily for 7 days were administered. Plasma concentrations of both telmisartan and

hydrochlorothiazide were assessed at steady state. Based on a comparative analysis, it was concluded that there is no pharmacokinetic interaction between telmisartan and hydrochlorothiazide when administered concomitantly.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature (15°C to 30°C). Protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance: Telmisartan

Proper name: Telmisartan

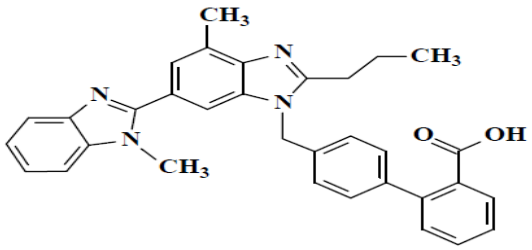
Chemical name: 4'-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-bezimidazol-1-yl]methyl]biphenyl-2-carboxylic acid

Or

4'-{[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl}-2-biphenyl carboxylic acid.

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

Structural formula:



Physicochemical properties:

Description:

A white or slightly yellowish, crystalline powder. Sparingly soluble in methylene chloride, slightly soluble in methanol, practically insoluble in water. It dissolves in 1M sodium Hydroxide.

Polymorphism:
Form A polymorphic form of telmisartan

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

Log P = 7.73 ± 1.04

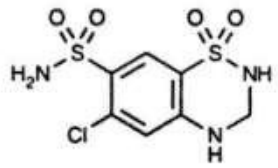
Drug Substance: Hydrochlorothiazide

Proper name: Hydrochlorothiazide

Chemical name*:* 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

Molecular formula and molecular mass: $C_7H_8ClN_3O_4S_2$, 297.75 g/mol

Structural formula:



Physicochemical properties:

Description: Hydrochlorothiazide is a white or almost white, crystalline powder.
In water - Very slightly soluble (1 part in 10000 parts)
In acetone –Soluble (1 part in 30 parts)
In alcohol - Sparingly soluble (1 part in 100 parts)
In dilute solutions of alkali hydroxides - Dissolves

Melting Point: 274°C

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Telmisartan and Hydrochlorothiazide Tablets (80 mg telmisartan/12.5 mg hydrochlorothiazide) is indicated for:

- **treatment of mild to moderate essential hypertension in patients in whom combination therapy with telmisartan and hydrochlorothiazide is considered appropriate.**

Table 9 - Summary of patient demographics for clinical trials in telmisartan (80 mg telmisartan/12.5 mg hydrochlorothiazide)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
502.261	Randomised, double-blind	80 mg telmisartan and 80 mg/12.5 mg telmisartan/hydrochlorothiazide, oral, 8 weeks	491 (245 telmisartan 80 mg; 246 telmisartan/hydrochlorothiazide (80 mg/12.5 mg) patients)	55.3 (20 – 79)	males and females
502.204	Randomized, double-blind, placebo-controlled	Combinations of telmisartan & hydrochlorothiazide (T/H): 20 mg/6.25 mg, 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/6.25 mg, 40 mg/12.5 mg, 40 mg/25 mg, 80 mg/6.25 mg, 80 mg/12.5 mg, 80 mg/25 mg, 160 mg/6.25 mg, 160 mg/12.5 mg, 160 mg/25 mg once daily, oral, 8 weeks	818	53.0* (19 – 80)	males and females

* median age
T = telmisartan
H = hydrochlorothiazide

In controlled clinical trials for Study 502.261 and Study 502.204, 571 patients were exposed to telmisartan 80 mg and concomitant hydrochlorothiazide 12.5 mg.

Table 10 - Results of Study# 502.261, and Study# 502.204 in telmisartan (80 mg telmisartan/ 12.5 mg hydrochlorothiazide)

Study #	Primary Measure of Efficacy	Patient Population	Summary of Results
502.261	Change from baseline in seated trough diastolic blood pressure (DBP) after 8 weeks of treatment.	Patients with mild to moderate hypertension who were taking no more than 3 antihypertensive agents at screening and who failed to respond adequately to telmisartan monotherapy	Treatment with telmisartan/ hydrochlorothiazide fixed dose combination (80 mg/12.5 mg) lowered trough DBP by an additional 3.1 mmHg and systolic blood pressure (SBP) by 5.7 mmHg compared to telmisartan 80 mg monotherapy. Reductions in both DBP and SBP were clinically and statistically significant ($p<0.01$).
502.204	Change from baseline in supine trough DBP after 8 weeks of treatment. Over 800 patients completed this study with approximately 70 patients in each of the primary dose groups	Patients with mild to moderate essential hypertension	The combination of telmisartan and hydrochlorothiazide (80 mg /12.5 mg) was significantly ($p<0.01$) better than either of its components administered as monotherapy in reducing trough supine diastolic blood pressure. Similar results were observed for supine systolic blood pressure and standing diastolic blood pressure.

