

**PRODUCT MONOGRAPH**

**Pr SEPTA-CANDESARTAN HCTZ**

**Candesartan Cilexetil/Hydrochlorothiazide Tablets**

**32 mg / 12.5 mg,**

**32 mg / 25 mg**

**Angiotensin II AT1 Receptor Blocker + Diuretic**

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# Pr SEPTA-CANDESARTAN HCTZ

Candesartan Cilexetil/Hydrochlorothiazide tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Oral	Tablet: 32mg/12.5mg,	Lactose Monohydrate, corn starch, carboxymethylcellulose calcium, hydroxypropyl cellulose, magnesium stearate, iron oxide yellow, and polyethylene glycol
	Tablet: 32mg/25mg	Lactose Monohydrate, corn starch, carboxymethylcellulose calcium, hydroxypropyl cellulose, magnesium stearate, iron oxide red and polyethylene glycol

### INDICATIONS AND CLINICAL USE

SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate.

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

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

**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.

**Pediatrics (< 18 years of age):** The safety and efficacy of candesartan cilexetil/hydrochlorothiazide have not been established in children.

## CONTRAINDICATIONS

SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/hydrochlorothiazide) is contraindicated in:

- Patients who are hypersensitive to any component of this product. (See DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Patients with anuria and patients who are hypersensitive to other sulfonamide-derived drugs, because of the hydrochlorothiazide component (see WARNINGS AND PRECAUTIONS, Immune and ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).
- Concomitant use of angiotensin receptor antagonists (ARBs), including the candesartan cilexetil component of SEPTA-CANDESARTAN HCTZ, with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m<sup>2</sup>) is contraindicated (see WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin System (RAS) and Renal, and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs or aliskiren-containing drugs).

## WARNINGS AND PRECAUTIONS

### **Serious Warnings and Precautions**

When used in pregnancy, angiotensin receptor (AT<sub>1</sub>) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, SEPTA-CANDESARTAN HCTZ should be discontinued as soon as possible (See WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women).

### **Cardiovascular**

#### **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 anaesthesia. 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.

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.

### **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.

### **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 SEPTA-CANDESARTAN HCTZ, 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<sup>2</sup>). Therefore, the use of SEPTA-CANDESARTAN HCTZ in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

Further, co-administration of ARBs, including the candesartan cilexetil component of SEPTA-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, renal failure, and hyperkalemia.

### **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. 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 (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

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.

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

### **Ophthalmologic**

#### **Acute Myopia and Secondary Angle-Closure Glaucoma**

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity 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 candesartan cilexetil/hydrochlorothiazide 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, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, 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 SEPTA-CANDESARTAN HCTZ, or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m<sup>2</sup>) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Use of candesartan cilexetil should include appropriate assessment of renal function.

Thiazides should be used with caution.

Because of the hydrochlorothiazide component, SEPTA-CANDESARTAN HCTZ is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m<sup>2</sup> BSA).

#### **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.

### **Special Populations**

**Pregnant Women:** Drugs that act directly on the renin-angiotensin-aldosterone-system (RAAS)

can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, SEPTA-CANDESARTAN HCTZ should be discontinued as soon as possible.

The use of ARBs is not recommended during pregnancy. Epidemiological evidence regarding the risk of teratogenicity following exposure to angiotensin converting enzyme inhibitors (another class of therapeutic products interfering with the RAAS) during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Given the current evidence available on the risk with 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 angiotensin receptor (AT<sub>1</sub>) blockers should be stopped immediately, and, if appropriate, alternative therapy should be started.

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

Infants with a history of *in utero* exposure to ARBs should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion 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.

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 fetoplacental 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  $\geq 10$  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 up to 1000 mg candesartan cilexetil/kg/day were administered to pregnant mice.

**Nursing Women:** 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 affecting the nursing infant adversely, 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.

**Pediatrics (< 18 years of age):** The safety and efficacy of candesartan cilexetil/hydrochlorothiazide have not been established in children.

**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.

## **ADVERSE REACTIONS**

### **Adverse Drug 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. 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.

### **Clinical Trial Adverse Drug Reactions**

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

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  $\geq 1\%$  of patients, regardless of drug relationship (see Table 1).

**Table 1: Adverse events reported with candesartan cilexetil/hydrochlorothiazide in  $\geq 1\%$  of patients regardless of causality in studies supporting the 16 mg / 12.5 mg strength**

	<b>Candesartan Cilexetil/Hydrochlorothiazide N=1025</b>	<b>Candesartan Cilexetil N=749</b>	<b>Hydrochloro- thiazide N=603</b>	<b>Placebo N=526</b>
	<b>(%)</b>	<b>(%)</b>	<b>(%)</b>	<b>(%)</b>
<b>Body as a Whole</b>				
Back pain	3.8	5.5	5.1	3.0
Arthralgia	1.5	1.3	1.3	0.8
Fatigue	1.4	1.2	1.7	1.0
Abdominal pain	1.3	1.7	0.7	1.1
<b>Urinary</b>				
Urinary tract infection	1.6	1.3	1.8	1.0
<b>Digestive</b>				
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
<b>Cardiovascular</b>				
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
<b>Metabolic Disorders</b>				
Hyperuricemia	1.1	0.7	0.8	0.4
Hyperglycemia	1.0	0.9	0.5	0.2
<b>Nervous/Psychiatric</b>				
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
<b>Respiratory</b>				
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
Cough	0.9	2.3	1.7	1.0
Rhinitis	1.2	1.5	1.2	0.4

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  $\geq 1\%$  of patients, regardless of drug relationship (see Table 2).

