PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}TEVA-CANDESARTAN/HCTZ

Candesartan Cilexetil/Hydrochlorothiazide Tablets

Tablets, 16 mg / 12.5 mg and 32 mg / 12.5 mg, Oral use

Teva Standard

Angiotensin II AT_1 Receptor Blocker + Diuretic

Teva Canada Limited
30 Novopharm Court
Toronto, ON
M1B 2K9
Canada
www.tevacanada.com

Date of Initial Authorization
October 25, 2012

Date of Revision:
November 15, 2023

Submission Control Number: 277728

RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions – Respiratory	11/2023
7 Warnings and Precautions – Ophthalmologic	11/2023

TABLE OF CONTENTS

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TEVA-CANDESARTAN/HCTZ (candesartan cilexetil/hydrochlorothiazide) is indicated for:

- the treatment of essential hypertension in patients for whom combination therapy is appropriate.

TEVA-CANDESARTAN/HCTZ is not indicated for initial therapy (see 4 DOSAGE AND ADMINISTRATION).

The dosage of TEVA-CANDESARTAN/HCTZ must be individualized. The dose of TEVA-CANDESARTAN/HCTZ should be determined by titration of the individual components.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

Candesartan cilexetil/hydrochlorothiazide is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with anuria and patients who are hypersensitive to other sulfonamide-derived drugs, because of the hydrochlorothiazide component (see Immune and 8.5 Post-Market Adverse Reactions).
- Pregnant women (see 7.1.1 Pregnant Women).
- Nursing women (see 7.1.2 Breast-feeding).
- Children aged < 1 year.
- Combination 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) (see Dual Blockade of the Renin-Angiotensin System (RAS), Renal, and 9.4 Drug-Drug Interactions).
- Patients with severe hepatic impairment and/or cholestasis.

- Patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2 BSA).
- Patients with gout.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- When used in pregnancy, angiotensin receptor (AT_1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, candesartan cilexetil/hydrochlorothiazide should be discontinued as soon as possible (see 7.1.1 Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The dosage of TEVA-CANDESARTAN/HCTZ PLUS must be individualized.
- The fixed combination is not for initial therapy.
- The dose of TEVA-CANDESARTAN/HCTZ PLUS should be determined by titration of the individual components.

4.2 Recommended Dose and Dosage Adjustment

Once the patient has been stabilized on the individual components, one TEVA-CANDESARTAN/HCTZ 16 mg / 12.5 mg or 32 mg / 12.5 mg tablet once daily may be taken if the doses on which the patient was stabilized are the same as those in the fixed combination (see 1 INDICATIONS).

Initiation of therapy requires consideration of recent antihypertensive treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors.

Candesartan cilexetil Monotherapy
The recommended initial dose of candesartan cilexetil is 16 mg, once daily. Total daily doses of candesartan cilexetil should range from 8 to 32 mg. Doses higher than 32 mg do not appear to have a greater effect on blood pressure reduction, and there is relatively little experience with such doses. Most of the antihypertensive effect is present within 2 weeks and the maximal blood pressure reduction is generally obtained within 4 weeks. For patients with possible depletion of intravascular volume (e.g. patients treated with diuretics, particularly those with impaired renal function) consideration should be given to administration of a lower dose. If blood pressure is not controlled by Candesartan cilexetil alone, a thiazide diuretic may be added (see 9.4 Drug-Drug Interactions).

Concomitant Diuretic Therapy
In patients receiving diuretics, candesartan cilexetil 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 candesartan cilexetil, to reduce the likelihood of hypotension (see Hypotension). If this is not possible because of the patient's condition, candesartan cilexetil 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.

As a rule, concomitant diuretic therapy is not necessary when TEVA-CANDESARTAN/HCTZ is used.

Dosage Adjustments in the Presence of Pathologies

Hepatic Impairment: Dose titration is recommended in patients with mild to moderate chronic liver disease.

TEVA-CANDESARTAN/HCTZ is contraindicated in patients with severe hepatic impairment and/or cholestasis (see 2 CONTRAINDICATIONS).

Renal Impairment: In patients with mild to moderate renal impairment (i.e., creatinine clearance between 30-80 mL/min/1.73m^2 BSA), a dose titration is recommended.

TEVA-CANDESARTAN/HCTZ is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2 BSA) (see 2 CONTRAINDICATIONS).

Dosage Adjustments in Special Populations

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 7.1.3. Pediatrics).

Geriatrics (> 65 years of age): No dose adjustment of TEVA-CANDESARTAN/HCTZ is necessary for elderly patients. As greater sensitivity of some older patients cannot be ruled out, appropriate caution is recommended (see 7.1.4 Geriatrics).

4.4 Administration

TEVA-CANDESARTAN/HCTZ should be taken once daily, at approximately the same time each day, with or without food.

4.5 Missed Dose

If a patient misses a dose of TEVA-CANDESARTAN/HCTZ and remembers within 12 hours, the patient should take the dose as soon as possible and then go back to the regular schedule. If it is more than 12 hours after the patient remembers, they should not take the missed dose; the next dose should be taken on time.

A double dose of TEVA-CANDESARTAN/HCTZ should never be taken to make up for a missed dose.

5 OVERDOSAGE

No specific information is available on the treatment of overdosage with candesartan cilexetil/hydrochlorothiazide. Treatment is symptomatic and supportive.

Candesartan cilexetil
Limited data are available in regard to overdosage of candesartan cilexetil in humans. The most likely manifestations of overdosage would be hypotension, dizziness and tachycardia; bradycardia could occur from reflex parasympathetic (vagal) stimulation. Thirst, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed. If symptomatic hypotension should occur, supportive treatment should be instituted and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic drugs may also be administered if the above-mentioned measures are not sufficient. In case reports detailing overdosage (≤ 672 mg candesartan cilexetil) patient recovery was uneventful.

Candesartan cilexetil is not removed from the plasma by hemodialysis.

Hydrochlorothiazide
The most common symptoms observed from overdosage of hydrochlorothiazide are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

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 Use	Tablet: 16 mg / 12.5 mg and 32 mg / 12.5 mg	Carmellose calcium, lactose monohydrate, magnesium

		stearate, microcrystalline cellulose, poloxamer 188, povidone, pregelatinized starch and red iron oxide (16mg/12.5 mg tablets).

TEVA-CANDESARTAN/HCTZ is available in tablets of 16 mg / 12.5 mg and 32 mg / 12.5 mg.

Each tablet contains candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg or 32 mg / 12.5 mg. Each tablet also contains the following non-medicinal ingredients: Carmellose calcium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone, pregelatinized starch, red iron oxide (16mg/12.5 mg tablets).

TEVA-CANDESARTAN/HCTZ 16 mg / 12.5 mg tablets are light pink, capsule shaped biconvex tablet, one side of the tablet is scored and debossed with “C” on the left side of the score and with “16” on the right side of the score. The other side of the tablet is scored. Tablets are available in bottles of 30 and 100 tablets and blister packs of 30 tablets.

TEVA-CANDESARTAN/HCTZ 32 mg / 12.5 mg tablets are White to off white, capsule shaped biconvex tablet, one side of the tablet is scored and debossed with “C” on the left side of the score and with “32” on the right side of the score. The other side of the tablet is scored. Tablets are available in bottles of 30 tablets and blister packs of 30 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 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

Dual blockade of the Renin-Angiotensin System (RAS): There is evidence that co-administration of angiotensin receptor antagonists (ARBs), such as the candesartan cilexetil component of Candesartan cilexetil/hydrochlorothiazide, 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 TEVA-CANDESARTAN/HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see 2 CONTRAINDICATIONS).

Further, co-administration of ARBs, including the candesartan cilexetil component of TEVA-CANDESARTAN/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, decreased renal function (including acute 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.