BP = blood pressure
DBP = diastolic blood pressure
H = hydrochlorothiazide
SBP = systolic blood pressure
T = telmisartan

Study 502.204

Table 11 - Observed Mean Reduction from Baseline in Trough Supine Diastolic Blood Pressure (mmHg) from BI Study# 502.204

	Placebo	**Telmisartan 80 mg**
Placebo	3.8	11.5[1]
HCTZ 12.5 mg	7.3[1]	14.9[2],3

[1] compared to placebo; p<0.01

[2] compared to HCTZ 12.5 mg alone; p<0.01

[3] compared to telmisartan 80 mg alone; p<0.01

(80 mg telmisartan/25 mg hydrochlorothiazide) is indicated for:

- **treatment of patients whose blood pressure is not adequately controlled by 80 mg telmisartan /12.5 mg hydrochlorothiazide or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately.**

Table 12 - Summary of patient demographics for clinical trials in 80 mg telmisartan/25 mg hydrochlorothiazide)

Study #	**Study design**	**Dosage, route of administration and duration**	**Study subjects (n)**	**Mean age (Range)**	**Sex**
502.480	Randomized, double-blind, placebo-controlled trial in non- responders of the 80 mg/12.5 mg strength	80 mg telmisartan/12.5 mg hydrochlorothiazide and 80 mg telmisartan/ 25 mg hydrochlorothiazide, oral, 8 weeks	713 (361 telmisartan/ hydrochlorothiazide (80 mg /12.5 mg); 352 telmisartan/ hydrochlorothiazide (80 mg /25 mg)	57.2 (28 – 93)	males and females

* median age

T = telmisartan

H = hydrochlorothiazide

Table 13 - Results of Study# 502.480 in 80 mg Telmisartan/ 25 mg hydrochlorothiazide

Study #	Primary Measure of Efficacy	Patient Population	Summary of Results
502.480	Change from baseline in trough seated DBP after 8 weeks of treatment or at last trough observation during the double-blind treatment period	Patients without adequately controlled BP who failed to respond adequately to telmisartan/ hydrochlorothiazide (80 mg/12.5 mg)	Treatment with T80/H25 in patients with hypertension not adequately controlled by T80/H12.5 led to an additional, clinically relevant BP reduction. T80/H25 was superior to T80/H12.5 in reducing trough seated DBP after 8 weeks of randomised treatment. All analyses of secondary efficacy endpoints such as trough seated SBP, standing BP, and BP control and response showed better results for the T80/H25 group than for the T80/H12.5 group. Both treatments were safe and well tolerated.

BP = blood pressure
DBP = diastolic blood pressure
H = hydrochlorothiazide
SBP = systolic blood pressure
T = telmisartan

Study 502.480

At baseline, trough seated DBP means were comparable for both treatment groups with a mean of 95.0 mmHg for T80/H12.5 and 95.3 mmHg for T80/H25. Both groups showed a reduction in DBP by the end of study, with a larger reduction being observed in the T80/H25 treatment group. An adjusted mean change from baseline of -5.5 mmHg was observed for the T80/H12.5 group compared with an adjusted mean change of -7.1 mmHg for the T80/H25 group. The difference (95% CI) in the adjusted means of -1.6 mmHg (-2.5 mmHg, -0.6 mmHg) indicated the additional reduction in mean trough DBP present in the T80/H25 group. This difference was statistically significant (p=0.0012), which shows the superiority of T80/H25 over T80/H12.5 in reducing mean trough seated DBP in patients not responding adequately to T80/H12.5.

The analysis of the change from baseline in trough seated SBP at the last visit during the

double-blind treatment phase was performed using the same methodology as for the primary endpoint. At baseline, trough seated SBP means of the 2 groups were comparable, with a mean of 147.4 mmHg for T80/H12.5 and 147.9 mmHg for T80/H25. Mean trough seated SBP decreased in both treatment groups by the end of study; the larger reduction was observed in the T80/H25 group. The adjusted mean change from baseline in the T80/H12.5 group was -7.1 mmHg, while for T80/H25 it was -9.8 mmHg. The difference (95% CI) between the groups in the adjusted means was -2.7 mmHg (-4.2 mmHg, -1.2 mmHg) with a p-value of 0.0003. The data show that treatment with T80/H25 reduced mean trough seated SBP more than T80/H12.5.

Table 14 - Analysis of Change from Baseline to the End of Study in Trough Seated DBP (FAS) Study# 502.480

Trough Seated DBP [mmHg]		**T80/H12.5 N = 347**	**T80/H25 N = 340**
Baseline:	Mean (SD)	95.0 (4.4)	95.3 (4.7)
End of Study:	Mean (SD)	89.6 (7.3)	88.3 (7.5)
	Adjust Mean* (SE)	89.6 (0.4)	88.0 (0.5)
Change to End of Study:	Mean (SD)	- 5.3 (6.4)	- 7.0 (6.8)
	Adjusted Mean* (SE)	- 5.5 (0.4)	- 7.1 (0.5)
Difference to T80/T12.5:	Adjusted Mean* (SE)	- 1.6 (0.5)	
	95% CI	(- 2.5, - 0.6)	
	p-value	0.0012	

*Adjusted for baseline trough seated DBP and pooled country.

Table 15 - Analysis of Change from Baseline to the End of Study in Trough Seated SBP (FAS) Study# 502.480

Trough Seated SBP [mmHg]		**T80/H12.5 N = 347**	**T80/H25 N = 340**
Baseline:	Mean (SD)	147.4 (13.2)	147.9 (12.8)
End of Study:	Mean (SD)	141.8 (13.8)	139.5 (12.3)
	Adjust Mean* (SE)	140.6 (0.7)	137.9 (0.7)
Change to End of Study:	Mean (SD)	- 5.7 (11.0)	- 8.4 (10.6)
	Adjusted Mean* (SE)	- 7.1 (0.7)	- 9.8 (0.7)
Difference to T80/T12.5:	Adjusted Mean* (SE)	- 2.7 (0.7)	
	95% CI	(- 4.2, - 1.2)	
	p-value	0.0003	

*Adjusted for baseline trough seated SBP and pooled country.

