

DATA SHEET

HYPOCART

candesartan cilexetil/hydrochlorothiazide

This product may not be interchangeable with similar products on the New Zealand market.

PRODUCT INFORMATION

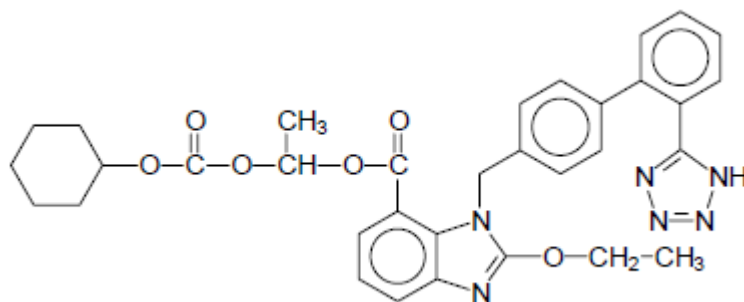
NAME OF THE MEDICINE

The active ingredients in HYPOCART are candesartan cilexetil and hydrochlorothiazide.

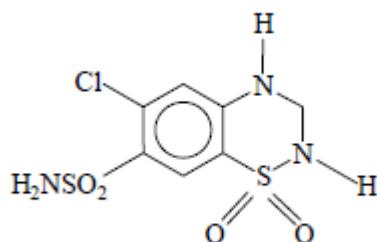
The CAS number for candesartan cilexetil is 145040-37-5.

The CAS number for hydrochlorothiazide is 58-93-5.

The chemical structure of candesartan cilexetil is:



The chemical structure of hydrochlorothiazide is:



DESCRIPTION

The chemical name for candesartan cilexetil is (±)-1-(cyclohexyloxycarbonyl-oxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl] methyl]-1H-benzimidazole-7-carboxylate.

It is a white to off white powder and is practically insoluble in water.

Molecular formula: C₃₃H₃₄N₆O₆ MW: 610.67

The chemical name for hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1, 1-dioxide. Hydrochlorothiazide is a sulfonamide

derived drug. It is a white, or almost white crystalline powder and is very slightly soluble in water.

Molecular formula: $C_7H_8N_3S_2O_4Cl$ MW: 297.75

HYPOCART 8/12.5 contains 8 mg candesartan cilexetil and 12.5 mg of hydrochlorothiazide.

HYPOCART 16/12.5 contains 16 mg candesartan cilexetil and 12.5 mg of hydrochlorothiazide.

In addition to candesartan cilexetil and hydrochlorothiazide, HYPOCART 8/12.5 and 16/12.5 also contain croscarmellose sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, maize starch and Triethyl citrate.

PHARMACOLOGY

Pharmacodynamics

Angiotensin II is the primary vasoactive hormone of the renin-angiotensinaldosterone system and plays a significant role in the pathophysiology of hypertension and other cardiovascular disorders. It also has an important role in the pathogenesis of end organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT_1) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II receptor antagonists are unlikely to be associated with cough. This has been confirmed in controlled clinical studies with candesartan. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide 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. Hydrochlorothiazide decreases plasma volume and extracellular fluid and reduces cardiac output and blood pressure. During long-term therapy, reduced peripheral resistance contributes to the blood pressure reduction.

Candesartan and hydrochlorothiazide have additive antihypertensive effects. In hypertensive patients, HYPOCART results in dose-dependent and long lasting reduction in arterial blood pressure without a reflex increase in heart rate. There is no

indication of serious or exaggerated first dose hypotension or rebound effect after cessation of treatment.

After administration of a single dose of HYPOCART, 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.

HYPOCART once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval. In double-blind, randomised studies, the incidence of cough was lower during treatment with candesartan cilexetil/hydrochlorothiazide than during treatment with combinations of ACE inhibitors and hydrochlorothiazide.

Age and gender have no influence on the efficacy of HYPOCART.

In a variety of preclinical safety studies conducted in several species, expected exaggerated pharmacological effects (e.g. renal changes leading to juxtaglomerular cell hypertrophy, adrenal gland zona glomerulosa atrophy and reduced heart weight related to reduced afterload), due to modification of the renin-angiotensin-aldosterone system homeostasis, have been observed. The incidence and severity of the effects induced were dose and time related and have been shown to be reversible in adult animals. Addition of hydrochlorothiazide caused a potentiation of the nephrotoxicity seen with candesartan alone, however, without any qualitatively new findings.