Hypotension: Occasionally, symptomatic hypotension has occurred after administration of candesartan cilexetil. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, or undergoing surgery with anesthesia. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident (see 8 ADVERSE REACTIONS).

Valvular Stenosis: There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Driving and Operating Machinery

The effect of candesartan cilexetil/hydrochlorothiazide on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties candesartan cilexetil/hydrochlorothiazide is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur

during treatment of hypertension. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Metabolism: Patients receiving thiazides, including hydrochlorothiazide (HCTZ), should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia).

Periodic determinations of serum electrolytes, to detect possible electrolyte disturbance, should be performed at appropriate intervals. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.

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

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

Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

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

Thiazides may decrease serum PBI (protein bound iodine) levels without signs of thyroid disturbance.

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

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

Treatment with a thiazide diuretic may impair glucose tolerance (see 9.4 Drug-Drug Interactions). Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. However, at the doses contained in candesartan cilexetil/hydrochlorothiazide tablets, minimal effects were observed.

Hepatic/Biliary/Pancreatic

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

Dose titration is recommended in patients with mild to moderate chronic liver disease (see Hepatic Impairment).

candesartan cilexetil/hydrochlorothiazide is contraindicated in patients with severe hepatic failure and/or cholestasis (see 2 CONTRAINDICATIONS).

No studies were carried out with candesartan cilexetil/hydrochlorothiazide fixed combination in patients with impaired hepatic function.

Immune

Hypersensitivity Reactions: Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.

Systemic Lupus Erythematosus: The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide.

Ophthalmologic

Choroidal Effusion, Acute Myopia and Secondary Angle-Closure Glaucoma related to Hydrochlorothiazide: Hydrochlorothiazide, a sulfonamide, can cause 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 weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue TEVA-CANDESARTAN/HCTZ as rapidly as possible. Prompt medical or surgical treatments 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.

Peri-Operative Considerations
Thiazides may increase the responsiveness to tubocurarine.

Renal

Renal Impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the RAAS, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk.

The use of ARBs, including the candesartan cilexetil component of TEVA-CANDESARTAN/HCTZ, or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 mL/min/1.73 m^2) (see 2 CONTRAINDICATIONS and 9.4 Drug-Drug Interactions).

Use of candesartan cilexetil should include appropriate assessment of renal function. Thiazides should be used with caution.

In patients with mild to moderate renal impairment (i.e., creatinine clearance between 30-80 mL/min/1.73m^2 BSA), a dose titration is recommended (see Renal Impairment).

Because of the hydrochlorothiazide component, TEVA-CANDESARTAN/HCTZ is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m^2 BSA) (see 2 CONTRAINDICATIONS and Renal Impairment).

Renal Transplantation: There is limited experience regarding the administration of candesartan in patients with renal transplant.

Azotemia: Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued.

Respiratory

Acute respiratory toxicity: 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. If diagnosis of ARDS is suspected, TEVA-CANDESARTAN/HCTZ should be withdrawn, and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

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

If photosensitivity reactions occur during treatment with hydrochlorothiazide-containing drugs, treatment should be stopped.

7.1 Special Populations

7.1.1 Pregnant Women

Candesartan cilexetil/hydrochlorothiazide is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). Drugs that act directly on the RAAS can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, candesartan cilexetil/hydrochlorothiazide should be discontinued as soon as possible.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACEIs 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 ARBs, 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 ARBs should be stopped immediately, and, if appropriate, alternative therapy should be started.

The use of ARBs during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during pregnancy may compromise feto placental perfusion and may cause fetal and neonatal effects like icterus, disturbance of electrolyte balance, thrombocytopenia and possibly other adverse experiences which have occurred in the adult. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia.

Animal Data: Oral doses ≥ 10 mg candesartan cilexetil/kg/day administered to pregnant rats during late gestation and continued through lactation were associated with reduced survival and an increased incidence of hydronephrosis in the offspring. Candesartan cilexetil given to pregnant rabbits at an oral dose of 3 mg/kg/day caused maternal toxicity (decreased body weight and death) but, in surviving dams, had no adverse effects on fetal survival, fetal weight, or external, visceral, or skeletal development. No maternal toxicity or adverse effects on fetal

development were observed when oral doses ≤1000 mg candesartan cilexetil/kg/day were administered to pregnant mice.

7.1.2 Breast-feeding

It is not known whether candesartan is excreted in human milk, but significant levels have been found in the milk of lactating rats. Thiazides appear in human milk. Because many drugs are excreted in human milk, and because of their potential for adversely affecting the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

TEVA-CANDESARTAN/HCTZ is contraindicated in children aged < 1 year (see 2 CONTRAINDICATIONS).

***In utero* exposure**: 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 or dialysis may be required as a means of reversing hypotension and/or substituting for impaired renal function; however, limited experience with those procedures has not been associated with significant clinical benefit. Candesartan cilexetil is not removed from plasma by dialysis.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between the younger and elderly patients but greater sensitivity of some older patients cannot be ruled out and appropriate caution is recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Candesartan cilexetil/hydrochlorothiazide has been evaluated for safety in over 2500 patients treated for hypertension, including more than 700 treated for six months or more, and 500 for about one year or more. In placebo controlled double blind studies to support candesartan cilexetil/hydrochlorothiazide 16 mg / 12. 5 mg, candesartan cilexetil/hydrochlorothiazide combination was administered to 1025 hypertensive patients. Approximately 600 patients received candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg. The overall exposure amounts to 977 patient-years. Safety of the higher strength combinations of candesartan cilexetil/hydrochlorothiazide, 32 mg / 12.5 mg and 32 mg / 25 mg, has also been evaluated. In

controlled clinical studies 718 patients were treated with candesartan/hydrochlorothiazide 32 mg / 12.5 mg and 1155 patients were treated with 32 mg / 25 mg; the total exposure in patient years in these studies was 107.8 and 175.3 years, respectively.

In general, adverse events were mild and transient in controlled clinical studies with various doses of candesartan cilexetil/hydrochlorothiazide (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg). The overall incidence of adverse events showed no association with age or gender.

In controlled clinical studies, discontinuation due to adverse events occurred in 2.3-3.3% and 2.7-4.3% of patients treated with candesartan cilexetil/hydrochlorothiazide and placebo, respectively. In studies to support the 16 mg / 12.5 mg strength, the incidence of serious adverse events observed with candesartan cilexetil/hydrochlorothiazide was 2.7% (71 out of 2582 patients). The incidence of serious adverse events was lower in the candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg dosage groups with the highest frequency of 0.8% (5 out of 664 patients) observed in the 32 mg / 25 mg group.

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.

In the double blind placebo controlled studies to support candesartan cilexetil/hydrochlorothiazide 16 mg / 12.5 mg, the overall incidence of adverse events showed no association with age or gender. In these studies the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in ≥ 1% of patients, regardless of drug relationship (see Table 2).