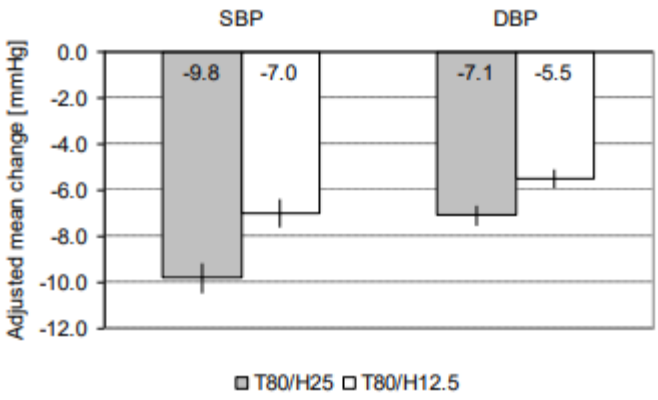


Figure 1: Adjusted (for baseline and country) mean change from baseline (with SE) of trough seated BP in the pivotal clinical trial study# 502.480

In this study, both treatments were generally well tolerated as evidenced by a similar incidence of adverse event (AE) frequencies between T80/H12.5 (29.6%) and T80/H25 (31.5%) and the data obtained were consistent with the known safety profile of telmisartan and hydrochlorothiazide tablets. Frequently reported AEs in one or the other treatment arm (overall incidence ≥1% or 8 patients) were back pain (1.9% of the T80/H12.5 patients and vs. 2.0% of the T80/H25 patients), bronchitis (2.2% vs. 1.1%), headache (2.8% vs. 0.6%), palpitations (1.4% vs. 0.9%), and nasopharyngitis (0.6% vs. 1.7%). The frequency of AEs events considered drug related was also similar (5.0% for T80/H12.5 and 5.7% for T80/H25). Two serious AEs considered drug-related by the investigators were reported in the trial (atrioventricular block third degree in the T80/H12.5 group and atrial flutter in the T80/H25 group).

14.2 Comparative Bioavailability Studies

An open-label, randomized, 4-way crossover, replicate-design study was conducted to compare the bioavailability following single oral administration of telmisartan (80 mg) and hydrochlorothiazide (12.5 mg) administered as either telmisartan and hydrochlorothiazide tablets or as the individual monotherapy formulations. Twenty (10M/10F) healthy subjects participated in this study. Comparative measures of exposure to telmisartan and hydrochlorothiazide were based on AUC and C_{max}. The results of this study demonstrated that both telmisartan and hydrochlorothiazide had similar bioavailabilities administered as either telmisartan and hydrochlorothiazide tablets or as the single entity formulations.

Conventional average bioequivalence, average scaled bioequivalence, and individual bioequivalence (as a secondary analysis) using a moment-based scaled approach were evaluated with respect to Telmisartan pharmacokinetic variables. With respect to HCTZ pharmacokinetic variables, conventional average bioequivalence was evaluated. The upper bounds of the one-sided 95% confidence interval for the average, scaled bioequivalence measure M_{as} are, on the ratio scale, 109.4% and 113.8% for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max}, respectively. These upper bounds of the confidence intervals are

below the upper bound of the bioequivalence range, 125%. Thus average, scaled bioequivalence with respect to the variables $AUC_{0-\infty}$ and C_{max} is shown. Similarly, average, scaled bioequivalence with respect to the secondary variable AUC_{0-48h} was shown. The 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables $AUC_{0-\infty}$ and C_{max} are 100.0% to 111.0% and 106.8% to 129.0%, respectively. The confidence interval for $AUC_{-0-\infty}$ falls in the bioequivalence range of 80% to 125%, while the confidence interval for C_{max} falls in the bioequivalence range of 75% to 133%. The confidence interval for the "test/reference" mean ratio of the secondary variable AUC_{0-48h} falls in the 80% to 125%, bioequivalence range.

Table 16 - Results for Telmisartan

Telmisartan (80 mg) From measured data Adjusted Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Fixed dose combination (Test)***	**Individual tablets (Reference)†**	**% Ratio of Adjusted Geometric Means**	**90% Confidence Interval**
AUC_{0-48h} (ng·h/ml)	875.9 1158 (85.51)	820.7 1082 (83.46)	106.7	101.1 - 112.7
AUC0-∞ (ng·h/ml)	1034.5 1414 (92.50)	981.9 1364 (91.97)	105.4	100.0 - 111.0
C_{MAX} (ng/mL)	196.4 251.5 (87.88)	167.3 207.0 (71.58)	117.4	106.8 - 129.0
T_{MAX}§ (h)	1.00 (0.50 - 2.00)	1.00 (0.50 - 2.00)	Not Applicable	Not Applicable
$T_{½}$[2] (h)	24.12 (29.65)	24.73 (35.90)	Not Applicable	Not Applicable

* batch no. 9960326

† Telmisartan 80 mg oblong tablet, batch no. 9960326;

§ Expressed as the median (range) only.