Pharmacokinetics

The individual pharmacokinetic profiles of candesartan and hydrochlorothiazide were not clinically significantly affected when given in combination.

Absorption and Distribution

Candesartan Cilexetil

Following oral administration, candesartan cilexetil is converted to the active drug candesartan. The absolute bioavailability of candesartan is approximately 40% after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34%, with little variability. The absolute bioavailability of candesartan following administration of the tablet is approximately 14%. The mean peak plasma concentration (C_{max}) is reached 3-4 hours after taking a tablet. The candesartan plasma concentrations increase linearly with increasing doses in the therapeutic dose range.

The area under the plasma concentration versus time curve (AUC) of candesartan is not significantly affected by food. The peak concentration (C_{max}) is increased by 26% and the rate of absorption is increased when taken with food. These changes are unlikely to result in clinically significant effects.

Candesartan is highly bound to plasma protein (more than 99%). The apparent volume of distribution (V_{ss}) of candesartan is 0.1 L/kg.

Hydrochlorothiazide

Hydrochlorothiazide is rapidly absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70%. Concomitant intake of food increases the absorption by approximately 15%. The bioavailability may decrease in patients with cardiac failure and pronounced oedema.

The plasma protein binding of hydrochlorothiazide is approximately 60%. The apparent volume of distribution is approximately 0.8 L/kg.

Metabolism and Elimination

Candesartan Cilexetil

Candesartan cilexetil is mainly eliminated unchanged via urine and bile and is eliminated by hepatic metabolism only to a minor extent (CYP2C9). The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

The half-life of candesartan remains unchanged (approximately 9 h) after administration of candesartan cilexetil in combination with hydrochlorothiazide. No accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

Total plasma clearance of candesartan is about 0.37 mL/min/kg, with a renal clearance of about 0.19 mL/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ¹⁴C-labelled candesartan cilexetil about 30% and 70% of the total radioactivity is recovered in the urine and faeces, respectively.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised 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 (approximately 8 h) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Pharmacokinetics In Special Populations

Candesartan Cilexetil

In the elderly (over 65 years) both C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of HYPOCART in young and elderly patients.

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70% respectively, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with severe renal impairment were approximately 50% and 110% respectively. The terminal $t_{1/2}$ of candesartan was approximately doubled in patients with severe renal impairment. The pharmacokinetics in patients

undergoing haemodialysis were similar to those in patients with severe renal impairment.

In patients with mild to moderate hepatic impairment, there was a 23% increase in the AUC of candesartan. No initial dosage adjustment is necessary in these patients.

Hydrochlorothiazide

The terminal $t_{1/2}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

CLINICAL TRIALS

In a randomised, double-blind, parallel group, 8 week clinical study, including 1975 randomised patients not adequately controlled on 32 mg candesartan cilexetil once daily, the addition of 12.5 mg or 25 mg hydrochlorothiazide resulted in additional blood pressure reductions of 7/3 mmHg and 9/4 mmHg respectively over 32 mg monotherapy. The combination of 32 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide, and 32 mg candesartan cilexetil and 25 mg hydrochlorothiazide produced overall mean blood pressure reductions of 13/9 mmHg and 16/10 mmHg, respectively. This study also demonstrated that the combination of 32 mg candesartan cilexetil and 25 mg hydrochlorothiazide was significantly more effective than the combination of 32 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide.

In two 8 week clinical studies (randomised, double-blind, placebo controlled, parallel group) including 275 and 1524 randomised patients respectively, the combination of 32 mg candesartan cilexetil and 12.5 mg hydrochlorothiazide, and 32 mg candesartan cilexetil and 25 mg hydrochlorothiazide resulted in blood pressure reductions of 21/14 mmHg for the highest dose, and were significantly more effective than the respective monotherapy components.

Epidemiological studies have shown that long term treatment with hydrochlorothiazide reduces the risk for cardiovascular morbidity and mortality. There are no data regarding the effects of candesartan cilexetil and candesartan cilexetil/hydrochlorothiazide on morbidity and mortality in hypertensive patients.

INDICATIONS

The treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

CONTRAINDICATIONS

Hypersensitivity to any component of HYPOCART or to sulfonamide derived drugs.

Pregnancy and lactation.