Table 2 Adverse events reported with candesartan cilexetil/hydrochlorothiazide in ≥ 1% of patients regardless of causality in studies supporting the 16 mg / 12.5 mg strength

	Candesartan cilexetil/ hydrochlorothiazide (n=1 025)	Candesartan cilexetil (n=749)	Hydrochlorothiazide (n=603)	Placebo (n=526)
	%	%	%	%
Cardiac Disorders				
tachycardia	1.3	0.9	1.2	0.8
ECG abnormal	1.2	1.2	0.3	0.8
edema peripheral	1.1	1.6	2.2	1.3
chest pain	1.0	0.7	1.0	0.6

Gastrointestinal Disorders				
nausea	1.5	0.9	1.2	0.6
diarrhea	1.1	0.7	0.5	1.3
gastroenteritis	1.0	0.5	1.0	0.4
General disorders				
fatigue	1.4	1.2	1.7	1.0
abdominal pain	1.3	1.7	0.7	1.1
Infections and Infestations				
urinary tract infection	1.6	1.3	1.8	1.0
Metabolism and Nutrition Disorders				
hyperuricemia	1.1	0.7	0.8	0.4
hyperglycemia	1.0	0.9	0.5	0.2
Musculoskeletal, connective tissue and bone disorders				
back pain	3.8	5.5	5.1	3.0
arthralgia	1.5	1.3	1.3	0.8
Nervous System Disorders				
headache	4.3	7.6	7.6	7.0
dizziness	3.1	3.9	2.0	1.5
inflicted injury	2.0	2.0	3.0	1.9
Respiratory, Thoracic and Mediastinal Disorders				
upper respiratory tract infection	3.7	5.1	5.6	1.9
influenza-like symptoms	2.8	2.3	3.0	2.9
sinusitis	2.3	2.9	3.5	1.9
bronchitis	2.1	2.8	2.5	2.5
pharyngitis	1.4	0.9	1.0	1.7
rhinitis	1.2	1.5	1.2	0.4
cough	0.9	2.3	1.7	1.0

In double blind, controlled studies with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg, and 32 mg / 25 mg the following adverse events reported with candesartan cilexetil/hydrochlorothiazide occurred in ≥ 1% of patients, regardless of drug relationship (see Table 3).

Table 3 Adverse events reported with candesartan cilexetil/hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg in ≥ 1% of patients regardless of causality

	Candesartan cilexetil/ hydrochlorothiazide (n=1 873)	Candesartan cilexetil (n=1188)	Hydrochlorothiazide (n=540)	Placebo (n=163)

	32 mg / 12.5 mg (n= 718)	32 mg / 25 mg (n=1155)			
	%	%	%	%	%
Gastrointestinal Disorders					
diarrhea	1.1	0.4	0.7	0.4	1.8
General disorders					
fatigue	1.1	0.9	0.8	0.4	2.5
Metabolism and Nutrition Disorders					
dyslipidemia	3.3	2.5	1.9	0.4	0
Musculoskeletal, connective tissue and bone disorders					
back pain	2.4	1.6	1.1	0.6	2.5
arthralgia	0.6	1.1	0.6	1.1	1.8
Nervous System Disorders					
dizziness	2.5	2.9	1.3	2.4	0.6
headache	2.4	2.0	5.1	7.6	7.4
Respiratory, Thoracic and Mediastinal Disorders					
cough	1.4	0.7	0.6	1.3	1.2
nasopharyngitis	1.3	1.4	1.0	0.6	0
upper respiratory tract infection	1.3	0.3	1.7	3.5	5.5
bronchitis	1.1	0.9	1.0	1.3	1.2

8.3 Less Common Clinical Trial Adverse Drug Reactions

Candesartan cilexetil

The following adverse events were reported at an incidence of <1% in controlled clinical trials (in more than one patient, with higher frequency than placebo):

- **Blood**: anemia, epistaxis.
- **Body as a Whole:** allergy, asthenia, pain, syncope.
- **Cardiovascular**: angina pectoris, circulatory failure, flushing, hypotension, myocardial infarction, peripheral ischemia, thrombophlebitis.
- **Central and Peripheral Nervous System**: hypertonia, hypoesthesia, paresthesia, vertigo.
- **Gastrointestinal:** constipation, dyspepsia, dry mouth, toothache.
- **Hearing**: tinnitus.
- **Metabolic and Nutritional**: diabetes mellitus, hyperkalemia, hyponatremia.

- **Musculoskeletal**: arthritis, arthropathy, myalgia, myopathy, skeletal pain, tendon disorder.
- **Psychiatric**: depression, impotence, neurosis.
- **Reproductive**: menopausal symptoms.
- **Resistance** Mechanism: otitis.
- **Respiratory**: laryngitis.
- **Skin**: eczema, pruritus, rash, skin disorder, sweating, (rarely) urticaria.
- **Urinary**: abnormal urine, cystitis.
- **Vision**: conjunctivitis.

There was no clear indication of dose-response relationship for any of the most common adverse events.

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

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of candesartan cilexetil/hydrochlorothiazide.

Blood glucose*:* in controlled clinical trials, elevations of blood glucose occurred in 1.0% of patients treated with candesartan cilexetil/hydrochlorothiazide compared to 0.2% of patients receiving placebo.

Creatinine*, Urea*: An increase in creatinine and urea has been observed with candesartan cilexetil/hydrochlorothiazide.

Hemoglobin and Hematocrit*:* small decreases in hemoglobin were observed in patients treated with candesartan cilexetil/hydrochlorothiazide but were rarely of clinical importance. Values of hemoglobin below the predefined critical limit were recorded in 0.9% of patients in controlled clinical trials with candesartan cilexetil/hydrochlorothiazide.

Hyperuricemia*:* increases in serum uric acid were found in 1.1% of patients treated with candesartan cilexetil/hydrochlorothiazide and 0.4% of patients treated with placebo.

Liver Function Tests*:* in controlled clinical trials, elevations of ALT (> 3 times the upper limit of normal) occurred in 0.9% of patients treated with candesartan cilexetil/hydrochlorothiazide compared to 0% of patients receiving placebo. Minor increases in serum AST have been observed in single patients receiving candesartan cilexetil/hydrochlorothiazide.

Serum Potassium, Sodium*:* a small decrease (mean decrease of 0.1 mmol/L) in serum potassium was observed in patients treated with candesartan cilexetil/hydrochlorothiazide but was rarely of clinical importance. Values of serum potassium below the predefined lower critical limit were recorded in 0.6% of patients in controlled clinical trials with candesartan cilexetil/hydrochlorothiazide. An increase in serum potassium has rarely been observed with

candesartan cilexetil/hydrochlorothiazide. A decrease in sodium has been observed with candesartan cilexetil/hydrochlorothiazide.

8.5 Post-Market Adverse Reactions

Candesartan cilexetil
Angioedema, (involving swelling of the face, lips and/or tongue) has been reported rarely in patients treated with candesartan cilexetil.

In other post-marketing experience, renal impairment, including renal failure in susceptible patients, has been observed (see Renal Impairment).

Very rare cases of abnormal hepatic function or hepatitis have also been reported.

Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of leukopenia, neutropenia and agranulocytosis.

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

Hydrochlorothiazide
Potentially serious clinical adverse events have been reported to occur with hydrochlorothiazide, such as:
Blood and lymphatic system disorders: aplastic anemia; hemolytic anemia; leukopenia; neutropenia/agranulocytosis; thrombocytopenia.
Eye Disorders: acute angle-closure glaucoma; acute myopia; choroidal effusion.
Endocrine and Metabolism: hypokalemia.
Gastrointestinal disorders: pancreatitis.
Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice).
Immune system disorders: anaphylactic reactions; photosensitivity reactions.
Musculoskeletal and connective tissue disorders: cutaneous lupus erythematosus; systemic lupus erythematosus.
Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis, pulmonary edema and acute respiratory distress syndrome) (see Respiratory).
Renal and urinary disorders: interstitial nephritis; renal dysfunction.
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis.
Vascular disorders: necrotising angitis (vasculitis).

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 that, with important uncertainty, 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).

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions

- candesartan cilexetil/hydrochlorothiazide is contraindicated in combination 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). See 2 CONTRAINDICATIONS, Dual blockade of the Renin-Angiotensin System (RAS), Renal and 9.4 Drug-Drug Interactions.