[2] Expressed as the arithmetic mean (CV%) only.

For Hydrochlorothiazide, the 90% confidence intervals for the "test/reference" mean ratio for the primary pharmacokinetic variables AUC0-∞and C_{max} are 91.8% to 109.5% and 90.8% to 107.4%, respectively. The confidence intervals for the "test/reference" mean ratio of the pharmacokinetic variable Ae_{0-48h} is 91.0% to 103.9%. All confidence intervals fall in the bioequivalence range of 80% to 125%.

Table 17 - Results for Hydrochlorothiazide

Hydrochlorothiazide (12.5 mg) From measured data Adjusted Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Fixed dose combination (Test)***	**Individual tablets (Reference)†**	**% Ratio of Adjusted Geometric Means**	**90% Confidence Interval**
AUC_{0-24h} (ng·h/ml)	478.1 493.9 (25.73)	467.2 475.04 (19.09))	102.3	97.3 - 107.6
AUC0-∞ (ng·h/ml)	575.4 580.4 (27.46)	574.0 563.9 (19.85)	100.3	91.8 - 109.5
C_{MAX} (ng/mL)	73.1 75.33 (26.14)	74.1 75.72 (26.61)	98.7	90.8 - 107.4
T_{MAX}§ (h)	2.00 (1.00 -3.00)	2.00 (1.00 -3.00)	Not Applicable	Not Applicable
$T_{½}$[2] (h)	11.35 (43.10)	11.51 (36.33)	Not Applicable	Not Applicable

* batch no. 9960326

† Hydrochlorothiazide 12.5 mg tablet, batch no. .F4260;

§ Expressed as the median (range) only.

2 Expressed as the arithmetic mean (CV%) only.

Telmisartan and Hydrochlorothiazide Tablets 80 mg/12.5 mg:

A double blind, randomized, two-way, crossover, single-dose, comparative oral bioavailability study of Auro-Telmisartan HCTZ Tablets, 80 mg/12.5 mg (Auro Pharma Inc.) and 1 x 80 mg/12.5 mg MICARDIS® Plus Tablets, 80 mg/12.5 mg (Boehringer Ingelheim (Canada) Ltd.) was conducted in 55 healthy, adult, male human, subjects under fasting conditions. A summary of the comparative bioavailability data is presented in the following table.

Summary Table of Comparative Bioavailability Data

Telmisartan (1 x 80 mg Telmisartan and 12.5 mg Hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (hr.ng/mL)	2234.7 2665.4(61.3)	2207.5 2670.5(60.0)	101.2	97.0 – 105.7
AUC_I (hr.ng/mL)	2364.6 2842.5(63.6)	2322.9 2816.7(61.6)	101.8	97.7 – 106.1
C_{max} (ng/mL)	439.0 495.5 (49.8)	462.9 536.7 (55.1)	94.8	84.3 – 106.7
T_{max}[3] (hr)	1.0 (0.5-4.0)	1.0 (0.5-3.0)		

$T_{½}$[4] (hr)	16.5 (43.7)	16.2 (39.9)		

[1]Auro-Telmisartan HCTZ (telmisartan and hydrochlorothiazide Tablets USP 80 /12.5 mg), by Auro Pharma Inc.
[2]MICARDIS® PLUS (telmisartan and hydrochlorothiazide) Tablets 80/12.5 mg, of (Boehringer Ingelheim (Canada) Ltd).
[3] Expressed as the median (range) only.
[4] Expressed as arithmetic mean (%CV) only.

Hydrochlorothiazide (1 x 80 mg Telmisartan and 12.5 mg Hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (hr.ng/mL)	655.2 676.2 (25.2)	634.6 658.7 (26.7)	103.3	99.2-107.5
AUC_I (hr.ng/mL)	734.6 757.0 (24.5)	712.6 738.7 (26.1)	103.1	99.2-107.2
C_{max} (ng/mL)	97.8 100.5 (24.0)	103.3 107.6 (28.7)	94.7	90.5 – 99.0
T_{max}[3] (hr)	1.8 (1.0-4.0)	1.8 (1.0-3.0)		
$T_{½}$[4] (hr)	8.4 (26.0)	8.1 (23.7)		

[1]Auro-Telmisartan HCTZ (telmisartan and hydrochlorothiazide) Tablets, 80 mg/12.5 mg (Auro Pharma Inc.)
[2]MICARDIS® PLUS (telmisartan and hydrochlorothiazide) Tablets, 80 mg/12.5 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only.
[4] Expressed as arithmetic mean (%CV) only.

Telmisartan and Hydrochlorothiazide Tablets 80 mg/25 mg:

A double blind, randomized, two-way, crossover, single-dose, comparative oral bioavailability study of Auro-Telmisartan HCTZ Tablets, 80 mg/25 mg (Auro Pharma Inc.) and 1 x 80/25 mg of MICARDIS® Plus Tablets, 80 mg/12.5 mg (Boehringer Ingelheim (Canada) Ltd.) was conducted in 51 healthy, adult, male human, subjects under fasting conditions. A summary of the comparative bioavailability data is presented in the following table.