Severe renal impairment (creatinine clearance < 30 mL/min/1.73 m² BSA).

Severe hepatic impairment and/or cholestasis.

Gout.

PRECAUTIONS

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with drugs that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Renal artery stenosis

Other drugs that affect the renin-angiotensin-aldosterone system, i.e. angiotensin converting enzyme (ACE) inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. A similar effect may be anticipated with angiotensin II receptor antagonists.

Aortic and Mitral Valve Stenosis (Obstructive Hypertrophic Cardiomyopathy)

As with other vasodilators, special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary Hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of candesartan in these patients is not recommended.

Fluid and Electrolyte Imbalance

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals.

Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis).

Hydrochlorothiazide dose-dependently increases urinary potassium excretion which may result in hypokalaemia. This effect of hydrochlorothiazide seems to be less evident when combined with candesartan cilexetil. The risk of hypokalaemia may be increased in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with an inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or adrenocorticotrophic hormone (ACTH).

Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of HYPOCART and potassium sparing diuretics,

potassium supplements or salt substitutes or other drugs that may increase serum potassium levels may lead to increases in serum potassium.

Renal Impairment

When HYPOCART is used in patients with renal impairment, periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Loop diuretics are preferred to thiazides in this population.

There is no experience regarding the administration of HYPOCART in patients with a recent kidney transplantation.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Hepatic Impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. There is no clinical experience with HYPOCART in patients with hepatic impairment.

Metabolic and Endocrine Effects

Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic drugs, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. At the doses contained in HYPOCART only minimal effects were observed. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Hypotension, volume depleted patients

HYPOCART like all anti-hypertensive agents may cause symptomatic hypotension in some patients. Symptomatic hypotension may be expected to occur more frequently in patients who have been sodium and/or volume depleted by vigorous diuretic therapy and/or dietary salt restrictions, or vomiting and/or diarrhoea or haemodialysis. Sodium and/or volume depletion should be corrected prior to administration of HYPOCART.

Postsympathectomy

The antihypertensive effects of thiazide diuretics may be increased in the postsympathectomy patient.

Systemic Lupus Erythematosus

Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin-aldosterone system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Paediatric use

Safety and efficacy have not been established in children.

Use in the elderly

For dosage recommendations for use of HYPOCART in elderly patients please see DOSAGE AND ADMINISTRATION.

Effects on fertility

The effects of hydrochlorothiazide alone or in combination with candesartan cilexetil on fertility have not been evaluated in animal studies. However, candesartan cilexetil alone had no adverse effects on the reproductive performance of male or female rats at oral doses up to 300 mg/kg/day.

Use in pregnancy – Category D

HYPOCART should not be used in pregnancy (see CONTRAINDICATIONS). Women of child-bearing age should be warned of the potential hazards to the fetus should they become pregnant while taking the drug.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of human pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported. Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia. Although these adverse effects do not appear to occur when drug exposure has been limited to the first trimester, the number of exposures is too small to determine conclusively that angiotensin II receptor antagonists are safe in the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist during the first trimester only should be so informed. When patients become pregnant, physicians should advise the patient to discontinue the use of candesartan cilexetil as soon as possible.

Use in lactation

It is not known whether candesartan is excreted in human milk. However, candesartan is excreted in the milk of lactating rats. Hydrochlorothiazide passes into human milk. Because of the potential for adverse effects on the nursing infant, breast feeding should be discontinued if the use of HYPOCART is considered essential.

Carcinogenicity

The carcinogenic potential of candesartan cilexetil in combination with hydrochlorothiazide has not been evaluated in animal studies.

Candesartan cilexetil alone was not carcinogenic when administered orally to mice and rats for 2 years at doses of up to 100 and 1000 mg/kg/day, corresponding to ca. 7 times and 260 times the clinical exposure at the maximum recommended daily human dose of 32 mg (based on AUC, respectively).

Hydrochlorothiazide alone was not carcinogenic in female mice in doses ca. 600 mg/kg/day, or in male and female rats at doses up to ca. 100 mg/kg/day in two year feeding studies. These doses correspond to ca. 110 times (female mice) or 40 times (male and female rats) the clinical exposure at the maximum recommended daily human dose of 25 mg (based on BSA). However, there was equivocal evidence for hepatocarcinogenicity in male mice that received ca. 600 mg/kg/day.

