PRODUCT MONOGRAPH

[Pr]Septa-Candesartan

candesartan cilexetil tablets

16 mg and 32 mg

Angiotensin II AT_1 Receptor Blocker

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[Pr]SEPTA-CANDESARTAN

candesartan cilexetil tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablets: 16 mg and 32 mg	Calcium carboxymethylcellulose, corn starch, hydroxypropylcellulose, iron oxide red, lactose monohydrate, magnesium stearate, polyethylene glycol

INDICATIONS AND CLINICAL USE

SEPTA-CANDESARTAN (candesartan cilexetil) is indicated for:

- Hypertension
  - The treatment of mild to moderate essential hypertension.
  - SEPTA-CANDESARTAN may be used alone or concomitantly with thiazide diuretics.
  - The safety and efficacy of concurrent use with calcium channel blockers and angiotensin converting enzyme inhibitors have not been established.
- Heart Failure
  - The treatment of NYHA Class II and III heart failure with ejection fraction ≤ 40% in addition to standard therapy, with or without an ACE inhibitor.

Geriatrics (> *65* years of age): No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

CONTRAINDICATIONS

SEPTA-CANDESARTAN (candesartan cilexetil) is contraindicated in:

- Patients who are hypersensitive to any component of this product (see DOSAGE FORMS, COMPOSITION AND PACKAGING).
- Concomitant use of angiotensin receptor antagonists (ARBs), including SEPTA-CANDESARTAN, with aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR < 60 ml/min/1.73m2) 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 (AT1) blockers (ARBs) can cause injury or even death of the developing fetus. When pregnancy is detected, SEPTA-CANDESARTAN 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.

Patients with heart failure given candesartan cilexetil commonly have some reduction in blood pressure. Caution should be observed when initiating therapy.

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

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 candesartan cilexetil, 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/1.73m2). Therefore, the use of SEPTA-CANDESARTAN in combination with aliskiren-containing drugs is contraindicated in these patients (see CONTRAINDICATIONS).

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

Endocrine and Metabolism

Hyperkalemia
In heart failure patients treated with SEPTA-CANDESARTAN, hyperkalemia may occur. During treatment with SEPTA-CANDESARTAN in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

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 SEPTA-CANDESARTAN, or ACEIs with aliskiren-containing drugs is contraindicated in patients with moderate to severe renal impairment (GFR < 60 ml/min/1.73m2) (see CONTRAINDICATIONS and DRUG INTERACTIONS, Dual Blockade of the Renin-Angiotensin-System (RAS) with ARBs, ACEIs, or aliskiren-containing drugs).

Use of SEPTA-CANDESARTAN should include appropriate assessment of renal function.

In heart failure patients, increases in serum creatinine may occur. Dosage reduction, and/or discontinuation of the diuretic, and/or SEPTA-CANDESARTAN, and/or volume repletion may be required. Monitoring of serum creatinine is recommended during dose escalation and periodically thereafter.

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

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 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 antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin receptor (AT1) 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, hyperkalaemia).

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.

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 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. 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 have not been established in children.

Geriatrics (> *65* years of age): no overall differences in safety or effectiveness were observed

between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Hypertension

Candesartan cilexetil has been evaluated for safety in more than 8700 patients treated for hypertension, including 677 treated for six months or more, and 626 for about one year or more. Of these, 8694 were treated with candesartan cilexetil monotherapy in controlled clinical trials.

In placebo-controlled clinical trials, discontinuation due to adverse events occurred in 2.9% and 2.7% of patients treated with candesartan cilexetil monotherapy and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with candesartan cilexetil in controlled clinical trials: syncope, hypotension.

Heart Failure

The adverse event profile of candesartan cilexetil in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the CHARM Alternative and CHARM-Added studies comparing candesartan cilexetil in total daily doses up to 32 mg once daily to placebo, 23.2 % of candesartan cilexetil and 18.4% of placebo patients discontinued the treatment due to adverse events.

Severe adverse reactions most commonly seen in CHARM-Alternative and CHARM Added were hypotension, hyperkalemia and renal impairment.