9.2 Drug Interactions Overview

In vitro studies indicate that cytochrome P450 isoenzyme CYP 2C9 is involved in the biotransformation of candesartan to its inactive metabolite. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4**.**

9.3 Drug-Behavioural Interactions

Consumption of alcohol while using candesartan cilexetil/hydrochlorothiazide may potentiate the risk of orthostatic hypotension (see 9.4 Drug-Drug Interactions)

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 4 Established or Potential Drug-Drug Interactions

Proper Name	Source of Evidence	Effect	Clinical Comment
Agents Increasing	T	Candesartan decreases the	Potassium-sparing diuretics,

Proper Name	Source of Evidence	Effect	Clinical Comment
Serum Potassium		production of aldosterone.	potassium supplements or other drugs that may increase serum potassium levels (e.g. heparin, co-trimoxazole) 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, or switching to candesartan cilexetil/hydrochlorothiazide may attenuate any effect that candesartan cilexetil may have on serum potassium.
Alcohol, barbiturates or narcotics	C	Potentiation of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amantadine	T	Co-administration of thiazide diuretics may increase the risk of adverse effects caused by amantadine.	Monitor the patient closely and adjust the dosage of either medication as required.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor serum potassium level.
Anti-cholinergic agents (e.g., atropine, biperiden, domperidone and metoclopramide)	CT,T	Bioavailability of thiazide diuretics 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 candesartan cilexetil/hydrochlorothiazide may be required.
Antidiabetic agents	CT	Thiazide-induced	Monitor glycemic control,

Proper Name	Source of Evidence	Effect	Clinical Comment
(e.g. insulin or oral hypoglycemic agents)		hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	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).	Dose adjustments of other concomitantly taken antihypertensive drugs may be required.
Antineoplastic drugs, including cyclophosphamide and methotrexate	C	Concomitant use of thiazide diuretics may reduce renal excretion of cytotoxic agents and enhance their myelosuppressive effects.	Hematologic status should be closely monitored in patients receiving this combination. Dose adjustment of cytotoxic agents may be required.
Bile acid sequestran e.g. cholestyramine	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 candesartan cilexetil/hydrochlorothiazide 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 candesartan cilexetil/hydrochlorothiazide, if necessary.
Calcium and Vitamin D supplements	C	Administration of thiazide with vitamin D, or with calcium salts may potentiate the rise in serum calcium. 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 hyponatremia. Concomitant use with thiazide diuretics	Monitor serum sodium levels. Use with caution.

Proper Name	Source of Evidence	Effect	Clinical Comment
		may potentiate hyponatremia.	
Corticosteroids, and adrenocorticotropic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with thiazide diuretics.	Monitor serum potassium and adjust medications, as required.
Cyclosporine	T	May increase the risk of hyperuricemia and gout type complications.	Serum uric acid levels should be closely monitored and medications adjusted, as required.
Diazoxide	C	Co-administration of thiazide diuretics enhances the hyperglycemic effect of diazoxide.	Blood glucose levels should be monitored and dose adjustment of insulin or antidiabetics may be required in diabetic patients.
Digoxin	CT	Combination treatment with candesartan cilexetil and digoxin in healthy volunteers had no effect on AUC or C max values for digoxin compared to digoxin alone. Similarly, combination treatment had no effect on AUC or C max values for candesartan compared to candesartan cilexetil alone. Thiazide-induced electrolyte disturbances, i.e. hypokalemia, hypomagnesemia, increase the risk of digoxin toxicity, which may lead to fatal arrhythmic events.	Concomitant administration of candesartan cilexetil/hydrochlorothiazide and digoxin requires caution. Monitor electrolytes and digoxin levels closely. Supplement potassium or adjust doses of digoxin or candesartan cilexetil/hydrochlorothiazide, as required.

Proper Name	Source of Evidence	Effect	Clinical Comment
Diuretics	CT	Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with candesartan cilexetil.	The possibility of symptomatic hypotension with the use of candesartan cilexetil can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of candesartan cilexetil (see Hypotension and 4 DOSAGE AND ADMINISTRATION). No drug interactions of clinical significance have been identified with thiazide diuretics. When candesartan cilexetil/hydrochlorothiazide is used, other diuretics are, as a rule, unnecessary.
Dual blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs	CT	Clinical trial data have shown that dual blockade of the RAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAS-acting agent.	Dual blockade of the RAS with ARBs or ACEIs and aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment (see 2 CONTRAINDICATIONS). The combined use of ARBs, ACEIs or aliskiren-containing drugs is generally not recommended (see Dual blockade of the Renin-Angiotensin System (RAS)).
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	Use of candesartan cilexetil/hydrochlorothiazide in patients with gout is contraindicated (see 2 CONTRAINDICATIONS).

Proper Name	Source of Evidence	Effect	Clinical Comment
		hypersensitivity reactions to allopurinol.	
Lithium Salts	CT	As with other drugs which eliminate sodium, lithium clearance may be reduced. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity.	Concomitant use of candesartan cilexetil/hydrochlorothiazide with lithium is generally not recommended. If such use is deemed necessary, reduce lithium dose by 50% and monitor closely. Serum lithium levels should be monitored carefully if lithium salts are to be administered.
Methyldopa	C	There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyldopa.	Monitor for symptoms of anemia. If anemia is confirmed, tests should be done for hemolysis. If hemolytic anemia is present, candesartan cilexetil/hydrochlorothiazide should be discontinued.
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	CT	In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Attenuation of the antihypertensive effect may occur when simultaneously administering ARBs and NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid and non-selective NSAIDs). As with ACE inhibitors, concomitant use of ARBs and NSAIDs may lead to an increased risk of worsening of renal function, including	When candesartan cilexetil/hydrochlorothiazide and NSAIDs are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained. The combination of ARBs and NSAIDs should be administered with caution, especially in older patients and in volume depleted patients. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy and periodically thereafter. If combination use is

Proper Name	Source of Evidence	Effect	Clinical Comment
		possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.	necessary, monitor renal function, serum potassium, and blood pressure closely. Dose adjustments may be required. Patients with heart failure may be at particular risk.
Pressor Amines (e.g., norepinephrine)	T	In the presence of thiazide diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.	Monitor and consider dose adjustments if required.
Selective Serotonin Reuptake Inhibitors (SSRIs, e.g., citalopram, escitalopram, sertraline)	T,C	Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Skeletal muscle relaxants of the curare family, e.g., tubocurarine	C	Thiazide drugs may increase the responsiveness of some nondepolarizing skeletal muscle relaxants, such as curare derivatives.	
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.
Warfarin	CT	When candesartan cilexetil was administered at 16 mg once daily under steady state conditions, no pharmacodynamic effect on prothrombin time was demonstrated in subjects stabilized on warfarin.	
Other	CT	No significant drug interactions have been reported with glyburide, nifedipine or oral	

Proper Name	Source of Evidence	Effect	Clinical Comment
		contraceptives co-administered with candesartan cilexetil to healthy volunteers.	

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

9.5 Drug-Food Interactions

TEVA-CANDESARTAN/HCTZ may be taken with or without food (see 4 DOSAGE AND ADMINISTRATION).

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

Candesartan cilexetil/hydrochlorothiazide combines the actions of candesartan cilexetil, an angiotensin II AT_1 receptor blocker, and that of a thiazide diuretic, hydrochlorothiazide.

Candesartan cilexetil

Candesartan cilexetil antagonizes the action of angiotensin II by blocking the angiotensin type one (AT1) receptor. Angiotensin II is the primary vasoactive hormone of the RAAS with effects that include vasoconstriction, stimulation of aldosterone secretion, and renal reabsorption of sodium.

Candesartan cilexetil, a prodrug, is rapidly converted to the active drug, candesartan, during absorption from the gastrointestinal tract.

Candesartan blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the

pathways for angiotensin II synthesis. There are also AT_2 receptors found in many tissues, but they play no known role in cardiovascular homeostasis to date. Candesartan has a much greater affinity (> 10,000-fold) for the AT_1 receptor than for the AT_2 receptor. The strong bond between candesartan and the AT_1 receptor is a result of tight binding to and slow dissociation from the receptor.