**Table 2: Adverse events reported with candesartan cilexetil/hydrochlorothiazide in  $\geq 1\%$  of patients regardless of causality in studies supporting the 32 mg / 12.5 mg strength and 32 mg / 25 mg strength**

	Candesartan Cilexetil/Hydrochlorothiazide N=1873 32mg/12.5mg (N=718)    32mg/25mg (N=1155)		Candesartan Cilexetil N=1188	Hydrochloro- thiazide N=540	Placebo N=163
	(%)		(%)	(%)	(%)
<b>Body as a Whole</b>					
Back pain	2.4	1.6	1.1	0.6	2.5
Fatigue	1.1	0.9	0.8	0.4	2.5
Arthralgia	0.6	1.1	0.6	1.1	1.8
<b>Digestive</b>					
Diarrhea	1.1	0.4	0.7	0.4	1.8
<b>Metabolic Disorders</b>					
Dyslipidaemia	3.3	2.5	1.9	0.4	0
<b>Nervous/Psychiatric</b>					
Headache	2.5	2.9	1.3	2.4	0.6
Dizziness	2.4	2.0	5.1	7.6	7.4
<b>Respiratory</b>					
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

**Less Common Clinical Trial Adverse Drug Reactions**  
**(<1%)**

**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):

**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, hyperkalaemia, hyponatraemia.

**Musculoskeletal:** arthritis, arthropathy, myalgia, myopathy, skeletal pain, tendon disorder.

**Blood:** anemia, epistaxis.

**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.

## **Abnormal Hematologic and Clinical Chemistry Findings**

### **Laboratory Test Findings**

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

### **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.

### **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.

### **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.

### **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.

### **Creatinine, Urea**

An increase in creatinine and urea has been observed in candesartan cilexetil/hydrochlorothiazide.

## **Post Market Adverse Drug 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 postmarketing experience, renal impairment, including renal failure in susceptible patients, has been observed (see WARNINGS AND PRECAUTIONS, Renal-Renal Impairment

for definition of susceptible patients).

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: jaundice (intrahepatic cholestatic jaundice), pancreatitis, leukopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anemia, haemolytic anemia, photosensitivity reactions, necrotizing angitis (vasculitis), toxic epidermal necrolysis, anaphylactic reactions, respiratory distress (including pneumonitis and pulmonary edema), hypokalemia, renal dysfunction, interstitial nephritis, acute myopia, and acute angle-closure glaucoma.

## **DRUG INTERACTIONS**

### **Overview**

#### **Warfarin**

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. Note: SEPTA-CANDESARTAN HCTZ is only available as 32 mg/12.5 mg and 32 mg/25 mg tablets.

#### **Pressor Amines (e.g. norepinephrine)**

In the presence of thiazide diuretics possible decreased response to pressor amines may be seen but not sufficient to preclude their use.

#### **Other**

No significant drug interactions have been reported with glyburide, nifedipine or oral contraceptives co-administered with candesartan cilexetil to healthy volunteers.

Co-administration of thiazide diuretics may increase the risk of adverse effects caused by amantadine and may enhance the hyperglycemic effect of diazoxide.

There have been reports in the literature of hemolytic anemia occurring with concomitant use of hydrochlorothiazide and methyl dopa.

Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

### **Drug-Drug Interactions**

The drugs listed in Table 3 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 3 Established or Potential Drug-Drug Interactions**

Proper Name	Ref.	Effect	Clinical Comment
Agents Increasing Serum Potassium	T	Candesartan cilexetil decreases the production of aldosterone.	Potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use, or switching to candesartan cilexetil/hydrochlorothiazide may attenuate any effect that candesartan cilexetil may have on serum potassium.
Alcohol, barbiturates or narcotics	C	Potential of orthostatic hypotension may occur.	Avoid alcohol, barbiturates or narcotics, especially with initiation of therapy.
Amphotericin B	T	Amphotericin B increases the risk of hypokalemia induced by thiazide diuretics.	Monitor 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 (e.g. insulin or oral hypoglycemic agents)	CT	Thiazide-induced hyperglycemia may compromise blood sugar control. Depletion of serum potassium augments glucose intolerance.	Monitor glycemic control, supplement potassium if necessary, to maintain appropriate serum potassium levels, and adjust diabetes medications as required.
Antihypertensive drugs	CT	Hydrochlorothiazide may potentiate the action of other antihypertensive drugs (e.g. guanethidine, methyl dopa, 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.