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.*

Hypertension

In the double blind, placebo-controlled trials, the overall incidence of adverse events showed no association with dose, age or gender. In these trials, the following adverse events reported with candesartan cilexetil occurred in ≥ 1% of patients, regardless of drug relationship:

Table 1 - Adverse events that occurred in ≥ 1% of patients, regardless of drug relationship

	candesartan cilexetil n= 1388 (%)	placebo n= 573 (%)
Body as a Whole		
Back pain	3.2	0.9
Fatigue	1.5	1.6
Abdominal pain	1.5	1.3
Peripheral edema	1.0	0.7
Digestive		
Nausea	1.9	1.3
Diarrhea	1.5	1.9
Vomiting	1.0	1.2
Nervous/Psychiatric		
Headache	10.4	10.3
Dizziness	2.5	2.3
Respiratory		
Upper respiratory infection	5.1	3.8
Coughing	1.6	1.1
Influenza-like symptoms	1.5	0.8
Pharyngitis	1.1	0.4
Bronchitis	1.0	2.2
Rhinitis	1.0	0.4

Clinical trials in which doses up to 32 mg were administered did not result in a significant increase in any of the adverse events listed above.

Heart Failure

In these trials, the following adverse events reported with candesartan cilexetil occurred in ≥ 1% of patients and with higher frequency than placebo, regardless of drug relationship.

Table 2 - Adverse events reported in CHARM-Alternative and CHARM-Added and occurring with frequency of ≥ 1% regardless of drug relationship

	candesartan cilexetil n= 2289 (%)	placebo n= 2287 (%)
Body as a Whole		
Fatigue	1.4	0.9
Cardiovascular Disorders		
Hypotension	20.9	11.0
Syncope	3.3	3.2
Coronary artery disorder	4.2	3.5
Cardiac arrest	1.3	1.1
Blood disorders		
Anemia	2.8	2.3
Gastro-Intestinal System disorders		
Diarrhea	2.4	1.1
Gastroenteritis	1.1	0.7
Liver and Biliary System Disorders		
Cholelithiasis	1.1	0.9
Metabolic and Nutritional Disorders		
Hyperkalemia	7.6	2.6
Dehydration	2.5	1.3
Nonprotein nitrogen increased	1.3	0.3
Uremia	1.1	0.5
Gout	1.0	0.9
Musculo-Skeletal System Disorders		
Arthrosis	1.2	1.0
Nervous System Disorders		
Dizziness	3.4	2.1

	candesartan cilexetil n= 2289 (%)	placebo n= 2287 (%)
Headache	1.0	0.7
Urinary System Disorders		
Renal function abnormal	14.3	7.2
Renal failure acute	3.0	1.8

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

Hypertension

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, hyperkalemia, hyponatremia.

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.

In studies using daily doses greater than 16 mg, the following adverse events were reported at a rate greater than 1% but at about the same or greater incidence in patients receiving placebo: chest pain, sinusitis, arthralgia and albuminuria. Other adverse events reported at an incidence of 0.5% or greater from more than 3200 patients treated worldwide include fever, gastroenteritis, tachycardia, palpitation, increased creatinine phosphokinase, hyperglycemia, hypertriglyceridemia, hyperuricemia, anxiety, somnolence, dyspnea, and hematuria.

Heart Failure

The following listed adverse events occurred in less than 1% of candesartan cilexetil treated patients but in at least 2 patients and with more frequent occurrence in the candesartan cilexetil group than in the placebo group (CHARM-Alternative and CHARM-Added).

Skin and Appendages Disorders: rash, pruritus, angioedema.

Liver and Biliary System Disorders: hepatic function abnormal.

White Cell and Resistance Disorders: granulocytopenia, leukopenia.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Test Findings

Hypertension

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

Liver Function Tests: in controlled clinical trials, elevations of AST and ALT (> 3 times the upper limit of normal) occurred in 0.3% and 0.5% of patients treated with candesartan cilexetil monotherapy compared to 0.2% and 0.4% of patients receiving placebo.

Serum Potassium: a small increase (mean increase of 0.1 mEq/L) was observed in hypertensive patients treated with candesartan cilexetil alone but was rarely of clinical importance.

Creatinine, Blood Urea Nitrogen, and Sodium: minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently, as were decreases in sodium.

Hemoglobin and Hematocrit: small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dL and 0.5 volume %, respectively) were observed in patients treated with candesartan cilexetil alone but were rarely of clinical importance. Anemia, leukopenia and thrombocytopenia were associated with withdrawal of one patient each from clinical trials.

Hyperuricemia: hyperuricemia was rarely found (0.6% of patients treated with candesartan cilexetil and 0.5% of patients treated with placebo).

Heart Failure
Increases in serum creatinine, potassium and urea, and decreases in hemoglobin and hematocrit were observed.

Post-Market Adverse Drug Reactions

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 elderly 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.

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.

Digoxin
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.