Candesartan does not inhibit ACE, also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

Hydrochlorothiazide is a diuretic and antihypertensive which interferes with the renal tubular mechanism of electrolyte reabsorption. It inhibits the active reabsorption of sodium, mainly in the distal kidney tubules, and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater extent. While this compound is predominantly a saluretic agent, *in vitro* studies have shown that it has a carbonic anhydrase inhibitory action which seems to be relatively specific for the renal tubular mechanism. It does not appear to be concentrated in erythrocytes or the brain in sufficient amounts to influence the activity of carbonic anhydrase in those tissues.

Hydrochlorothiazide is useful in the treatment of hypertension. It may be used alone or as an adjunct to other antihypertensive drugs. Hydrochlorothiazide does not affect normal blood pressure.

10.2 Pharmacodynamics

Candesartan cilexetil
Candesartan inhibits the pressor effects of angiotensin II infusion in a dose-dependent manner. After 1 week of once-daily dosing of 8 mg candesartan cilexetil, the pressor effect was inhibited by approximately 90% at peak (4-8 hours after dosing) with approximately 50% inhibition persisting at 24 hours. Plasma concentrations of angiotensin I, angiotensin II (AII), and plasma renin activity, increased in a dose-dependent manner after single and repeated administration of candesartan cilexetil to healthy subjects and hypertensive patients. A decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients.

Hydrochlorothiazide
Onset of the diuretic action following oral administration occurs in 2 hours and the peak action in about 4 hours. Diuretic activity lasts about 6 to 12 hours.

In Vitro and Animal Pharmacology: In an in vitro assay system, hydrochlorothiazide at 10^{-5} M did not affect the inhibition of binding of [^{125}I]-labeled AII to the AII receptor by candesartan.

HCTZ at 10 mg/kg/day had no effect on blood pressure in conscious spontaneously hypertensive rats. HCTZ combined with 0.1 or 1 mg/kg of candesartan cilexetil synergistically intensified the reduction in blood pressure induced by candesartan cilexetil.

10.3 Pharmacokinetics

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicinal product.

Candesartan cilexetil

Absorption: Following oral administration of candesartan cilexetil as a tablet, the absolute bioavailability of candesartan is estimated to be approximately 15%. After tablet ingestion, the peak serum concentration (C_{max}) is reached after 3-4 hours. Food does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Distribution: The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan does cross the blood-brain barrier. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Metabolism: Candesartan cilexetil is rapidly and completely bioactivated to candesartan by ester hydrolysis during absorption from the gastrointestinal tract. It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. *In vitro* studies indicate that cytochrome P450 isoenzyme CYP 2C9 is involved in the biotransformation of candesartan to its inactive metabolite. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

Elimination: Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. Candesartan is mainly excreted unchanged in urine and feces (via bile). When candesartan cilexetil is administered orally, about 26% of the dose is excreted as candesartan in urine. Following an oral dose of 14 C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous (iv) dose of 14 C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear, for oral doses ≤ 32 mg.

Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Hydrochlorothiazide

Absorption: Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant food intake increases the absorption by approximately 15%.

Distribution: The bioavailability may decrease in patients with cardiac failure and pronounced edema. The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 L/kg.

Elimination: Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal $t_{½}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (8 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with chronic heart failure.

Special Populations and Conditions

- **Geriatrics:** The plasma concentration of candesartan was higher in the elderly (≥ 65 years old) (C_{max} was approximately 50% higher and AUC was approximately 80% higher) compared to younger subjects administered the same dose. The pharmacokinetics of candesartan were linear in the elderly, and candesartan and its inactive metabolite did not accumulate in the serum of these subjects upon repeated, once-daily administration.

  The terminal $t_{½}$ of hydrochlorothiazide is prolonged in the elderly.

- **Sex:** No gender-related differences in the pharmacokinetics of candesartan have been observed.

- **Pregnancy and Breast-feeding:** Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

- **Hepatic Insufficiency**

  Mild to moderate hepatic impairment: There was an increase in the AUC of candesartan of approximately 20%. There was no drug accumulation in plasma in these patients.

Moderate to severe hepatic impairment: C_{max} and AUC increased up to 5x in a very small group administered a single dose of 16 mg candesartan (see 2 CONTRAINDICATIONS and Hepatic Impairment).

- **Renal Insufficiency**

  The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal failure.

  Mild to moderate renal impairment (Cl_{creat} 31-60 mL/min/1.73m^2): C_{max} and AUC of candesartan increased by 40-60% and 50-90%, respectively, but $t_{½}$ was not altered, compared to patients with normal renal function (Cl_{creat} > 60 mL/min/1.73m^2) during repeated dosing. There was no drug accumulation in plasma.

  Severe renal impairment (Cl_{creat} 15-30 mL/min/1.73m^2): The increases in C_{max} and AUC were 40-60% and 110%, respectively. The terminal $t_{½}$ of candesartan was approximately 2x in patients with severe renal impairment, and these changes resulted in some accumulation in plasma.

  Patients undergoing hemodialysis: The pharmacokinetics of candesartan were similar to those in patients with severe renal impairment (see 2 CONTRAINDICATIONS and Renal Impairment).

11 STORAGE, STABILITY AND DISPOSAL

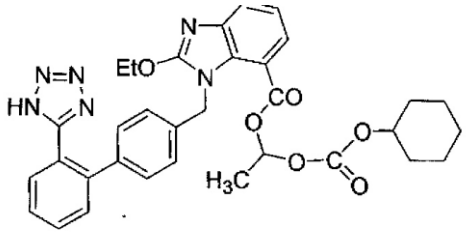
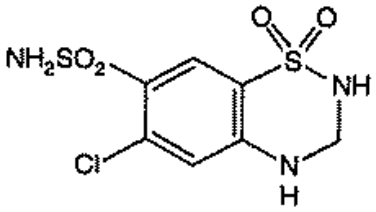
Store at 15-30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Proper name:	candesartan cilexetil	hydrochlorothiazide
Chemical name:	(±)-1-[[(cyclohexyloxy)carbonyl] oxy]ethyl-2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'biphenyl]-4-yl]methyl]-1H-benzimidazole-7-carboxylate	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1- dioxide.
Molecular formula:	$C_{33}H_{34}N_6O_6$	$C_7H_8ClN_3O_4S_2$
Molecular mass:	610.66	297.74
Structural formula:		
Physicochemical properties:		
Description:	Candesartan cilexetil is a white to off-white crystalline powder.	Hydrochlorothiazide is a white, or practically white, crystalline powder.
Solubility:	Candesartan cilexetil is insoluble in isopropyl alcohol, butyl alcohol and acetonitrile. It is slightly soluble in methylene chloride; soluble in dimethyl formaldehyde and dimethyl sulfoxide.	Hydrochlorothiazide is slightly soluble in water, but freely soluble in sodium hydroxide solution.
pKa:	6.0 ± 0.1	-
Melting Point:	160.6 - 162.3°C	268°C
Hygroscopicity:	Weight increase after 24 hours was less than 0.1% (exposed to 80% relative humidity for 24 hours).	-

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Essential Hypertension

The details of the trial designs and study demographics for the studies on which the original indication was authorized are not available.

Candesartan cilexetil: In hypertension, candesartan cilexetil causes a dose-dependent reduction in arterial blood pressure (BP). Systemic peripheral resistance is decreased, while heart rate, stroke volume and cardiac output are not significantly affected. No first-dose hypotension was observed during controlled clinical trials with candesartan cilexetil.

Most of the antihypertensive effect was seen within 2 weeks of initial dosing, and the full effect in 4 weeks. With once-daily dosing, BP effect was maintained over 24 hours, with trough to peak ratios of BP effect generally > 80%. Candesartan cilexetil had an additional BP lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients < 65 and ≥ 65 years. Candesartan was effective in reducing BP regardless of race, although the effect was somewhat less in Black patients (usually a low-renin population) than in Caucasian patients.

In long-term studies of ≤ 1 year, the antihypertensive effectiveness of candesartan cilexetil was maintained and there was no rebound after abrupt withdrawal.

