Treatan-D®

(Candesartan Cilexetil & Hydrochlorothiazide)

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COMPOSITION

Each tablet contains:
Candesartan Cilexetil USP ... 16mg
Hydrochlorothiazide USP ... 12.5mg

DESCRIPTION

Treatan-D (candesartan cilexetil and hydrochlorothiazide) combines an angiotensin II receptor (type AT1) antagonist and a diuretic, hydrochlorothiazide. The empirical formula of candesartan cilexetil is $C_{33}H_{34}N_6O_6$,and that of hydrochlorothiazide is $C_7H_8ClN_3O_4S_2$. The molecular weight of candesartan cilexetil is 610.67 and that of hydrochlorothiazide is 279.92.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

Absorption
Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3 to 4 hours. Food with a high fat content 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.

Metabolism
It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

Excretion
Candesartan is mainly excreted unchanged in urine and feces (via bile). The elimination half-life of candesartan is approximately 9 hours. Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged 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. Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. At least 61% of the oral dose is eliminated unchanged within 24 hours.

INDICATIONS AND USAGE

Treatan-D is indicated for the treatment of hypertension.

CONTRAINDICATIONS

Treatan-D is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity and Mortality

Because candesartan cilexetil is a component of Treatan-D. When pregnancy is detected, Treatan-D should be discontinued as soon as possible.

Hypotension in Volume- and Salt-Depleted Patients

Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume- or sodium-depletion, eg, in patients treated vigorously with diuretics or in patients on dialysis. These conditions should be corrected prior to administration of Treatan-D, or the treatment should start under close medical supervision.

PRECAUTIONS

Impaired Renal Function

Candesartan and Thiazides should be used with caution in severe renal disease (see DOSAGE AND ADMINISTRATION).

Impaired Hepatic Function

Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease (see DOSAGE AND ADMINISTRATION).

Drug Interactions

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these subjects and younger subjects. 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

Candesartan cilexetil-hydrochlorothiazide has been evaluated for safety in more than 2,800 patients treated for hypertension. More than 750 of these patients were studied for at least six months and more than 500 patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse events reported with candesartan cilexetil-hydrochlorothiazide was comparable to placebo. The overall frequency of adverse experiences was not related to dose, age, gender, or race.

In placebo-controlled trials that included 1,089 patients treated with various combinations of candesartan cilexetil (doses of 2-32 mg) and hydrochlorothiazide (doses of 6.25-25 mg) and 592 patients treated with placebo, adverse events, whether or not attributed to treatment, occurring in greater than 2% of patients treated with candesartan cilexetil-hydrochlorothiazide and that were more frequent for candesartan cilexetil-hydrochlorothiazide than placebo were: Respiratory System Disorder: upper respiratory tract infection (3.6% vs 3.0%); Body as a Whole: back pain (3.3% vs 2.4%); influenza-like symptoms (2.5% vs 1.9%); Central/Peripheral Nervous System: dizziness (2.9% vs 1.2%). The frequency of headache was greater than 2% (2.9%) in patients treated with candesartan cilexetil-hydrochlorothiazide but was less frequent than the rate in patients treated with placebo (5.2%).

OVERDOSAGE

Limited data are available in regard to overdosage with candesartan cilexetil in humans. The most likely manifestations of overdosage with candesartan cilexetil would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be initiated. For hydrochlorothiazide, the most common signs and symptoms observed 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.
Candesartan cannot be removed by hemodialysis. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of candesartan cilexetil is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily. The maximal antihypertensive effect of any dose of Treatan-D can be expected within 4 weeks of initiating that dose.

Patients with Renal Impairment

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

Patients with Hepatic Impairment

Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of Treatan-D.

Dosage & Instructions:
As advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from heat, light and moisture.
Store below 30°C.

HOW SUPPLIED

Treatan-D is supplied in the pack of 28's .

خوراک وہدایات:
ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔
تمام دوائیں بچوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 30°C سے کم درجہ حرارت پر رکھیں۔

Rev: 01 12/2015

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