<b>Proper Name</b>	<b>Ref.</b>	<b>Effect</b>	<b>Clinical Comment</b>
Bile acid sequestrants, 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	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Carbamazepine	C	Carbamazepine may cause clinically significant hyponatremia. Concomitant use with thiazide diuretics may potentiate hyponatremia.	Monitor serum sodium levels. Use with caution.
Corticosteroids, and adrenocorticotrophic hormone (ACTH)	T	Intensified electrolyte depletion, particularly hypokalemia, may occur when given concomitantly with thiazide diuretics.	Monitor serum potassium and adjust medications, as required.
Digoxin	CT	Combination treatment with candesartan cilexetil and digoxin in healthy volunteers had no effect on AUC or C <sub>max</sub> values for digoxin compared to digoxin alone. Similarly, combination treatment had no effect on AUC or C <sub>max</sub> 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.
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 WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interactions of clinical significance have been identified with thiazide diuretics. When candesartan

Proper Name	Ref.	Effect	Clinical Comment
			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	Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs or ACEIs and aliskiren-containing drugs is contraindicated in patients with diabetes and/or renal impairment. Co-administration of ARBs, ACEIs or aliskiren-containing drugs is generally not recommended in other patients, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.	See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS).
Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors)	T, RC	Thiazide-induced hyperuricemia may compromise control of gout by allopurinol and probenecid. The co-administration of hydrochlorothiazide and allopurinol may increase the incidence of hypersensitivity reactions to allopurinol.	Dosage adjustment of gout medications may be required.
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.
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 possible acute	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 necessary, monitor renal function, serum potassium, and blood pressure closely. Dose



Proper Name	Ref.	Effect	Clinical Comment
		renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.	adjustments may be required. Patients with heart failure may be at particular risk.
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., tubocurane	C	Thiazide drugs may increase the responsiveness of some 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.

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

### **Drug-Food Interactions**

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

## DOSAGE AND ADMINISTRATION

### **Dosing Considerations**

**The dosage of SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/hydrochlorothiazide) must be individualized. The fixed combination is not for initial therapy. The dose of SEPTA- CANDESARTAN HCTZ should be determined by titration of the individual components.**

### **Recommended Dose and Dosage Adjustment**

Once the patient has been stabilized on the individual components one SEPTA-CANDESARTAN HCTZ 32 mg/12.5 mg or 32 mg/ 25 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 INDICATIONS AND CLINICAL USE).

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

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

### **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 DRUG INTERACTIONS, Drug-Drug Interactions, Diuretics).

**Note:** SEPTA-CANDESARTAN HCTZ is only available as 32 mg/12.5 mg and 32 mg/25 mg tablets.

### **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 WARNINGS AND PRECAUTIONS, Cardiovascular, 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 SEPTA-CANDESARTAN HCTZ is used.

## **Dosing Considerations in Special Populations**

### **Hepatic Impairment**

No dosage adjustment of SEPTA-CANDESARTAN HCTZ is necessary in patients with mild to moderate chronic liver disease.

Since dosage adjustment of candesartan cilexetil is necessary in patients with severely impaired hepatic function and/or cholestasis, and thiazide diuretics may precipitate hepatic coma, use of SEPTA-CANDESARTAN HCTZ is not recommended in these patients (see WARNINGS AND PRECAUTIONS, Hepatic Impairment).

### **Renal Impairment**

No dosage adjustment of candesartan cilexetil is necessary in patients with mildly impaired renal function.

In patients with moderately or severely impaired renal function, or in patients undergoing dialysis, a lower initial dose of 4 mg should be considered.

The usual regimens of therapy with SEPTA-CANDESARTAN HCTZ may be followed as long as the patient's creatinine clearance is  $>30$  mL/min/1.73 m<sup>2</sup> BSA. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so SEPTA-CANDESARTAN HCTZ is not recommended.

### **Geriatrics (> 65 years of age)**

No dose adjustment of SEPTA-CANDESARTAN HCTZ is necessary for elderly patients. As greater sensitivity of some older patients cannot be ruled out, appropriate caution is recommended (see WARNINGS AND PRECAUTIONS, Geriatrics).

### **Pediatrics (< 18 years of age)**

The safety and efficacy of candesartan cilexetil/hydrochlorothiazide have not been established in children.

### **Missed Dose**

If a patient misses a dose of SEPTA-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 SEPTA-CANDESARTAN HCTZ should never be taken to make up for a missed dose.

## OVERDOSAGE

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

No specific information is available on the treatment of overdose with SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/hydrochlorothiazide). Treatment is symptomatic and supportive.

### **Candesartan Cilexetil**

Limited data are available in regard to overdose of candesartan cilexetil in humans. The most likely manifestations of overdose would be hypotension, dizziness and tachycardia; bradycardia could occur from reflex parasympathetic (vagal) stimulation. 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 overdose (up to 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 overdose 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.

## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

Candesartan cilexetil/hydrochlorothiazide combines the actions of candesartan cilexetil, an angiotensin II AT<sub>1</sub> 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 (AT<sub>1</sub>) receptor. Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system 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<sub>1</sub> 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<sub>2</sub> 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<sub>1</sub> receptor than for the AT<sub>2</sub> receptor. The strong bond between candesartan and the AT<sub>1</sub> receptor is a result of tight binding to and slow dissociation from the receptor.

Candesartan does not inhibit angiotensin converting enzyme (ACE), also known as kininase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it 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.

### **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, 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.

### **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 was 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 by ester hydrolysis during absorption from the gastrointestinal tract to candesartan. 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.

**Excretion:** 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 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 up to 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.

**Excretion:** Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal  $t_{1/2}$  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  $t_{1/2}$  of hydrochlorothiazide is prolonged in the elderly and in patients with renal

failure or chronic heart failure.

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

### **Special Populations and Conditions**

**Geriatrics:** The plasma concentration of candesartan was higher in the elderly ( $\geq 65$  years) ( $C_{\max}$  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.

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

**Hepatic Insufficiency:** In patients with 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. In patients with moderate to severe hepatic impairment, the  $C_{\max}$  and AUC increased up to five times in a very small group administered a single dose of 16 mg candesartan (see DOSAGE AND ADMINISTRATION, Hepatic Impairment).

**Renal Insufficiency:** In patients with mild to moderate renal impairment ( $Cl_{\text{creat}}$  31-60 mL/min/1.73 m<sup>2</sup>),  $C_{\max}$  and AUC of candesartan increased by 40-60% and 50-90%, respectively, but  $t_{1/2}$  was not altered, compared to patients with normal renal function ( $Cl_{\text{creat}} > 60$  mL/min/1.73 m<sup>2</sup>) during repeated dosing. There was no drug accumulation in plasma in patients with mild to moderate renal impairment. The increases in  $C_{\max}$  and AUC in patients with severe renal impairment ( $Cl_{\text{creat}}$  15-30 mL/min/1.73 m<sup>2</sup>) were 40-60% and 110%, respectively. The terminal  $t_{1/2}$  of candesartan was approximately doubled in patients with severe renal impairment, and these changes resulted in some accumulation in plasma. The pharmacokinetics of candesartan in patients undergoing hemodialysis were similar to those in patients with severe renal impairment (see DOSAGE AND ADMINISTRATION, Renal Impairment).

### **STORAGE AND STABILITY**

Store at 15-30°.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Forms**

SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/hydrochlorothiazide) is available in tablets of 32 mg / 12.5 mg and 32 mg / 25 mg.

### **Composition**

Each SEPTA-CANDESARTAN HCTZ (candesartan cilexetil/ hydrochlorothiazide) 32/12.5 mg tablet contains 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide as the active ingredients. The other strength includes 32 mg / 25 mg. Nonmedicinal ingredients include: lactose monohydrate, corn starch, carboxymethylcellulose calcium, hydroxypropyl cellulose, magnesium stearate, iron oxide red, iron oxide yellow and polyethylene glycol.

### **Availability**

**Tablets of 32 mg/12.5 mg** - Light Yellow, oval shape, biconvex, uncoated mottled tablets debossed with 'L3' and '04' on either side of breakline on one side and break line on other side.

**Tablets of 32 mg/25 mg** - Light Pink, oval shape, biconvex, uncoated mottled tablets debossed with 'L3' and '04' on either side of breakline on one side and break line on other side.

### **Packaging**

All strengths are offered in 30-count HDPE bottles, 1000-count HDPE bottles and blister package of 80 tablets (10 blisters of 8 tablets each) in one carton box.



## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

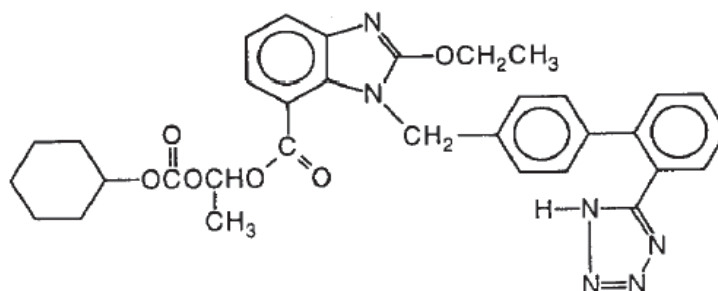
Common Name: candesartan cilexetil

Chemical Name: (±)-1-(Cyclohexyloxycarbonyloxy)ethyl-2-ethoxy-1-[[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl]-1*H*-benzimidazole-7-carboxylate

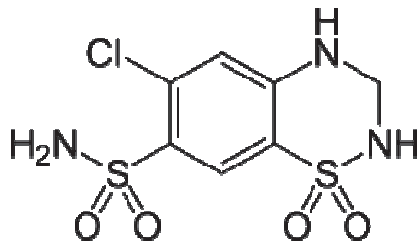
Molecular Formula: C<sub>33</sub>H<sub>34</sub>N<sub>6</sub>O<sub>6</sub>

Molecular Mass: 610.67 g/mol

Structural Formula:



Proper Name: hydrochlorothiazide (Ph.Eur.)  
Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide  
Molecular Formula: C<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S<sub>2</sub>  
Molecular Mass: 297.7 g/mol  
Structural Formula:



#### Physicochemical Properties:

Description: Candesartan cilexetil is a white to off-white powder. The solubility in benzyl alcohol is 205 g/L, and the solubility in water is  $<5 \times 10^{-5}$  g/L.