Candesartan cilexetil also reduces urinary albumin excretion in patients with type II diabetes mellitus, hypertension, and microalbuminuria. In a 12-week study of 161 mildly hypertensive patients with type II diabetes mellitus, candesartan cilexetil 8-16 mg had no effect on mean HbA1c.

Comparative Effects: The antihypertensive efficacy of candesartan cilexetil and losartan potassium have been compared at their approved once daily maximum doses, 32 mg and 100 mg, respectively, in patients with mild to moderate essential hypertension. Candesartan cilexetil lowered systolic and diastolic blood pressure by 2 to 3 mm Hg on average more than losartan potassium when measured at the time of either peak or trough effect. Both agents were well tolerated.

Candesartan cilexetil/hydrochlorothiazide: Candesartan cilexetil and hydrochlorothiazide have additive antihypertensive effects. After administration of a single dose of candesartan cilexetil/hydrochlorothiazide in hypertensive patients, onset of the antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment. candesartan cilexetil/hydrochlorothiazide given once daily provides effective and smooth dose-

dependent blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval and without reflex increase in heart rate. There is no indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

Randomized placebo controlled studies with the combination of candesartan cilexetil and hydrochlorothiazide 32 mg / 12.5 mg or 32 mg / 25 mg once daily demonstrated a dose-dependent blood pressure lowering effect of candesartan cilexetil/hydrochlorothiazide. The combination produced a statistically significant effect larger than candesartan cilexetil or hydrochlorothiazide monotherapy. The proportion of patients with controlled blood pressure was larger and the effect of the combination was dose-related.

Candesartan cilexetil/hydrochlorothiazide is similarly effective in patients irrespective of age and gender.

14.2 Comparative Bioavailability Studies

The data below is from a single-dose, two-period, two-sequence, two-treatment, crossover comparative bioavailability study of Teva-Candesartan/HCTZ Tablets 32/25 mg (Teva Canada Ltd.) versus Atacand® Plus 32 mg/25 mg Tablets (AstraZeneca Canada Inc., Canada) in 23 healthy male and female subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Candesartan (1 x 32 mg candesartan / 1 x 25 mg hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	2826.58 2966.99 (33)	2945.16 3011.42 (33)	95.97	90.37 – 101.93
AUC_I (ng*h/mL)	2883.44 3023.88 (32)	2997.43 3063.86 (23)	96.20	90.62 – 102.12
C_{max} (ng/mL)	224.09 243.17 (42)	247.82 264.04 (36)	90.42	78.68 – 103.92
T_{max}§ (h)	5.14 (31)	4.57 (34)		
$T_{½}$§ (h)	10.29 (33)	10.19 (28)		

* Teva-Candesartan/HCTZ 32 mg/25 mg tablets (Teva Canada Ltd.)

† Atacand® Plus 32 mg/25 mg tablets (AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Hydrochlorothiazide (1 x 32 mg candesartan / 1 x 25 mg hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	1117.565 1167.595 (33)	1147.605 1178.393 (25)	97.38	93.63 – 101.29
AUC_I (ng*h/mL)	1131.066 1181.937 (33)	1161.636 1193.165 (25)	97.37	93.60 – 101.29
C_{max} (ng/mL)	173.841 183.352 (34)	179.119 184.261 (25)	97.05	89.13 – 105.68
T_{max}§ (h)	1.69 (36)	1.51 (42)		
$T_{½}$§ (h)	9.78 (14)	9.60 (13)		

* Teva-Candesartan/HCTZ 32 mg/25 mg tablets (Teva Canada Ltd.)
† Atacand® Plus 32 mg/25 mg tablets (AstraZeneca Canada Inc.) were purchased in Canada.
§ Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON- CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity:

Table 5 Acute Toxicity

Route	Species	Sex	LD_{50} (mg/kg) values
oral gavage	rat	Male Female	>2000 candesartan cilexetil &

			>1000 HCTZ

Chronic Toxicity: The toxic potential of candesartan cilexetil was evaluated in a series of repeated-dose oral toxicity studies of ≤ 13 weeks in rats and dogs. The no toxic effect dose level for candesartan cilexetil/hydrochlorothiazide was 1/10 mg/kg/day in rats.

Table 6 Toxicity Upon Repeated Oral Administration

Species/ Strain	No. Of Animals per Group	Duration and Route of Administration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Rat / Fischer 344/DuCrj	10M + 10F	4 weeks dietary	0/0 0/10 300/0 3/10 30/10 300/10	No deaths and no treatment related abnormalities in clinical signs, urine chemistry, or gross pathology, or upon urinanalysis or ophthalmic examinations. Decr. in body weight, food consumption, heart weight and osmolality and increase in incidence of basophilic renal tubules, hypertrophy of juxtaglomerular cells for grps 300/0 and 300/10. Grps 300/0, 30/10 and 300/10 had an incr. in urine output, water intake, urea nitrogen, total chol. and atrophy of zona glomerulosa and a decr. in osmolality, erythrocytes, hematocrit and hemoglobin conc. and triglycerides. Grps 30/10 and 300/10 had an incr. in creatinine, ALP, LAP and inorganic phosphorus. M in grps 300/0 and 30/10 had an incr. in potassium as well as M and F in grp 300/10. F in grp 3/10 had an incr. in urine output, water intake, ALP, LAP and atrophy of the zona glomerulosa. F in grp 0/10 and 3/10 had a decr. in chloride.
Rat / Fischer	10M + 10F	13 weeks dietary	0/0 1/10	No deaths and no abnormal signs. No toxicokinetic interactions

344/DuCrj			10/10 100/10	occurred btw candesartan cilexetil and HCTZ. Grps 10/10 and 100/10 had an increase in basophilia of the renal tubules, calcification in the renal papilla, blood urea nitrogen, inorganic phosphorus and a decr. in calcium, total protein, red blood cells, hemoglobin and hematocrit. The 100/10 grp had atrophy of the zona glomerulosa, urinary casts, white kidney patches, and an incr. in creatinine, and corpuscular volume.
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 0/30 100/0 100/30	No deaths occurred and no abnormal signs. Toxic effects were seen in the 100/30 grp which included basophilic renal tubules and erosion/regeneration of the stomach. Decr. in body weight, urine osmolality and increases in water intake, urine volume, serum blood nitrogen and pathological changes noted above increased with concurrent administration. The 100/30 grp had an incr. in serum creatinine and inorganic phosphorus as well as shortening of prothrombin time and activated partial thromboplastin time.

Species/ Strain	No. Of Animals per Group	Duration and Route of Administration	Daily Dose candesartan cilexetil/HCTZ (mg/kg)	Results
Beagle	3M + 3F	4 weeks dietary	0/0 0/10 4/0 20/0 100/0 4/10 20/10 100/10	2 M were sacrificed after the 11th and 24th dose and 3 F died: 2 after the 10th dose and 1 after the 14th dose in the 100/10 (N=6) grp due to decreased locomotor activity, lack of food consumption and increase in plasma urea nitrogen concentration and creatinine. Increases in regeneration of renal tubules, hypertrophy of the juxtaglomerular cells, erosion or ulcer of the stomach were noted in most of the 100/10 grp and in some animals of the 20/10 group. Other abnormalities were decreases in osmolality, reticulocytes, chloride and potassium and increases in urea nitrogen, calcium, inorganic potassium, creatinine, erthyrocytes, hematocrit and hemoglobin which were observed in various groups other than the control.
Beagle	3M + 3F	13 weeks dietary	0/0 0.8/10 4/10 20/10	2 F were sacrificed after the 31st dose and 38th dose in the 20/10 grp due to a decr. in movement and food consumption, hypothermia, paleness of conjuctival and oral mucosa and constipation. These F had an incr. in serum urea nitrogen, creatinine, inorganic phosphates and a decr. in sodium and chloride. The kidneys had tubular dilatation, severe regeneration of renal tubules, hypertrophy of juxtaglomerular

				cells and vacuolization and calcification in papilla. The stomach had erosion, mucosal hemorrhage and calcification and glands demonstrated atrophy. Decr. in urinary osmotic pressure for grp 20/10 and F of grps 0.8/10 and 4/10 as well as an incr. in sodium content for the latter. All other animals sacrificed on schedule showed no treatment change except for histological changes to kidneys.
Beagle	3M + 3F	13 weeks dietary	0/0 4/0 0/30 4/30	Treatment related deaths or severe toxic signs or symptoms did not occur in any animal. Hypertrophy of the juxtaglomerular cells occurred in the 4/0 and 4/30 animals. Increased urine vol. and decr. serum potassium occurred in the 0/30 and 4/30 grps.