Other
No significant drug interactions have been reported with glyburide, nifedipine or oral contraceptives co-administered with candesartan cilexetil to healthy volunteers. While there is no clinically relevant interaction between candesartan and enalapril, patients with renal impairment showed a higher exposure to both drugs. This is consistent with known pharmacokinetics of these two compounds.

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 with candesartan cilexetil

Proper Name	Reference	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 SEPTA-CANDESARTAN.	The possibility of symptomatic hypotension with the use of SEPTA-CANDESARTAN can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of SEPTA-CANDESARTAN (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and DOSAGE AND ADMINISTRATION). No drug interactions of clinical significance have been identified with thiazide diuretics in patients treated with up to 25 mg hydrochlorothiazide with 16 mg candesartan cilexetil for 8 weeks.
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.
Lithium Salts	CT	As with other drugs which eliminate sodium, lithium clearance may be reduced.	Serum lithium levels should be monitored carefully if lithium salts are to be administered.

Proper Name	Reference	Effect	Clinical comment
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	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 angiotensin-converting enzyme (ACE) inhibitors, concomitant use of ARBs and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function.	The combination 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.
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).

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

Drug-Food Interactions

Candesartan cilexetil may be taken with or without food (see DOSAGE AND ADMINISTRATION).

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of SEPTA-CANDESARTAN (candesartan cilexetil) must be individualized.

Recommended Dose and Dosage Adjustment

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

Hypertension
Initiation of therapy requires consideration of recent antihypertensive treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with SEPTA-CANDESARTAN may need to be adjusted. Blood pressure response is dose related over the range of 4 to 32 mg.

The recommended initial dose of SEPTA-CANDESARTAN is 16 mg, once daily when used as monotherapy. Total daily doses of SEPTA-CANDESARTAN 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 SEPTA-CANDESARTAN alone, candesartan cilexetil may be used together with a thiazide diuretic (See DRUG INTERACTIONS, Drug-Drug Interactions, Diuretics). **Note: SEPTA-CANDESARTAN is only available as 16 mg and 32 mg tablets.**

Concomitant Diuretic Therapy

In patients receiving diuretics, SEPTA-CANDESARTAN 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 SEPTA-CANDESARTAN, to reduce the likelihood of hypotension (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension). If this is not possible because of the patient's condition, SEPTA-CANDESARTAN 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.

Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate chronic liver disease. There is only limited experience available in patients with severe hepatic impairment and/or cholestasis. In patients with severely impaired hepatic function, a lower initial dose of 4 mg should be considered. **Note: SEPTA-CANDESARTAN is only available as 16 mg and 32 mg**

tablets.

Renal Impairment

No dosage adjustment 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. **Note: SEPTA-CANDESARTAN is only available as 16 mg and 32 mg tablets.**

Geriatrics (> 65 years of age)

No dosage adjustment 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 have not been established in children.

Heart Failure

The usual recommended initial dose for treating heart failure is 4 mg once daily. The target dose is 32 mg once daily which is achieved by doubling the dose at approximately 2 week intervals, as tolerated by the patient. SEPTA-CANDESARTAN can be administered with other heart failure treatments including ACE inhibitors, beta-blockers, diuretics, digoxin, and/or spironolactone. No initial dose adjustment is necessary for elderly patients or in patients with renal or hepatic impairment. **Note: SEPTA-CANDESARTAN is only available as 16 mg and 32 mg tablets.**

Missed Dose

If a patient misses a dose of SEPTA-CANDESARTAN 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 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.

Limited data are available in regard to overdosage in humans. The most likely manifestations of overdosage would be hypotension, dizziness and tachycardia; bradycardia could occur from reflex parasympathetic (vagal) stimulation. In case reports detailing overdosage (up to 672 mg candesartan cilexetil) patient recovery was uneventful.

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. Candesartan cilexetil is not removed from the plasma by hemodialysis.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Candesartan cilexetil antagonizes angiotensin II by blocking the angiotensin type one (AT1) receptor. Angiotensin II is the primary vasoactive hormone of the reninangiotensin- 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_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis. There is also an AT_2 receptor found in many tissues, but it plays 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 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.

Pharmacodynamics

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, hypertensive, and heart failure patients. A decrease in the plasma concentration of aldosterone was observed when 32 mg of candesartan cilexetil was administered to hypertensive patients.

Pharmacokinetics

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 (Cmax) 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 bloodbrain 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 14C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of 14C-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.