Hydrochlorothiazide is a white, or almost white, odourless, crystalline powder. Hydrochlorothiazide is very slightly soluble in water, soluble in acetone, and sparingly soluble in ethanol (96%).

Melting Point: Candesartan cilexetil: 163°C with decomposition.  
Hydrochlorothiazide: 268°C.

pKa: 6 (approx.) – Candesartan cilexetil  
7.9, 9.2 - Hydrochlorothiazide

## CLINICAL TRIALS

### Comparative Bioavailability Study

A double blind, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of SEPTA-CANDESARTAN HCTZ (candesartan cilexetil and hydrochlorothiazide) 32 mg/25 mg Tablets, Manufactured by Alembic Pharmaceuticals Limited, India and <sup>Pr</sup>Atacand<sup>®</sup> Plus (Candesartan cilexetil and hydrochlorothiazide) 32 mg/25 mg Tablets, Manufactured by AstraZeneca Canada Inc., Canada, was performed in 37 healthy, adult, human male subjects under fasting conditions.

### SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA (For Candesartan)

**Table 4**

Candesartan (1 x 32 mg Candesartan Cilexetil/25 mg Hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test <sup>#</sup>	Reference <sup>†</sup>	% Ratio of Geometric Means	90% Confidence Interval
AUC <sub>0-∞</sub> (ng.hr/mL)	3930.6 4122.8 (30.1)	3719.9 3854.6 (25.5)	105.7	98.0-113.9
AUC <sub>0-t</sub> (ng.hr/mL)	4081.5 4277.3 (29.8)	3865.0 4011.6 (26.1)	105.6	98.0-113.8
C <sub>max</sub> (ng/mL)	294.4 314.9 (38.2)	290.5 304.9 (31.6)	101.3	92.1-111.5
T <sub>max</sub> <sup>*</sup> (hr)	3.3 (1.5- 8.0)	3.8 (2.0- 8.0)		
t <sub>1/2</sub> <sup>‡</sup> (hr)	8.7 (21.0)	8.8 (32.5)		

<sup>#</sup>SEPTA-CANDESARTAN HCTZ (Candesartan Cilexetil and Hydrochlorothiazide) 32 mg/25 mg tablets (Septa Pharmaceuticals Inc).

<sup>†</sup> Atacand<sup>®</sup> Plus (Candesartan Cilexetil and Hydrochlorothiazide) 32 mg/25 mg tablets (Astra Zeneca Canada Inc., Canada) was purchased in Canada.

\* Expressed as the median (range) only.

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

**SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA  
(For Hydrochlorothiazide)**

**Table 5**

Hydrochlorothiazide (1 x 25 mg Candesartan Cilexetil/25 mg Hydrochlorothiazide) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test <sup>#</sup>	Reference <sup>†</sup>	% Ratio of Geometric Means	90 % Confidence Interval
AUC <sub>0-∞</sub> (ng.hr/mL)	1367.8 1405.6 (23.7)	1382.5 1415.1 (21.5)	98.9	94.8-103.3
AUC <sub>0-t</sub> (ng.hr/mL)	1412.3 1451.0(23.7)	1428.4 1461.4 (21.4)	98.9	94.7-103.2
C <sub>max</sub> (ng/mL)	180.5 185.8 (24.0)	187.1 192.8 (25.0)	96.5	91.3-102.0
T <sub>max</sub> * (hr)	2.0 (1.0- 4.5)	2.0 (1.0- 4.3)		
t <sub>1/2</sub> (hr)	9.3 (19.7)	9.1 (17.7)		

<sup>#</sup>SEPTA-CANDESARTAN HCTZ (Candesartan Cilexetil and Hydrochlorothiazide) 32 mg/25 mg tablets (Septa Pharmaceuticals Inc).

<sup>†</sup> Atacand® Plus (Candesartan Cilexetil and Hydrochlorothiazide) 32 mg/25 mg tablets (Astra Zeneca Canada Inc., Canada) was purchased in Canada.

\* Expressed as the median (range) only.

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

### **Candesartan Cilexetil**

In hypertension, candesartan cilexetil causes a dose-dependent reduction in arterial blood pressure. 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, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally greater than 80%. Candesartan cilexetil had an additional blood pressure lowering effect when added to hydrochlorothiazide.

The antihypertensive effect was similar in men and women and in patients older and younger than 65. Candesartan was effective in reducing blood pressure 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 up to 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 to 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.

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

## **DETAILED PHARMACOLOGY**

### **Animal Pharmacology**

In an *in vitro* assay system, hydrochlorothiazide at  $10^{-5}$  M did not affect the inhibition of binding of [ $^{125}$ I] 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.