Carcinogenicity
No carcinogenicity studies were carried out with the candesartan cilexetil/hydrochlorothiazide combination.

Candesartan cilexetil: The carcinogenic potential of candesartan cilexetil was studied in rats after administration in the diet for 24 months. Dose levels were 100, 300 and 1000 mg/kg/day (50 male and 50 female rats per group). No alteration in tumour profile was observed. A 2-year oral gavage study of candesartan cilexetil in mice was performed at daily dosages of 3, 10, 30 and 100 mg/kg/day. There was no alteration in the tumour profile.

There is no evidence that candesartan cilexetil is carcinogenic.

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 and adrenal pheocytochroma 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 repair deficient 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.

Genotoxicity
The studies performed show that the 1:2 mixture of candesartan cilexetil and hydrochlorothiazide is devoid of genotoxic activity in a range of *in vitro* studies in bacteria and in *in vivo* studies. These studies showed that candesartan cilexetil did not have a synergistic mutagenic effect when administered with hydrochlorothiazide. Taking into consideration all the studies conducted on the components and the combination it is concluded that the probability that the combination of candesartan cilexetil and hydrochlorothiazide being genotoxic to humans is extremely low.

Reproductive and Developmental Toxicology
Reproductive studies were performed in rats, mice and rabbits. In rats, effects upon the maternal as well as upon the fetal body weight were recorded at 100/10 mg/kg/day and a minor skeletal effect was recorded upon the fetuses at 30/10 mg/kg/day with candesartan cilexetil/ hydrochlorothiazide. The no observed adverse effect dose level in rats was 10/10 mg/kg of candesartan cilexetil and hydrochlorothiazide combination. The maternal toxicity was similar after monotherapy and the combination treatment. In mice, no maternal or fetal effects were seen at doses of up to 1000/10 mg/kg/day. In rabbits maternal toxicity with abortions and deaths was seen with doses from 1/10 mg/kg. The addition of hydrochlorothiazide did not significantly affect the outcome of the fetal development studies in any of the three species tested.

Effects on the development of the kidneys: Animal studies with candesartan cilexetil have demonstrated late fetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the RAAS. The RAAS plays a critical role in kidney development. RAAS blockade has been shown to lead to abnormal kidney development in very young mice. Administering drugs that act directly on the RAAS, such as candesartan cilexetil, can alter normal renal development. Therefore, candesartan cilexetil and hydrochlorothiazide is contraindicated in children <1 year old (see 2 CONTRAINDICATIONS).

17 SUPPORTING PRODUCT MONOGRAPH

1. PrATACAND® PLUS (candesartan cilexetil/hydrochlorothiazide Tablets, 16 mg / 12.5 mg, 32 mg / 12.5 mg and 32 mg / 25 mg), submission control #268325, Product Monograph, AstraZeneca Canada Inc. (March 02, 2023).

2. A Single-Dose Comparative Bioavailability Study of Two Formulations of Candesartan/HCTZ Tablets Under Fasting Conditions. Data on file at Teva Canada Limited.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] TEVA-CANDESARTAN/HCTZ
(candesartan cilexetil/hydrochlorothiazide tablets)

Read this carefully before you start taking **TEVA-CANDESARTAN/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 **TEVA-CANDESARTAN/HCTZ**.

Serious Warnings and Precautions

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

What is TEVA-CANDESARTAN/HCTZ used for?

- TEVA-CANDESARTAN/HCTZ is used in adults to lower high blood pressure.

How does TEVA-CANDESARTAN/HCTZ work?

TEVA-CANDESARTAN/HCTZ is a combination of 2 drugs, candesartan cilexetil and hydrochlorothiazide.

- Candesartan is an angiotensin receptor blocker (ARB). It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or “water pill” that increases urination. This also helps to lower blood pressure.

This medicine does not cure high blood pressure. It helps to control it. Therefore it is important to continue taking TEVA-CANDESARTAN/HCTZ regularly even if you feel fine.

What are the ingredients in TEVA-CANDESARTAN/HCTZ?

Medicinal ingredients: candesartan cilexetil and hydrochlorothiazide
Non-medicinal ingredients: Carmellose calcium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone, pregelatinized starch, red iron oxide (16 mg/12.5 mg tablets).

TEVA-CANDESARTAN/HCTZ comes in the following dosage forms:

Candesartan cilexetil / hydrochlorothiazide tablets: 16 mg / 12.5 mg, 32 mg / 12.5 mg

Do not use TEVA-CANDESARTAN/HCTZ if :

- You are allergic to candesartan cilexetil, hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- You have severe liver disease.
- You have severe kidney disease.
- You are allergic to any sulfonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in “-MIDE”.
- You have diabetes or kidney disease and are already taking a blood pressure-lowering medicine that contains aliskiren.
- 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 TEVA-CANDESARTAN/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 intend to become pregnant. Taking TEVA-CANDESARTAN/HCTZ during pregnancy can cause injury and even death to your baby.
- You are breastfeeding. TEVA-CANDESARTAN/HCTZ passes into breast milk.
- You have gout.
- You have one of the following rare hereditary diseases, because TEVA-CANDESARTAN/HCTZ contains lactose:
    - Galactose intolerance,
    - Lapp lactase deficiency,
    - Glucose-galactose malabsorption.

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

- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- Have a liver or kidney disorder.
- Are taking an angiotensin converting enzyme inhibitor (ACEI). You can recognize ACEIs because their medicinal ingredient ends in '-PRIL'.
- Have narrowing of an artery or a heart valve.
- Have heart failure.
- Have diabetes, liver, heart or kidney disease.
- Have lupus.
- Are on dialysis.
- Are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, a potassium-sparing diuretic (a specific kind of "water pill") or other drugs that may increase potassium levels such as heparin, co-trimoxazole.
- Are on a low-salt diet.
- Have had a heart attack or stroke.
- Have had breathing or lung problems (including inflammation or fluid in the lungs) after taking hydrochlorothiazide in the past. If you develop any severe shortness of breath or difficulty breathing after taking TEVA-CANDESARTAN/HCTZ, stop the medication and seek medical attention immediately.
- Have had skin cancer or have a family history of skin cancer.
- Have a greater chance of developing skin cancer because you have light-coloured skin, get sunburned easily, or are taking drugs to suppress your immune system.

Other warnings you should know about:

Use of anesthesia: If you are about to have a surgery or dental procedure with anesthesia, be sure to tell your healthcare professional that you are taking TEVA-CANDESARTAN/HCTZ.

Risk of skin cancer: TEVA-CANDESARTAN/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 TEVA-CANDESARTAN/HCTZ for many years (more than 3) or at a high dose. While taking TEVA-CANDESARTAN/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 get more sensitive to the sun or UV light or if you develop an unexpected skin lesion (such as a lump, bump, sore, or patch) during the treatment.

Sudden eye disorders: Treatment with hydrochlorothiazide in TEVA-CANDESARTAN/HCTZ can cause sudden eye problems such as:

- **Myopia:** sudden nearsightedness or blurred vision.

- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.
- **Choroidal effusion:** an abnormal building of liquid in your eye that may result in vision changes.