Summary Table of Comparative Bioavailability Data

Telmisartan (1 x 80 mg Telmisartan and 25 mg Hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (hr.ng/mL)	2631.7 2953.6 (47.8)	2508.1 2894.3 (51.7)	104.9	99.8 - 110.3

AUC_I (hr.ng/mL)	2781.4 3136.6 (48.9)	2660.2 3089.8 (53.9)	104.6	99.6 - 109.8
C_{max} (ng/mL)	532.6 593.8 (45.5)	491.1 571.0 (54.5)	108.5	97.1 - 121.1
T_{max}[3] (hr)	1.2 (0.3-3.0)	1.0 (0.3-3.0)		
$T_{½}$[4] (hr)	17.9 (43.5)	17.3 (38.4)		

[1]Auro-Telmisartan HCTZ (telmisartan and hydrochlorothiazide) Tablets, 80 mg /25 mg (Auro Pharma Inc.)
[2]MICARDIS®PLUS (telmisartan and hydrochlorothiazide) Tablets, 80 mg/25 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only.
[4] Expressed as arithmetic mean (%CV) only.

Hydrochlorothiazide (1 x 80 mg Telmisartan and 25 mg Hydrochlorothiazide) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (hr.ng/mL)	1444.2 1494.4 (27.2)	1513.1 1564.9 (25.7)	95.5	91.8 - 99.2
AUC_I (hr.ng/mL)	1530.9 1577.9 (25.7)	1607.0 1654.1 (24.0)	95.3	91.9 - 98.7
C_{max} (ng/mL)	193.8 199.7 (24.4)	214.8 223.8 (28.0)	90.2	85.5 - 95.2
T_{max}[3] (hr)	1.8 (1.3-5.0)	1.5 (1.0-5.0)		
$T_{½}$[4] (hr)	9.0 (16.6)	9.2 (13.7)		

[1]Auro-Telmisartan HCTZ (telmisartan and hydrochlorothiazide) Tablets, 80 mg/25 mg) (Auro Pharma Inc.)
[2]MICARDIS®PLUS (telmisartan and hydrochlorothiazide) Tablets, 80 mg/25 mg (Boehringer Ingelheim (Canada) Ltd.)
[3] Expressed as the median (range) only.
[4] Expressed as arithmetic mean (%CV) only.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Telmisartan and Hydrochlorothiazide

Repeated-dose toxicity studies of 26 weeks duration were conducted in both rats and dogs. These studies were designed to compare the toxicological profiles of telmisartan, and hydrochlorothiazide administered alone, with that of the drugs given in combination.

Table 18 - Repeat Dose Toxicity Studies Conducted with Telmisartan/Hydrochlorothiazide

Species	Dose Telmisartan/HCTZ (mg/kg/day)	Duration	NOTEL (mg/kg/day)
Rat (Chbb:THOM) (20/sex/dose)	0/0 0.1/0.03 4/1.2 50/7.8 50/15.6 50/0 0/15.6	26 weeks	0.1/0.03
Dogs (Beagle) (4/sex/dose)	0/0 0.25/0.08 1/0.31 4/0.63 4/1.25 4/0 0/1.25	26 weeks	0.25/0.08

HCTZ = hydrochlorothiazide

Repeated, oral doses of telmisartan with and without hydrochlorothiazide for 26 weeks in rats induced a pronounced and persistent dose-related decrease of blood pressure without reflex tachycardia. At 50 mg/kg of telmisartan, the addition of hydrochlorothiazide had an additive effect on the blood pressure-lowering effect of telmisartan. Clinical laboratory and histopathological changes were similar to those observed in previous toxicity studies in rats with telmisartan alone. Essentially, there were no new toxicities observed with the addition of hydrochlorothiazide.
In dogs, repeated oral doses of telmisartan with hydrochlorothiazide administered for 26 weeks was associated with nephrotoxicity, which is consistent with the findings from previous studies with telmisartan alone. The addition of 0.63 mg/kg of hydrochlorothiazide to 4 mg/kg telmisartan did not increase renal toxicity whereas the co-administration of 1.25 mg/kg hydrochlorothiazide significantly increased toxicity. The exacerbation of nephrotoxicity in this species can be ameliorated by saline supplementation.

No effects of telmisartan on male or female fertility were observed.

Carcinogenicity

No carcinogenicity or mutagenicity studies have been conducted with the combination of telmisartan and hydrochlorothiazide. However, these studies have been conducted for telmisartan and hydrochlorothiazide alone. Based on the preclinical safety profile of the

telmisartan and hydrochlorothiazide combination and on human pharmacokinetic studies, there is no indication of any adverse interaction between telmisartan and hydrochlorothiazide.

Telmisartan

The carcinogenic potential of telmisartan was assessed in 2-year feeding studies in mice at doses of 10, 100 and 1000 mg/kg/day in rats at 3, 15, and 100 mg/kg/day. Drug administration did not affect overall survival time in either study nor did it affect the rate of tumour-induced mortality. There were no increases in overall tumour incidence, incidence of benign or malignant tumours or in tumour multiplicity associated with telmisartan administration.

The standard battery of genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with Salmonella typhimurium and E. coli, a gene mutation test with CHO cells, a cytogenetic test with human lymphocytes and an in vivo mouse micronucleus assay.