## TOXICOLOGY

### Acute Toxicity

**Table 6: Acute Toxicity**

Route	Species	Sex	LD <sub>50</sub> (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 up to 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 7. 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	<p>No deaths, and no treatment-related abnormalities in clinical signs, urine chemistry, or gross pathology, or upon urinalysis or ophthalmic examinations.</p> <p>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.</p> <p>Grps 30/10 and 300/10 had an incr. in creatinine, ALP, LAP and inorganic phosphorus.</p> <p>M in grps 300/0 and 30/10 had an incr. in potassium as well as M and F in grp 300/10.</p> <p>F in grp 3/10 had an incr. in urine output, water intake, ALP, LAP and atrophy of the zona glomerulosa.</p> <p>F in grp 0/10 and 3/10 had a decr. in chloride.</p>
Rat / Fischer 344/DuCrj	10M + 10F	13 weeks dietary	0/0 1/10 10/10 100/10	<p>No deaths, and no abnormal signs.</p> <p>No toxicokinetic interactions 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.</p>

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.
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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 11 <sup>th</sup> and 24 <sup>th</sup> dose and 3 F died: 2 after the 10 <sup>th</sup> dose and 1 after the 14 <sup>th</sup> 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, erythrocytes, 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 31 <sup>st</sup> dose and 38 <sup>th</sup> dose in the 20/10 grp due to a decr. in movement and food consumption, hypothermia, paleness of conjunctival 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.



## **Reproduction Studies**

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.

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 renin-angiotensin-aldosterone system.

## **Mutagenicity**

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.

## **Carcinogenicity**

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

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 two-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 either candesartan cilexetil or hydrochlorothiazide are carcinogenic.

## REFERENCES

1. Bell TP, DeQuattro V, Lasseter KC, Ruff D, Hardison JD, Cushing D, Kezer AE, Michelson EL.  
Effective dose range of candesartan cilexetil for systemic hypertension. *Am J of Cardiology* 1999; 83: 272-275.
2. Bönner G for the Multicentre Study Group.  
Antihypertensive efficacy and tolerability of candesartan–hydrochlorothiazide 32 mg / 12.5 mg and 32 mg / 25 mg in patients not optimally controlled with candesartan monotherapy. *Blood Pressure* 2008; 17 (Suppl 2): 22–30.
3. Delacrétaz E, Nussberger J, Biollaz J, Waeber B, Brunner HR.  
Characterization of the angiotensin II receptor antagonist TCV-116 in healthy volunteers. *Hypertension* 1995; 25: 14-21.
4. Edes I, for the Multicentre Study Group.  
Combination therapy with candesartan cilexetil 32 mg and hydrochlorothiazide 25 mg provides the full additive antihypertensive effect of the components. A randomized, double- blind, parallel-group study in primary care.  
*Clin Drug Invest* 2009;29(5):293-304.
5. Malerczyk C, Fuchs B, Belz GG, Roll S, Butzer R, Breithaupt-Grogler, Herrmann V, Magin SG, Högemann A, Voith B, Mutschler E.  
Angiotensin II antagonism and plasma radioreceptor-kinetics of candesartan in man. *Br J of Clin Pharmacol* 1998; 45: 567-573.
7. Oparil S, Levine JH, Zuschke CA, Gradman AH, Ripley E, Jones DW, Hardison JD, Cushing DJ, Prasad R, Michelson EL.  
Effects of candesartan cilexetil in patients with severe systemic hypertension. *Am J Cardiol* 1999; 84: 289-293.
8. Papademetriou V, Reif M, Henry D, Neutel JM, Levine JH, Hardison D et al. Combination therapy with candesartan cilexetil and hydrochlorothiazide in patients with systemic hypertension. *J Clin Hypertens* 2000; 2: 2-8.
9. Philipp T, Letzel H, Arens H-J.  
Dose-finding study of candesartan cilexetil plus hydrochlorothiazide in patients with mild to moderate hypertension. *J of Hum Hypertension* 1997; 11 (suppl 2): S67-S68.
10. Plouin PF.  
Combination therapy with candesartan cilexetil plus hydrochlorothiazide in patients unresponsive to low-dose hydrochlorothiazide. *J Hum Hypertension* 1997; 11(suppl 2): S65- S66.
11. AstraZeneca Canada Inc., Product Monograph, <sup>Pr</sup>ATACAND<sup>®</sup> PLUS, Control No.: 165653, Date of Revision: September 10, 2013

## PART III: CONSUMER INFORMATION

### PrSEPTA-CANDESARTAN HCTZ

Candesartan Cilexetil/Hydrochlorothiazide Tablets  
32 mg / 12.5 mg and 32 mg / 25 mg

Angiotensin II AT<sub>1</sub> Receptor Blocker + Diuretic

This leaflet is part III of a three-part “Product Monograph” published when SEPTA-CANDESARTAN HCTZ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SEPTA-CANDESARTAN HCTZ. Contact your doctor or pharmacist if you have any questions about the drug.