These eye disorders are related and can develop within hours to weeks of starting TEVA-CANDESARTAN/HCTZ. If you earlier have had a penicillin or sulfonamide allergy, you can be at higher risk of developing this. If you experience the above symptoms, stop taking TEVA-CANDESARTAN/HCTZ and seek immediate medical help.

Monitoring: During your treatment with TEVA-CANDESARTAN/HCTZ, your healthcare professional may monitor:
- Your kidney function.
- Your blood pressure.
- The amount of electrolytes in your blood (such as potassium).

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to TEVA-CANDESARTAN/HCTZ. Dizziness, lightheadedness, or fainting can occur especially after the first dose and when the dose is increased.

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

Serious Drug Interactions
• Aliskiren-containing drugs if you have diabetes or kidney disease.

The following may interact with TEVA-CANDESARTAN/HCTZ:

- Adrenocorticotropic hormone (ACTH), which may be used to treat diseases such as nephrotic syndrome or collagen diseases and in diagnostic tests.
- 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.
- Amantadine used to treat the flu and reduce symptoms of Parkinson's Disease.
- Amphotericin B, an antifungal drug.
- Drugs used to treat cancer such as cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs) such as citalopram, escitalopram and sertraline.
- Drugs used to treat diabetes such as insulin and oral medicines.
- Bile acid resins used to lower cholesterol such as cholestyramine.
- Other blood pressure lowering drugs such as:
  - Diuretics ("water pills").
  - Guanethidine.
  - Diazoxide.
  - Methyldopa.
  - Beta-blockers, such as atenolol, metoprolol, propranolol.
  - Vasodilators.
  - Calcium channel blockers, such as felodipine and amlodipine.
  - Angiotensin converting enzyme inhibitors (ACEIs).
  - Angiotensin receptor blockers (ARBs), such as valsartan and losartan.
  - Direct renin inhibitors.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine used to treat autoimmune diseases.
- Digoxin, a heart medication.

- Drugs that slow down or speed up bowel function such as atropine, biperiden, domperidone and metoclopramide.
- Drugs used to treat epilepsy such as carbamazepine and topiramate.
- Gout medications such as allopurinol, probenecid, uricosurics and xanthine oxidase inhibitors.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling such as ibuprofen, naproxen, acetylsalicylic acid and celecoxib.
- Drugs that can increase blood potassium levels such as heparin, co-trimoxazole, potassium supplements or potassium-containing salt substitutes.
- Pressor amines such as norepinephrine.
- Skeletal muscle relaxants used to relieve muscle spasmssuch as tubocurarine.

How to take TEVA-CANDESARTAN/HCTZ:
- Take TEVA-CANDESARTAN/HCTZ exactly as prescribed.
- It is recommended to take your dose at about the same time everyday.
- TEVA-CANDESARTAN/HCTZ can be taken with or without food but it should be taken the same way each day. If TEVA-CANDESARTAN/HCTZ causes upset stomach, take it with food or milk.
- Swallow TEVA-CANDESARTAN/HCTZ with a glass of water.
- To help you keep track of your doses, TEVA-CANDESARTAN/HCTZ comes in a Compliance Pack with days of the week printed on the back of the blister. Start with the tablet that matches the day of the week and continue taking them in order until they are all finished.
- There are 14 days of labeled tablets in each blister, with one extra to make 15. All 15 tablets, including the one labeled “Take this tablet last”, are exactly the same. Once you have finished the 14 labeled tablets take the one marked “Take this tablet last” before starting your next blister pack.
- The package protects each tablet. When you first open the package, if you find any damage to the plastic seal or foil which exposes the tablet, ask your pharmacist to check the package.
- Do not transfer TEVA-CANDESARTAN/HCTZ to other pill containers. To protect your TEVA-CANDESARTAN/HCTZ tablets, keep them in the original package.
- Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

Usual dose:
Your healthcare professional has decided the best dose for you. The recommended dose is 1 tablet once daily.

Overdose:

If you think you, or a person you are caring for, have taken too much TEVA-CANDESARTAN/HCTZ, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of TEVA-CANDESARTAN/HCTZ and remember within 12 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. But if it is more than 12 hours when you remember, do not take the missed dose. Just take the next dose on time. Do not take a double dose.

What are possible side effects from using TEVA-CANDESARTAN/HCTZ?
These are not all the possible side effects you may have when taking TEVA-CANDESARTAN/HCTZ. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:
- back or leg pain, muscle cramps, spasms and pain, weakness, restlessness.
- cold or flu-like symptoms.
- dizziness, pins and needles in your fingers, headache.

- urinary tract infections.
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth.
- cough.
- bleeding under skin, rash, red patches on the skin, itching.
- drowsiness, insomnia.
- low sex drive.
- nose bleeds.

TEVA-CANDESARTAN/HCTZ can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

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			
Decreased or increased levels of potassium in the blood: irregular heartbeats, muscle weakness and generally feeling unwell.		√	
Edema: unusual swelling of the arms, hands, legs, ankles or feet.		√	
High blood sugar: frequent urination, thirst and hunger.	√		
Low Blood Pressure: dizziness, fainting, lightheadedness. May occur when you go from lying or sitting to standing up.	√		
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.		√	
Tachycardia (abnormally fast heartbeat): dizziness, light-headedness, shortness of breath, racing heart.		√	
UNCOMMON			
Allergic reactions: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			√
Electrolyte Imbalance: weakness, drowsiness, muscle pain or cramps, irregular heartbeat.		√	
Kidney Disorder: change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue.		√	
Liver Disorder: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		√	
RARE			
Acute Respiratory Distress: (inflammation of			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate**
lung tissue or excess fluid in the lungs)**:** severe shortness of breath or difficulty breathing, fever, weakness, confusion, cough, wheezing, clammy skin, fatigue, blue-tinged lips.			
Decreased Platelets: bruising, bleeding, fatigue, weakness, small purple or red dots under the skin.		√	
Decreased White Blood Cells: infections, fatigue, fever, aches, pains and flu-like symptoms.		√	
Rhabdomyolysis (breakdown of damaged muscle): muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine.		√	
Vasculitis (inflammation of the blood vessels): fever, confusion, fatigue, unexplained weight loss, sweats, joint or muscle pain or swelling, numbness, tingling, weakness, a rash of bluish purple spots or blotches.			√
VERY RARE			
Toxic Epidermal Necrolysis (severe skin reaction): redness, blistering and/or severe skin peeling, especially in the mouth and eyes.			√
UNKNOWN FREQUENCY			
Anemia (decreased number of red blood cells): fatigue, loss of energy, weakness, shortness of breath.		√	
Eye disorders: **-Choroidal effusion** (buildup of liquid in your eye): blind spots, eye pain, blurred vision. **-Glaucoma**: increased pressure in your eyes, eye pain, decrease in vision. **-Myopia**: sudden near sightedness or blurred vision.			√
Lupus (an autoimmune disease that occurs when your body's immune system attacks your own tissues and organs): fever, malaise, joint or muscle pain, fatigue. Conditions may be activated or made worse.		√	
Pancreatitis (inflammation of the pancreas): abdominal pain that lasts and gets worse when you lie down, nausea, vomiting.		√	

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:

- Although the TEVA-CANDESARTAN/HCTZ tablets are protected in their package, it is best to keep the package at normal room temperature (15°C to 30°C) and in a dry place. Do not keep TEVA-CANDESARTAN/HCTZ in the bathroom.
- **Keep out of sight and reach of children.** Never take medicine in front of small children as they will want to copy you.
- Do not keep or use TEVA-CANDESARTAN/HCTZ after the expiry date indicated on the package. Unused medicines, which you know you will no longer need, should be carefully discarded. You may wish to seek advice from your pharmacist.

If you want more information about TEVA-CANDESARTAN/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.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited Toronto, Ontario M1B 2K9.

Last revised: November 15, 2023