Special Populations and Conditions

Geriatrics: the plasma concentration of candesartan was higher in the elderly (≥ 65 years) (Cmax 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 Cmax 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_{creat} 31-60 mL/min/1.73m2), C_{max} and AUC of candesartan increased by 40-60% and 50-90%, respectively, but t1/2 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 in patients with mild to moderate renal impairment. The increases in C_{max} and AUC in patients with severe renal impairment (Cl_{creat} 15-30 mL/min/1.73m2) were 40-60% and 110%, respectively. The terminal $t_{½}$ 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°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

SEPTA-CANDESARTAN (candesartan cilexetil) is available in tablets of 16 mg and 32 mg.

Composition

Each tablet contains candesartan cilexetil 16 mg or 32 mg. Each tablet also contains the following non-medicinal ingredients: Calcium carboxymethylcellulose, corn starch, hydroxypropylcellulose, iron oxide red, lactose monohydrate, magnesium stearate, polyethylene glycol

Packaging

SEPTA-CANDESARTAN 16 mg tablets are light pink, round, biconvex uncoated mottled tablets debossed with ‘L293’ on one side and break line on other side. Available in bottles of 30 or 1000 tablets and blisters of 100’s (10x10’s).

SEPTA-CANDESARTAN 32 mg tablets are light pink, round, biconvex uncoated mottled tablets debossed with ‘L294’ on one side and break line on other side. Available in bottles of 30 or 1000 tablets and blisters of 100’s (10x10’s).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

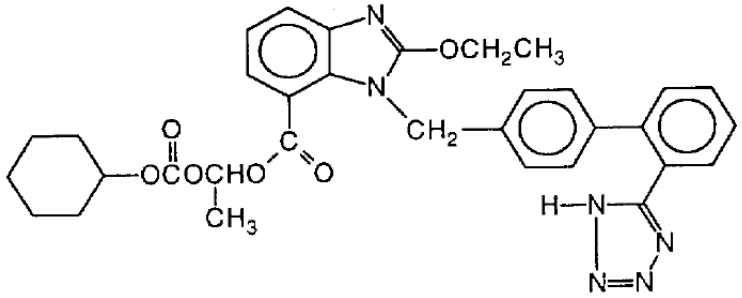
Drug Substance

Proper 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 and molecular mass: $C_{33}H_{34}N_6O_6$
610.67 g/mol

Structural formula:



Physicochemical properties: Description:
Candesartan cilexetil is a white to off-white powder. Soluble in chloroform, sparingly soluble in Methanol and practically insoluble in water.

Melting Point:
163° C

Partition Coefficient:

pH of Aqueous Layer	Partition Coefficient (K at 20°C)	
	Ethyl Ether	1-Octanol
1.1	> 1000	> 1000
6.9	> 1000	> 1000
8.9	141	> 1000

$$K = \frac{\text{Concentration of Candesartan Cilexetil in the organic layer}}{\text{Concentration of Candesartan Cilexetil in the aqueous layer}}$$

CLINICAL TRIALS

Comparative Bioavailability Studies

A double blind, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover oral bioequivalence study of Candesartan cilexetil tablets 32 mg vs. ATACAND® (reference) tablets 32 mg was conducted in 34 healthy, adult, human male subjects under fasting conditions. Bioavailability data were measured and the results are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Candesartan (1 x 32 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval**
AUC_T‡ (ng.hr/mL)	4918.9 5188.6 (36.3)	4731.3 5061.0 (41.4)	103.5	96.9-110.4
AUC_I (ng.hr/mL)	5039.7 5315.6 (36.5)	4860.9 5198.3 (41.4)	103.2	96.7-110.1
C_{MAX} (ng/mL)	438.1 474.6(42.9)	470.7 514.9 (47.7)	92.5	84.1-101.8
T_{MAX}§ (h)	3.6 (1.5- 8.0)	3.9 (2.0-8.0)		
$T_{½}$‖ (h)	8.1(18.2)	8.3 (23.8)		

* Candesartan cilexetil tablets 32 mg, Manufactured by Alembic Pharmaceuticals Limited, India

† Atacand® (Candesartan cilexetil Tablets) 32 mg, Manufactured under License from Takeda Pharmaceutical Company limited by AstraZeneca Canada Inc. Mississauga, Ontario L4Y 1M4

§ Expressed as median (range).

2 Expressed as the arithmetic mean (CV%) only

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 blacks (usually a low-renin population) than in Caucasians.

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 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 A1c.

Comparative Effects
The antihypertensive efficacy of candesartan cilexetil and losartan potassium have been compared at their 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.

Heart Failure
In heart failure patients, candesartan cilexetil administration resulted in a dose-related increase in plasma renin activity and angiotensin II concentration, and a decrease in aldosterone levels.