Hydrochlorothiazide

According to the experimental data available, hydrochlorothiazide revealed inconsistent evidence of carcinogenic activity in rats and mice, with conflicting evidence of hepatic adenoma in male mice at the highest dose (dietary concentrations of 2000 ppm in rats and 5000 ppm in mice) and adrenal pheochromocytoma in one rat study but not in another. Current evidence is inadequate to draw a clear conclusion for a carcinogenic effect of hydrochlorothiazide in animals.

The mutagenic potential was assessed in a series of in vitro and in vivo test systems. While some positive results were obtained in vitro, all in vivo studies provided negative results. Hydrochlorothiazide enhanced the UVA-induced formation of pyrimidine dimers in vitro and in the skin of mice following oral treatment. It is therefore concluded that although there is no relevant mutagenic potential in vivo, hydrochlorothiazide could enhance the genotoxic effects of UVA light. This mechanism of photosensitization could be associated with a higher risk for non-melanoma skin cancer.

Reproductive and Developmental Toxicology

Telmisartan and hydrochlorothiazide: A developmental toxicity study was conducted in rats with oral doses of telmisartan and hydrochlorothiazide used in combination (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 to the dams than either drug alone, the results indicated the lack of teratogenic, fetotoxic or embryotoxic potential of the telmisartan/hydrochlorothiazide combination at the doses tested in this animal model.

Telmisartan: 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 oral doses of 5-100 mg/kg. No teratogenic or

embryotoxic potential in rats was observed at oral doses of ≤50 mg/kg administered during gestation. 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.

Hydrochlorothiazide: Hydrochlorothiazide was orally administered to pregnant mice and rats during gestation, at doses of up to 3000 and 1000 mg/kg/day respectively. There was no evidence of fetotoxicity or teratogenicity.

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

Non-Clinical Pharmacodynamics

The effect of telmisartan in combination with hydrochlorothiazide was investigated in spontaneously hypertensive rats. Repeated oral administration of telmisartan at a dose of 3 mg/kg/day for 5 days to conscious rats reduced mean arterial blood pressure (MAP) significantly and persistently with maximal decrease in MAP of approximately 36 mmHg. Hydrochlorothiazide alone (10 mg/kg/day) had no effect on blood pressure in this model, however when administered in combination with telmisartan (3 mg/kg/day), induced a significantly greater antihypertensive effect than with telmisartan alone, with a maximal reduction of about 53 mmHg. Furthermore, the telmisartan/hydrochlorothiazide combination ameliorated the alteration in potassium balance when compared to hydrochlorothiazide alone in this model.

A slight, significant increase in heart rate (~ 20 bpm) was observed during treatment with telmisartan and hydrochlorothiazide in combination; this increase reverted to control values during the washout period.

17 SUPPORTING PRODUCT MONOGRAPHS

1. MICARDIS® PLUS (Telmisartan and Hydrochlorothiazide Tablets 80mg/12.5mg and 80 mg/25 mg), submission control number: 287669, Product Monograph, Boehringer Ingelheim (Canada) Ltd. November 28, 2024

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] Auro-Telmisartan HCTZ

Telmisartan/Hydrochlorothiazide Tablets

Read this carefully before you start taking **Auro-Telmisartan HCTZ** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Auro-Telmisartan HCTZ**.

Serious Warnings and Precautions - Pregnancy

- Auro-Telmisartan HCTZ should not be used during pregnancy. Taking Auro-Telmisartan HCTZ during pregnancy can cause injury or even death to your baby.
- If you discover that you are pregnant while taking Auro-Telmisartan HCTZ, stop the medication and contact your healthcare professional as soon as possible.

What is Auro-Telmisartan HCTZ used for?

- Auro-Telmisartan HCTZ is used in adults to lower high blood pressure.

How does Auro-Telmisartan HCTZ work?

Auro-Telmisartan HCTZ contains a combination of 2 drugs, telmisartan and hydrochlorothiazide:

- Telmisartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in "-SARTAN". It works by blocking a substance in the body that causes blood vessels to tighten. It helps lower blood pressure.

- Hydrochlorothiazide is a diuretic or "water pill" that increases urination. It works by causing the kidneys to get rid of unneeded water and salt from the body into the urine. It also helps lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore, it is important to continue taking Auro-Telmisartan HCTZ regularly even if you feel fine. Do not stop taking your medicine without talking to your healthcare professional.

What are the ingredients in Auro-Telmisartan HCTZ?

Medicinal ingredients: Telmisartan and hydrochlorothiazide

Non-medicinal ingredients:

Colloidal silicon dioxide, hydroxyl propyl cellulose, lactose monohydrate, mannitol, meglumine, povidone, red ferric oxide (80 mg/12.5 mg), sodium hydroxide pellets, sodium stearyl fumarate & yellow ferric oxide (80 mg/25 mg).