Genotoxicity

Candesartan cilexetil alone or in combination with hydrochlorothiazide showed no evidence of genotoxic potential in a series of assays for gene mutations (*Salmonella typhimurium* and *Escherichia coli*), chromosomal aberrations (mouse micronucleus assay) and DNA damage (unscheduled DNA synthesis in rat liver). In addition, candesartan cilexetil alone showed no evidence of genotoxic potential in further assays for gene mutations (mouse L5178Y cells and Chinese hamster ovary cells). The active metabolite, candesartan, caused an increase in chromosomal aberrations in vitro (Chinese hamster lung cells) but not in vivo (mouse micronucleus test and chromosomal aberrations in rat bone marrow). However, hydrochlorothiazide had mutagenic activity in a mammalian cell assay (mouse L5178Y cells) and caused an increase in chromosomal aberrations in vitro (Chinese hamster lung cells). Candesartan at subclastogenic concentration did not modify these effects of hydrochlorothiazide. Hydrochlorothiazide also had a genotoxic activity in the sister chromatid exchange assay in Chinese hamster ovary cells and a non-disjunction assay in *Aspergillus nidulans*.

Effects on ability to drive and use machines

When driving vehicles or operating machines, it should be taken into account that dizziness or weariness may occur during treatment of hypertension.

Interactions with other medicines

The antihypertensive effect of HYPOCART may be enhanced by other antihypertensives.

Candesartan Cilexetil

No drug interactions of clinical significance have been identified with candesartan cilexetil. Compounds which have been investigated include hydrochlorothiazide, warfarin, digoxin (see Hydrochlorothiazide below), oral contraceptives (i.e. ethinyloestradiol/levonorgestrel), glibenclamide and nifedipine.

Candesartan is eliminated only to a minor extent by hepatic metabolism (CYP2C9).

Interaction studies performed to date show no effect of candesartan on the metabolising capacity of CYP2C9 and CYP3A4. 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.

Hydrochlorothiazide

Alcohol, barbiturates or opioids

Potential of thiazide diuretic induced orthostatic hypotension may occur.

Anti-diabetic agents (oral and insulin)

Thiazides may increase blood glucose concentration and adjustment of anti-diabetic medication may be required.

Cardiac glycosides and other anti-arrhythmics

Thiazide induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when HYPOCART is administered with such drugs.

Calcium salts

Thiazide diuretics may increase the serum calcium concentration due to decreased excretion. If calcium is prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly.

Cholestyramine resin and colestipol hydrochloride

The absorption of thiazide may be delayed or decreased in the presence of bile acids sequestrants. HYPOCART should be taken at least one hour before or after such drugs.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or hydrochlorothiazide. A similar effect may occur with angiotensin II receptor antagonists and careful monitoring of serum lithium levels is recommended during concomitant use.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

Hypokalaemic Agents

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, salicylic acid derivatives).

Potassium Sparing Agents

Based on experience with the use of other drugs that affect the renin-angiotensinaldosterone system, concomitant use of HYPOCART and potassium sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.

Nondepolarizing muscle relaxants (e.g. tubocurarine)

The effect of nondepolarising skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Pressor Amines

Hydrochlorothiazide may cause the arterial response to pressor amines to decrease but not enough to exclude a pressor effect.

Iodinated Contrast Media

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with high doses of iodinated contrast media.

Corticosteroids, ACTH

The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotrophic hormone (ACTH).

Amantadine

Thiazide may increase the risk of adverse effects caused by amantadine.

Beta-Blockers and Diazoxide

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by thiazides.

Anticholinergic Agents (e.g. Atropine)

Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic Drugs (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

ADVERSE EFFECTS

Adverse events were mild and transient in controlled clinical studies with various doses of combined candesartan cilexetil and hydrochlorothiazide (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg). The overall incidence of adverse events showed no association with age or gender. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (2.3-3.3%) and placebo (2.7-4.3%).

Clinical adverse events, regardless of causal relationship, with a cumulative 8-week incidence rate of $\geq 1\%$ during treatment with candesartan cilexetil/hydrochlorothiazide up to 16/12.5 mg in double-blind placebo-controlled trials are presented in the following table.