The effects of candesartan cilexetil on mortality and hospitalization due to Congestive Heart Failure (CHF) were evaluated in two studies, CHARM-Alternative and CHARM-Added. These were multinational, placebo controlled, double blind studies in patients with New York Heart Association (NYHA) functional class II to class IV CHF. Class IV CHF was a baseline characteristic for only 3% of the patient population within each of these studies. CHARM-Alternative (n=2,028) included patients with LVEF $\leq$ 40% not treated with ACE inhibitors because of intolerance. CHARM-Added (n=2,548) was carried out in patients with LVEF $\leq$ 40% tolerant of ACE inhibitors and treated with ACE inhibitors. In these studies patients were randomised to receive either placebo or candesartan cilexetil in addition to standard therapy. Candesartan cilexetil was titrated from 4 mg or 8 mg once daily to 32 mg once daily (mean 23 mg) or the highest tolerated dose. Patients were followed for up to 4 years, with a median of 40 months. Standard therapy included diuretics, β-blockers, ACE inhibitors, digoxin and spironolactone.

The primary composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan cilexetil in comparison with placebo in CHARM Alternative (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, p<0.001) and in CHARM-Added (HR 0.85, 95% CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 23% and 15% respectively.

Table 4. CHARM Alternative: Primary Endpoint and its Components

Enpoint (time to first event)	Candesartan Cilexetil (n=1013)	Placebo (n=1015)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction	Absolute Risk Reduction
CV death or CHF hospitalisation	334	406	0.77 (0.67-0.89)	<0.001	23%	7.0%
CV death	219	252	0.85 (0.71-1.02)	0.072	15%	3.2%
CHF hospitalisation	207	286	0.68 (0.57-0.81)	<0.001	32%	7.7%

NOTE: In CHARM Alternative 14 patients needed to be treated for the duration of the study (median 34 months) to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure.

Table 5. CHARM Added: Primary Endpoint and its Components

Enpoint (time to first event)	Candesartan Cilexetil (n= 1276)	Placebo (n= 1272)	Hazard Ratio (95% CI)	p-value (logrank)	Relative Risk Reduction	Absolute Risk Reduction
CV death or CHF hospitalisation	483	538	0.85 (0.75-0.96)	0.011	15%	4.4%
CV death	302	347	0.85 (0.72-0.98)	0.029	16%	3.6%
CHF hospitalisation	309	356	0.68 (0.71-0.96)	0.013	17%	3.8%

NOTE: In CHARM Added 23 patients needed to be treated for the duration of the study (median 41 months) to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure.

The secondary composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan cilexetil in CHARM Alternative (HR 0.80, 95% CI 0.70-0.92, p=0.001) and CHARM Added (HR 0.87, 95% CI 0.78-0.98, p=0.02l). This corresponds to a relative risk reduction of 20% and 13% respectively.

Treatment with candesartan cilexetil resulted in improved NYHA functional class in CHARM Alternative and CHARM Added (p=0.008 and p=0.020 respectively).

DETAILED PHARMACOLOGY

Animal Pharmacology

In isolated rabbit aorta helical strips, candesartan at 3 x 10^{-11} to 10^{-9} M decreased the maximal contractile response induced by angiotensin II. Candesartan at a concentration of 1 nM completely inhibits the response to angiotensin II in a concentration range of 10^{-10}-10^{-7} M, an angiotensin II concentration which elicits a full concentration-response curve in the absence of candesartan. The dissociation rate of [^{3}H] candesartan binding from bovine adrenal cortical membranes, *in vitro*, was 5 times slower (t½ = 66 min) than that of [^{125}I] angiotensin II binding (t½ = l2 min).

TOXICOLOGY

ACUTE TOXICITY

Table 6. Acute Toxicity

Route	Species	Sex	LD_{50} Values
Intraperitoneal	mouse	female male	891 807
Intraperitoneal	rat	female male	1210 940
Intravenous	mouse	female male	1,170 1,120
Intravenous	rat	female male	1,550 1,350
Oral study with active metabolite (candesartan) and related substances	mouse	female male	>2,000 mg/kg for all substances tested
Oral	mouse	female male	>2,000 mg/kg
Oral	rat	female male	>2,000 mg/kg
Oral	dog	female male	>2,000 mg/kg
Oral (4 week study)	monkey	female male	>60 mg/kg

Chronic Toxicity

The toxic potential of candesartan cilexetil was evaluated in a series of repeated dose oral toxicity studies of up to 26 weeks in rats and up to one year in dog. The "no tox effect" dosage levels were concluded to be 10 mg/kg/day in the rat and 20 mg/kg/day in the dog.