### ABOUT THIS MEDICATION

#### What the medication is used for:

SEPTA-CANDESARTAN HCTZ lowers high blood pressure.

#### What it does:

SEPTA-CANDESARTAN HCTZ contains a combination of 2 drugs, candesartan cilexetil and hydrochlorothiazide.

- Candesartan is an angiotensin receptor blocker (ARB). You can recognize an ARB because its medicinal ingredient ends in “-SARTAN”. It lowers blood pressure.
- Hydrochlorothiazide is a diuretic or “water pill” that increases urination. This lowers blood pressure.

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

#### When it should not be used:

Do not take SEPTA-CANDESARTAN HCTZ if you:

- are allergic to candesartan cilexetil, hydrochlorothiazide or to any non-medicinal ingredient in the formulation.
- Are allergic to any sulphonamide-derived drugs (sulfa drugs); most of them have a medicinal ingredient that ends in “-MIDE”.
- Are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.
- 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 candesartan cilexetil). Be sure to tell your doctor, nurse, or pharmacist that this has happened to you.
- Have difficulty urinating or produce no urine.
- Are pregnant or intend to become pregnant. Taking SEPTA-CANDESARTAN HCTZ during pregnancy can cause injury and even death to your baby.
- Are breastfeeding. SEPTA-CANDESARTAN HCTZ passes into breast milk.
- Have one of the following rare hereditary diseases:
  - o Galactose intolerance

o Lapp lactase deficiency

o Glucose-galactose malabsorption

- Because lactose is a non-medicinal ingredient in SEPTA-CANDESARTAN HCTZ.

#### What the medicinal ingredients are:

Candesartan cilexetil and hydrochlorothiazide.

#### What the non-medicinal ingredients are:

Lactose monohydrate, corn starch, carboxymethylcellulose calcium, hydroxypropyl cellulose, magnesium stearate, iron oxide yellow (32 mg / 12.5 mg), iron oxide red (32 mg / 25 mg) and polyethylene glycol.

#### What dosage forms it comes in:

Tablets in two strengths:

candesartan cilexetil/hydrochlorothiazide 32 mg/12.5 mg

candesartan cilexetil/hydrochlorothiazide 32 mg/25 mg

### WARNINGS AND PRECAUTIONS

#### **Serious Warnings and Precautions-Pregnancy**

SEPTA-CANDESARTAN HCTZ should not be used during pregnancy. If you discover that you are pregnant while taking SEPTA-CANDESARTAN HCTZ, stop taking the medication and contact your physician, nurse or pharmacist as soon as possible.

BEFORE you use SEPTA-CANDESARTAN HCTZ talk to your doctor, nurse or pharmacist if you:

- Are allergic to any drug used to lower blood pressure, including angiotensin converting enzyme (ACE) inhibitors, or penicillin.
- Are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with SEPTA-CANDESARTAN HCTZ is not recommended.
- 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 or gout.
- Are on dialysis.
- Are dehydrated or suffer from excessive vomiting, diarrhea or sweating.
- Are taking a salt substitute that contains potassium, potassium supplements, or a potassium-sparing diuretic (a specific kind of “water pill”).
- Are on a low-salt diet.
- Are less than 18 years old.
- Are having any kind of surgery or dental procedure with anesthesia.
- Have had a heart attack or stroke.

**Hydrochlorothiazide in SEPTA-CANDESARTAN HCTZ can cause Sudden Eye Disorders:**

- **Myopia:** sudden nearsightedness or blurred vision.
- **Glaucoma:** an increased pressure in your eyes, eye pain. Untreated, it may lead to permanent vision loss.

These eye disorders are related and can develop within hours to weeks of starting **SEPTA-CANDESARTAN HCTZ**.

You may become sensitive to the sun while taking **SEPTA-CANDESARTAN HCTZ**. Exposure to sunlight should be minimized until you know how you respond.

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

## INTERACTIONS WITH THIS MEDICATION

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

The following may interact with **SEPTA-CANDESARTAN HCTZ**:

- Adrenocorticotropic hormone (ACTH) used to treat West Syndrome.
- Alcohol, barbiturates (sleeping pills), or narcotics (strong pain medications). They may cause low blood pressure and dizziness when you go from lying or sitting to standing up.
- Amantadine.
- Amphotericin B, an antifungal drug.
- Anticancer drugs, including cyclophosphamide and methotrexate.
- Antidepressants, in particular selective serotonin reuptake inhibitors (SSRIs), including citalopram, escitalopram and sertraline.
- Antidiabetic drugs, including insulin and oral medicines.
- Bile acid resins used to lower cholesterol.
- Other blood pressure lowering drugs, including diuretics (“water pills”), aliskiren-containing products (e.g. Rasilez), or angiotensin converting enzyme inhibitors (ACEIs). When taken in combination with ATACAND PLUS, they may cause excessively low blood pressure.
- Calcium or vitamin D supplements.
- Corticosteroids used to treat joint pain and swelling.
- Cyclosporine.
- Digoxin, a heart medication.
- Drugs that slow down or speed up bowel function, including atropine, biperiden, domperidone and metoclopramide.
- Drugs used to treat epilepsy, including carbamazepine and topiramate.
- Gout medications, including allopurinol and probenecid.
- Lithium used to treat bipolar disease.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), used to reduce pain and swelling. Examples include ibuprofen, naproxen and celecoxib.
- Pressor amines such as norepinephrine.