Auro-Telmisartan HCTZ comes in the following dosage forms:

Tablets: 80 mg / 12.5 mg and 80 mg / 25 mg

Do not use Auro-Telmisartan HCTZ if:

- you are allergic to telmisartan, hydrochlorothiazide or to any non-medicinal ingredient in Auro-Telmisartan HCTZ (see **What are the ingredients in Auro-Telmisartan HCTZ?**).
- you are allergic to any sulfonamide-derived drugs (sulfa drugs), most of them have a medicinal ingredient that ends in "-MIDE". This includes other diuretics ("water pills").
- you have experienced an allergic reaction (angioedema) with swelling of the hands, feet or ankles, face, lips, tongue, throat, or sudden difficulty breathing or swallowing to any ARB (any drug in the same class as Auro-Telmisartan HCTZ). Be sure to tell your healthcare professional that this has happened to you.
- you have difficulty urinating or produce no urine.
- you are pregnant or planning to become pregnant. Taking Auro-Telmisartan HCTZ during pregnancy can cause injury and even death to your baby.
- you are breastfeeding. Auro-Telmisartan HCTZ passes into breast milk.
- you are allergic to some sugars (fructose, lactose and/or mannitol).
- you have been diagnosed with hereditary fructose intolerance, a rare genetic disorder where you cannot break down fructose. Auro-Telmisartan HCTZ 80 mg/12.5 mg and 80 mg/25 mg tablets contain 477.18 mg of a similar type of sugar called mannitol.
- you are already taking a blood pressure-lowering medicine that contains aliskiren and you have diabetes or kidney problems.
- you have one of the following rare hereditary diseases:
  - Galactose intolerance;
  - Lapp lactase deficiency;
  - Glucose-galactose malabsorption.

  This is because lactose is a non-medicinal ingredient in Auro-Telmisartan HCTZ.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Auro-Telmisartan HCTZ. Talk about any health conditions or problems you may have, including if you:

- have a history of allergic reactions (angioedema).
- are allergic to penicillin.
- have narrowing of an artery or a heart valve.
- have heart failure.
- have diabetes. Auro-Telmisartan HCTZ may cause low blood sugar levels.

- have liver or kidney problems.
- are taking any of the following:
    - blood pressure lowering medicines, such as aliskiren
    - an angiotensin-converting-enzyme inhibitor (ACEI)
    - beta blockers (i.e., acebutolol, metoprolol). Do NOT stop taking your beta-blocker without talking to your healthcare professional as this can cause serious side effects.
- have lupus, an autoimmune disease that can affect many parts of the body.
- have gout, a type of arthritis.
- are on dialysis.
- are dehydrated or if you suffer from excessive vomiting, diarrhea, or sweating.
- 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 less than 18 years old.
- have been told by your healthcare professional that you have an intolerance to some sugars.
- have had skin cancer or have a family history of skin cancer.
- are taking a medicine that contains lithium. The combination with Auro-Telmisartan HCTZ is not recommended.
- have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking medicines to suppress your immune system.

Other warnings you should know about:

Risk of skin cancer:

- Auro-Telmisartan HCTZ contains hydrochlorothiazide. Treatment with hydrochlorothiazide may increase the risk of developing non-melanoma skin cancer. The risk is higher if you have been taking Auro-Telmisartan HCTZ for many years (more than 3) or at a high dose.
- While taking Auro-Telmisartan HCTZ:
    - Make sure to regularly check your skin for any new lesions. Check areas that are most exposed to the sun, such as the face, ears, hands, shoulders, upper chest and back.
    - Limit your exposure to the sun and to indoor tanning. Always use sunscreen (SPF-30 or higher) and wear protective clothing when going outside.

Talk to your healthcare professional immediately if you become more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) while you are taking Auro-Telmisartan HCTZ.

Increased sensitivity of the skin to sun: Your skin may become sensitive to the sun while taking Auro-Telmisartan HCTZ. Limit your exposure to the sun and to indoor tanning. Always use

sunscreen (SPF-30 or higher) and wear protective clothing when going outside.

Surgery: Before surgery and general anesthesia (even at the dentist's office), tell the healthcare professional that you are taking Auro-Telmisartan HCTZ, as there may be a sudden fall in blood pressure associated with general anesthesia.

Allergic Reactions / Angioedema: Allergic reactions (angioedema) causing swelling of tissues under the skin, sometimes affecting the face and throat, have happened in people taking Auro-Telmisartan HCTZ. These allergic reactions may happen at any time during treatment with Auro-Telmisartan HCTZ and can be life threatening. Very rarely, cases have been fatal. If you experience an allergic reaction, stop taking Auro-Telmisartan HCTZand get immediate medical help.

Blood Tests: Auro-Telmisartan HCTZcan cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Driving and using machines: Before you perform tasks, which may require special attention, wait until you know how you respond to Auro-Telmisartan HCTZ. Dizziness, lightheadedness, sensation that you, or the environment around you, is moving or spinning (Vertigo) or fainting can occur, especially after the first dose and when the dose is increased.

If patients experience these adverse events, they should avoid potentially hazardous tasks such as driving or operating machinery.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions
Do not take Auro-Telmisartan HCTZwith other blood pressure lowering drugs, including diuretics ("water pills"), aliskiren-containing products, or angiotensin-converting-enzyme inhibitors (ACEI) if you have diabetes (type 1 or type 2) or serious kidney problems. When taken together with Auro-Telmisartan HCTZ, they may cause very low blood pressure.