Table 7. Toxicity Upon Repeated Oral Administration.

Species/ Strain	Number of Animals per Group	Duration and Route of Administration	Daily Dose (mg/kg)	Results
rat/F344	4 M + 4 F	4 weeks dietary	0 600 2,000 6,000	Food consumption decr. in F at 2,000 mg and in M+F at 6,000 mg dose level. Urea N2 incr. in M at ≥600 mg dosing, and in F at 6,000 mg dosing. Erythrocyte count, hematocrit value, hemoglobin concentration decr. In ≥2,000 mg groups. Extramedullary hemapoiesis in all male spleens, hypocellularity in bone marrow of 2 F and gastric ulcer/erosion in 2 F of 6,000 mg group. Hypertrophy of juxtaglomerular cells in kidneys and atrophy of zona glomerulosa in adrenal gland in all treated groups – expected pharmacological responses. "No toxic effect": 2,000 mg/kg/day.

Species/ Strain	Number of Animals per Group	Duration and Route of Administration	Daily Dose (mg/kg)	Results
rat/F344	10 M + 10 F	13 weeks dietary	0 300 1,000 3,000	No deaths. Body weight gain suppression in M at ≥1,000 mg level. Slight decr. in erythrocyte count, hematocrit value, hemoglobin concentration in F of 300 mg group, M+F at ≥1,000 mg dose. Incr. inorganic phosphorus in all M groups, decr. triglycerides (≥1,000 mg male group) and incr. cholesterol (3000 mg male group).
Rat/F344/Jcl	10 M + 10 F	26 weeks oral	0 1 10 100 1,000	No treatment-related deaths, nor abnormal appearance, clinical signs, opthalmoscopy and urinalysis. Decr. in body weight gain and food consumption (M, 1000 mg dose, week 25). H2O intake + urine output incr. (M, 100, 1,000 mg dose). RBC parameter values decr. (M: 10-1,000 dose; F: 100-1,000 dose). Heart wt. decr. in all except M at 1 mg dose. Ratio of kidney wt: body wt. incr. in M ≥l0 mg dose, and in F ≥100 mg dose level. In M at 1000 mg level, incr. in adrenal wt., decr. in thymus wt. Hypertrophy of juxtaglomerular cell and intimal proliferation of interlobular arteries on kidneys of M+F at 10-1,000 mg. Minor incr. in erosion of stomach in M+F at 1,000 mg. "No toxic effect": 10 mg/kg/day.
rat/F344/ Jcl	10 M + 10 F	2 week study of candesartan cilexetil and rel. substances, oral	200 (283.2 mg can.cil. +16.8 mg rel.sub.)	No effects by related substances on the changes caused by candesartan cilexetil alone. No toxic effects caused by related substances.
dog/ Beagle	3 M+3 F	29-31 days oral gavage	0 20 100 300	No animals died during dosing. Decr. Erythrocyte parameters in 1 F in each of 100 mg and 300 mg groups. Dark red focus in stomach mucosa in 1 F at 300 mg dose level. Regeneration of tubular epithelium and dilatation of kidney tubules in 1 F at 100 mg level, 2 F at 300 mg level. Mononuclear cell infiltration in kidney in 2 F in both 100 mg and 300 mg groups. Erosion of stomach mucosa in 1 F at 300 mg. No testicular abnormalities. "No toxic effect": 20 mg/kg/day.
dog/ Beagle	4 M+4 F	26 weeks oral	0 4 20 100	Suppression of body wt. and decr. Erythrocyte parameters in F at 100 mg. Hypertrophy of juxtaglomerular cells at all dosage levels. Plasma levels of candesartan cilexetil dose-dependent.
dog/ Beagle	4 M+4 F	52 weeks oral	0 4 20 100 300	No clinical signs, effects on body wt., food consumption, physiological measurements, urine output, H2O intake, hematology, coagulation, or organ wts. Hypertrophy of juxtaglomerular cells at all dosage levels. Regeneration of renal tubule incr. in 100-

Species/ Strain	Number of Animals per Group	Duration and Route of Administration	Daily Dose (mg/kg)	Results
				300 mg dose groups. Plasma levels of candesartan cilexetil and metabolite M II dosedependent. "No toxic effect" at 20 mg/kg/day in dog.

Reproduction Studies
In studies concerning male and female rat fertility, no adverse effects were found on the reproductive organs. Mating performance, fertility and necropsy findings were unaffected by candesartan cilexetil treatment of males at 0-300 mg/kg/day from nine weeks before mating to the day before necropsy, and similar findings were observed in females treated from two weeks before mating to day 7 of gestation. Fetuses showed no treatment-related abnormalities in mortality, weight, sex ratio, placentae or upon external, visceral or skeletal examinations.