- Skeletal muscle relaxants used to relieve muscle spasms, including tubocurane.

## PROPER USE OF THIS MEDICATION

Take **SEPTA-CANDESARTAN HCTZ** exactly as prescribed. It is recommended to take your dose at about the same time everyday.

**SEPTA-CANDESARTAN HCTZ** can be taken with or without food but it should be taken the same way each day. Swallow **SEPTA-CANDESARTAN HCTZ** with a glass of water.

If **SEPTA-CANDESARTAN HCTZ** causes upset stomach, take it with food or milk.

The blister 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 **SEPTA-CANDESARTAN HCTZ** to other pill containers. To protect your **SEPTA-CANDESARTAN HCTZ** tablets, keep them in the container received from your pharmacist.

**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 Adult Dose:

Usual maintenance dose is: 1 tablet daily

The dosage of **SEPTA-CANDESARTAN HCTZ** is individualized.

**SEPTA-CANDESARTAN HCTZ** is not for initial therapy. You must first be stabilized on the individual components (candesartan cilexetil and hydrochlorothiazide) of **SEPTA-CANDESARTAN HCTZ**.

**Overdose:**

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

**Missed dose:**

If you miss a dose of SEPTA-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 double dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Side effects may include:

- back or leg pain, muscle cramps, spasms and pain, weakness, restlessness
- dizziness, pins and needles in your fingers, headache
- constipation, diarrhea, nausea, vomiting, decreased appetite, upset stomach, enlargement of the glands in your mouth
- bleeding under skin, rash, red patches on the skin
- drowsiness, insomnia
- reduced libido
- throat infections

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

SEPTA-CANDESARTAN HCTZ can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate emergency medical assistance
		Only if severe	In all cases	
<b>Common</b>	<b>Low Blood Pressure:</b> dizziness, fainting, lightheadedness  May occur when you go from lying or sitting to standing up	✓		
	<b>Decreased or</b>		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek
	<b>increased levels of potassium in the blood:</b> irregular heartbeats, muscle weakness and generally feeling unwell			
	<b>Tachycardia:</b> increased heart beats		✓	
	<b>Edema:</b> swelling of hands, ankles or feet		✓	
<b>Un-common</b>	<b>Allergic reactions:</b> rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
	<b>Kidney Disorder:</b> change in frequency of urination, nausea, vomiting, swelling of extremities, fatigue		✓	
	<b>Liver Disorder:</b> yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
	<b>Increased blood sugar:</b> frequent, urination, thirst, and hunger	✓		
	<b>Electrolyte Imbalance:</b> weakness, drowsiness, muscle pain or cramps, irregular heartbeat		✓	
<b>Rare</b>	<b>Rhabdomyolysis:</b> muscle pain that you cannot explain, muscle tenderness or weakness, dark brown urine		✓	
	<b>Decreased White Blood Cells:</b> infections, fatigue, fever, aches, pains		✓	

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

Symptom / effect	Talk with your doctor, nurse or pharmacist	Stop taking drug and seek
and flu-like symptoms		
<b>Decreased Platelets:</b> bruising, bleeding, fatigue and weakness		✓
<b>Very rare</b> <b>Toxic Epidermal Necrolysis:</b> severe skin peeling, especially in the mouth and eyes		✓
<b>Unknown</b> <b>Eye disorders:</b> <b>-Myopia:</b> sudden near sightedness or blurred vision <b>-Glaucoma:</b> increased pressure in your eyes, eye pain		✓
<b>Anemia:</b> fatigue, loss of energy, weakness, shortness of breath		✓
<b>Inflammation of the Pancreas:</b> abdominal pain that lasts and gets worse when you lie down, nausea, vomiting		✓

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

## HOW TO STORE IT

- Although SEPTA-CANDESARTAN HCTZ tablets are protected in their package, it is best to store them at normal room temperature between 15 and 30°C and in a dry place. Do not keep SEPTA-CANDESARTAN HCTZ in the bathroom.
- Keep **SEPTA-CANDESARTAN HCTZ out of reach of children**. Never take medicine in front of small children as they will want to copy you.
- Do not keep or use SEPTA-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.

## REPORTING SUSPECTED SIDE EFFECTS

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

Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or
- Mail to:  
Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, ON K1A 0K9

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

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

## MORE INFORMATION

This document, plus the full Product Monograph prepared for health professionals, can be found at: [www.septapharmaceuticals.com/](http://www.septapharmaceuticals.com/) or by contacting the sponsor, Septa Pharmaceuticals Inc, at: 1-905-564-5665 or by email, at: [info@septapharmaceuticals.com](mailto:info@septapharmaceuticals.com)

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

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