The following may interact with Auro-Telmisartan HCTZ:

- adrenocorticotropic hormone (ACTH) used to treat West Syndrome
- alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- amphotericin B, an antifungal drug
- anticancer drugs, including cyclophosphamide and methotrexate
- antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram, and sertraline

- antidiabetic drugs, including insulin and oral medicines, such as repaglinide
- beta-blockers, medications for heart problems
- bile acid resins used to lower cholesterol, such as cholestyramine and colestipol resins
- calcium or vitamin D supplements
- corticosteroids used to treat joint pain and swelling
- digoxin, a heart medication
- drugs that slow down or speed up bowel function, including atropine, metoclopramide, and domperidone
- drugs used to treat epilepsy, including carbamazepine and topiramate
- gout medications, including allopurinol and probenecid
- lithium used to treat bipolar disease
- nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling (such as ibuprofen, naproxen, and celecoxib)
- medicines that increase the levels of potassium in your blood. These include:
  - potassium-sparing diuretics,
  - potassium supplements or
  - potassium-containing salt substitutes.
- pressor amines, such as norepinephrine
- skeletal muscle relaxants used to relieve muscle spasms, including tubocurare
- warfarin used to thin the blood to prevent blood clots

How to take Auro-Telmisartan HCTZ:

- Auro-Telmisartan HCTZ is not for initial therapy. You must first be stabilized on the individual components of Auro-Telmisartan HCTZ (i.e., telmisartan and hydrochlorothiazide).
- Take Auro-Telmisartan HCTZ exactly as prescribed. It is recommended to take your dose at about the same time everyday preferably in the morning.
- Auro-Telmisartan HCTZ can be taken with or without food, but it should be taken the same way each day.
- Auro-Telmisartan HCTZ tablets are for once-daily oral administration and should be swallowed whole with liquid.
- If Auro-Telmisartan HCTZ causes upset stomach, take it with food or milk.

Usual dose:

Adults: One tablet daily.

Overdose:

If you think you, or a person you are caring for, have taken too much Auro-Telmisartan HCTZ, contact a healthcare professional, 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.

What are possible side effects from using Auro-Telmisartan HCTZ?

These are not all the possible side effects you may have when taking Auro-Telmisartan HCTZ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Back or leg pain, muscle cramps, joint pain, muscle spasms, pain, weakness, restlessness;
- Headache, anxiety, dizziness, pins and needles in your fingers;
- Diarrhea, constipation, nausea, vomiting, upset stomach, abdominal pain, flatulence, decreased appetite, enlargement of the glands in your mouth;
- Dry mouth;
- Rash, eczema, skin eruptions, bleeding under the skin, red patches on the skin;
- Drowsiness, insomnia, fatigue;
- Upper respiratory infection;
- Reduced libido.
- Very rare: Acute respiratory distress (signs include severe shortness of breath, fever, weakness, and confusion).

If you experienced breathing or lung problems (including inflammation or fluid in the lungs) following hydrochlorothiazide intake in the past or if you develop any severe shortness of breath or difficulty breathing after taking Auro-Telmisartan HCTZ, seek medical attention immediately.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Low Blood Pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up	√		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Anemia: fatigue, loss of energy, weakness, shortness of breath		√	
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat		√	
Chest Pain		√	
Non Melanoma Skin Cancer*:* lump or discoloured patch on the skin that stays after a few weeks and slowly changes. Cancerous lumps are red/pink and firm and sometimes turn into ulcers. Cancerous patches are usually flat and scaly		√	
UNCOMMON			
Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		√	
Increased Blood Sugar: frequent urination, thirst, and hunger	√		
Urinary Tract Infection (Cystitis): frequent or painful urination, feeling unwell		√	
RARE			
Depression: low mood, loss of interest in activities, change in appetite and sleep patterns	√		
Decreased or Increased Levels of Potassium in the Blood: irregular heartbeat, muscle weakness and generally feeling unwell		√	
Liver Problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
Low Blood Sugar (hypoglycemia): shaky, irregular heartbeat, sweating, hunger, dizziness		√	
Decreased Platelets: bruising, bleeding, fatigue and weakness, small purple or red dots under the skin		√	
Hyponatraemia (decreased blood sodium): nausea, vomiting, abdominal cramps, agitation, confusion and hallucinations		√	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains, and flu-like symptoms		√	
VERY RARE			

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Acute respiratory distress (ARDS): Severe shortness of breath, fever, weakness or confusion			√
Skin Reactions (Steven-Johnson Syndrome, Toxic Epidermal Necrolysis): any combination of itchy skin rash, redness, blistering and peeling of the skin and/or of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or joint pain, yellowing of the skin or eyes, dark urine			√
UNKNOWN			
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Rhabdomyolysis (breakdown of damaged muscle): muscle pain that you cannot explain, muscle tenderness or weakness, dark brown (tea-coloured) urine			√
Heart Rhythm or Heart Rate Disturbances: heart racing or skipping a beat		√	
Sepsis (blood poisoning): chills, confusion, fever or low body temperature, shakiness, irregular heartbeat (including fatal outcome)		√	
Inflammation of the Pancreas: abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		√	
Eye Disorders: • **Myopia:** sudden near sightedness or blurred vision • **Glaucoma:** increased pressure in your eyes, eye pain • **Choroidal effusion (build up of liquid in your eye):** blind spots, eye pain, blurred vision			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at controlled room temperature (15°C to 30°C). Protect from moisture.

Store Auro-Telmisartan HCTZ out of the reach and sight of children and pets.

If you want more information about Auro-Telmisartan HCTZ:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http:// www.auropharma.ca , or by calling 1-855-648-6681

This leaflet was prepared by Auro Pharma Inc.

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