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
In vitro studies (bacterial mutagenicity, gene mutation in mammalian (mouse) cells, and cytogenic tests (hamster lung cells) showed candesartan cilexetil has no mutagenic activity in these systems. Study at the highest doses of the candesartan metabolites (2.5 and 5 mM in the 24- hour treatment series, and 1.25 and 2.5 mM in the 48-hour treatment series) suggest cytotoxicity-mediated clastogenicity as a mechanism for the breakage-type chromosome aberration effects observed. *In vivo* studies (micronucleus test in mice, and unscheduled DNA synthesis assay in rat) indicate that candesartan cilexetil and its metabolites have no mutagenic nor clastogenic potential.

Carcinogenicity
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.

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PART III: CONSUMER INFORMATION

[Pr]Septa-Candesartan

candesartan cilexetil tablets

16 mg and 32 mg

Angiotensin II AT_1 Receptor Blocker

This leaflet is part III of a three-part "Product Monograph" published when SEPTA-CANDESARTAN 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. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
SEPTA-CANDESARTAN is used to treat hypertension (high blood pressure).

You may not experience any signs of high blood pressure. It is important to take SEPTA-CANDESARTAN as directed by your doctor. If high blood pressure is not treated, damage may result to vital organs such as the heart or the kidneys. High blood pressure can lead to strokes, heart attacks, heart failure, kidney failure, or blindness.

SEPTA-CANDESARTAN can also be taken for treatment of a heart condition known as heart failure. This is a condition in which your heart does not pump blood around your body as well as it should.

It is important to take SEPTA-CANDESARTAN as directed by your doctor.

What it does:
SEPTA-CANDESARTAN is the brand name for this drug, candesartan cilexetil. It belongs to the group of drugs called "angiotensin II receptor blockers". Its main action is to relax the arteries, letting the blood flow more freely, thereby lowering the blood pressure.

When it should not be used:
You should not take SEPTA-CANDESARTAN if:

- You are already taking a blood pressure-lowering medicine that contains aliskiren (such as Rasilez) and you have diabetes or kidney disease.
- You are allergic to "non-medicinal" substances like food products, preservatives, or dyes, which may be present in SEPTA-CANDESARTAN tablets (See What the nonmedicinal ingredients are).
- You have ever had a bad, unusual or allergic reaction to candesartan cilexetil.

What the medicinal ingredient is:
Candesartan cilexetil.

What the non-medicinal ingredients are:
Most medicines contain more ingredients than just the active drug. These ingredients are needed to keep medicines in a form that you can swallow. Check with your doctor if you think you might be allergic to any of the following items (listed in alphabetical order): calcium carboxymethylcellulose, corn starch, hydroxypropylcellulose, iron oxide red, lactose monohydrate, magnesium stearate, polyethylene glycol.

What dosage forms it comes in:
SEPTA-CANDESARTAN is available as 16 mg and 32 mg tablets.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
SEPTA-CANDESARTAN should not be used during pregnancy. If you discover that you are pregnant while taking SEPTA-CANDESARTAN, stop the medication and please contact your physician.

Before you start SEPTA-CANDESARTAN, talk to your doctor, nurse or pharmacist:

- **If you are pregnant, breast feeding or thinking about becoming pregnant.** Taking SEPTA-CANDESARTAN during pregnancy can cause injury and even death to your baby. This medicine should not be used during pregnancy. If you are planning to become pregnant while taking SEPTA-CANDESARTAN, contact your doctor immediately.
  It is possible that SEPTA-CANDESARTAN passes into breast milk. You should discuss with your doctor about taking SEPTA-CANDESARTAN while breast feeding.
- If you are taking a medicine that contains aliskiren, such as Rasilez, used to lower high blood pressure. The combination with SEPTA-CANDESARTAN is not recommended.
- If you are taking an angiotensin converting enzyme inhibitor (ACEI). You can recognize ACEIs because their medicinal ingredient ends in "-PRIL".
- About all health problems you have or have had in the past including any heart, liver or kidney problems.
- If you are taking a diuretic therapy (water pills) or are on salt restrictive diet.
- If you are undergoing dialysis.
- If you are vomiting or have diarrhea.

The treatment of high blood pressure may cause dizziness or weariness in some patients. Make sure you are not affected in this way before driving or operating machinery.

If you are currently taking SEPTA-CANDESARTAN and are going to have an operation, be sure to tell your doctor or dentist about your medication before you are given an anaesthetic.

INTERACTIONS WITH THIS MEDICATION

Before taking SEPTA-CANDESARTAN be sure your doctor knows about all medicines you take, including ones you can buy without a prescription. If you visit more than one doctor make sure that each knows about all the medicines you are taking.

Drugs that may interact with SEPTA-CANDESARTAN include:
- Other medicines used to lower blood pressure, including diuretics (water pills), aliskiren-containing products (e.g. Rasilez), or angiotensin converting enzyme inhibitors (ACEIs)
- Potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes;
- Lithium therapy;
- Nonsteroidal anti-inflammatory agents (NSAIDs) such as aspirin, acetaminophen, and ibuprofen. NSAIDs are used to reduce pain, fever, and swelling.

PROPER USE OF THIS MEDICATION

Remember, you may not notice any signs of high blood pressure. **Therefore, it is important to take SEPTA-CANDESARTAN even when you feel well.** A constant amount of drug is needed in your body to control your blood pressure. **Do not stop taking SEPTA-CANDESARTAN on your own.**

Usual dose:
Take SEPTA-CANDESARTAN exactly as your doctor tells you. Do not miss doses or take extra doses, unless your doctor tells you. If you are not clear about the directions, ask your doctor or pharmacist.

The dosage of SEPTA-CANDESARTAN is individualized.

SEPTA-CANDESARTAN is not for use in children under 18 years of age.

Try to take SEPTA-CANDESARTAN with something you do regularly each day; for example, upon waking or at breakfast. This will help you remember each dose.

SEPTA-CANDESARTAN may be taken with food or on an empty stomach but it should be taken consistently the same way each day.

Swallow SEPTA-CANDESARTAN with a glass of water.

SEPTA-CANDESARTAN is taken once a day. Even if your doctor has prescribed 2 tablets a day, both should be taken at the same time, unless otherwise indicated.

Remember to get a new prescription from your doctor or a refill from your pharmacy a few days before all your tablets are taken.

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 SEPTA-CANDESARTAN to other pill containers. To protect your SEPTA-CANDESARTAN tablets, keep them in the original package.

Overdose:

In case of drug overdose, contact a health care practitioner, 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 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.

Never take a double dose of SEPTA-CANDESARTAN to make up for missed tablets. If you are still unsure, check with your doctor or pharmacist to see what you should do.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Along with its effects on controlling blood pressure, SEPTA-CANDESARTAN, like any medication, may cause side effects. These side effects are usually mild and should go away as your body gets used to SEPTA-CANDESARTAN. Talk to your doctor if you suffer from any of these effects or if you get any other unusual or unexpected symptoms.

Common side effects that may occur (in 1% or more of patients but less than 10%):
- Dizziness
- Headache
- Cold symptoms
- Worsening of the kidney function (especially in patients with existing kidney problems or heart failure)
- Abnormally low blood pressure (especially in patients with heart failure)
- High levels of potassium in the blood (especially in patients with heart failure)
- Back pain

Rare side effects that may occur (in between 0.01% and 1% of patients):
- Fainting spells

Very rare side effects that may occur (in less than 0.01% of patients):
- Changes to the way the liver works, including inflammation of the liver

Side effects such as muscle pain, muscle weakness, muscle inflammation and rhabdomyolysis (a muscle-wasting disease), in rare cases leading to kidney failure, have been reported with the use of angiotensin II receptor blockers, the class of drugs to which SEPTA-CANDESARTAN belongs.

Blood samples may be taken occasionally to check whether SEPTA-CANDESARTAN has had any effect on your blood or on your kidneys.

Medicines affect different people in different ways. Just because

side effects have occurred in other patients does not mean you will get them. Discuss how you feel on SEPTA-CANDESARTAN with your doctor and pharmacist. **Do not stop taking SEPTA-CANDESARTAN on your own.**

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Rare	Allergic reactions: swelling of the face, lips, tongue and/or throat; rash or other skin reactions			**X**
	Jaundice (yellow skin and/or eyes)			**X**
	Muscle pain that you cannot explain, muscle tenderness or weakness, generalized weakness		**X**	
	Dark/brown urine		**X**	

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

HOW TO STORE IT

- It is best to keep SEPTA-CANDESARTAN tablets at normal room temperature (15-30 ºC) and in a dry place. Do not keep SEPTA-CANDESARTAN in the bathroom.
- Keep SEPTA-CANDESARTAN out of sight and 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 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
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.septapharmaceuticals.com
or by contacting the sponsor, Septa Pharmaceuticals Inc:
905-564-5665

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