	Placebo (n=526) %	Candesartan cilexetil/Hydrochlorothiazide (n=1025) %
Cardiovascular		
Tachycardia	0.8	1.1
Gastrointestinal		
Abdominal pain	0.8	1.0
Nausea	0.6	1.3
Musculo-skeletal		
Back pain	2.4	3.0
Nervous System		
Headache	5.5	3.2
Dizziness	1.2	2.6
Respiratory		
Respiratory Infection	1.4	2.5
Bronchitis	1.4	1.7
Pharyngitis	1.0	1.0
Sinusitis	1.6	1.7
Other		
Influenza-like symptoms	1.6	2.1
Urinary tract infection	0.4	1.4

	Placebo (n=526) %	Candesartan cilexetil/Hydrochlorothiazide (n=1025) %
Inflicted injury	1.2	1.2
Fatigue	0.8	1.1

The following clinical adverse events occurred with a frequency of 0.5% to <1% with no occurrence in the placebo group: AV-block, vomiting.

Clinical adverse events, regardless of causal relationship, occurring in $\geq 1\%$ of the patients during 8-week randomised treatment with combinations of 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide, and 32 mg of candesartan cilexetil and 25 mg of hydrochlorothiazide in double-blind clinical trials are presented in the following table.

	Placebo (n=163) %	Candesartan cilexetil/Hydrochlorothiazide (n=1873) %
Metabolism and nutrition disorders		
Dyslipidaemia	0	2.8
Nervous system disorders		
Dizziness	0.6	2.8
Headache	7.4	2.1
Musculoskeletal and connective tissue disorders		
Back pain 2.5 1.9	2.5	1.9
Infections and infestations		
Nasopharyngitis	0	1.4
Bronchitis	1.2	1.0
Respiratory, thoracic and mediastinal disorders		
Cough	1.2	1.0
General disorders and administration site conditions		
Fatigue	2.5	1.0

Adverse Events on Individual Components

Candesartan cilexetil

The following clinical adverse events, regardless of whether attributed to therapy, have been reported to occur with a cumulative 8-week incidence rate of $\geq 1\%$ in placebo-controlled clinical trials with candesartan cilexetil monotherapy: cough, diarrhoea, peripheral oedema and rhinitis. Angioedema, urticaria, pruritis and rash have been reported very rarely in patients treated with candesartan cilexetil. Very rare cases of increased liver enzymes, abnormal hepatic function or hepatitis have also been reported. Very rare adverse reactions include hyponatraemia, hyperkalaemia and renal impairment, including renal failure in susceptible patients see PRECAUTIONS. Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of leukopenia, neutropenia and agranulocytosis.

Hydrochlorothiazide

The following clinical adverse events have been reported to occur with hydrochlorothiazide monotherapy: anorexia, loss of appetite, gastric irritation, diarrhoea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, hemolytic anaemia, bone marrow depression, photosensitivity reactions, fever, rash, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, urticaria, necrotising angiitis (vasculitis, cutaneous vasculitis), anaphylactic reactions, toxic epidermal necrolysis, respiratory distress (including pneumonitis and pulmonary oedema), hyperglycaemia, glycosuria, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), increases in cholesterol and triglycerides, increases in BUN and serum creatinine, renal dysfunction, interstitial nephritis, muscle spasm, weakness, restlessness, transient blurred vision, light-headedness, postural hypotension, vertigo, paraesthesia, cardiac arrhythmias, sleep disturbances, depression.

Laboratory Findings

In general, there were no clinically important influences of candesartan cilexetil/hydrochlorothiazide on routine laboratory variables. Increases in creatinine, urea, potassium, uric acid, glucose and ALAT (SGPT) and decreases in sodium have been observed. Minor decreases in haemoglobin and increases in ASAT (SGOT) have been observed in single patients.

Post marketing

The following adverse reactions have been reported very rarely ($<0.01\%$) in post marketing experience:

Musculoskeletal, connective tissue and bone disorders:

Myalgia

Rare reports of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Although causality to candesartan has not been established, the following neuropsychiatric cardiovascular adverse reactions have been very rarely reported during post-marketing surveillance. These were: agitation, anxiety, depression, insomnia, somnolence, nervousness, nightmare, sleep disorder and palpitations.

DOSAGE AND ADMINISTRATION

The dose of HYPOCART must be determined by careful titration of the dose of each of the individual components.

The recommended dose of HYPOCART is 1 tablet once daily. HYPOCART may be taken with or without food. Do not halve tablets.

HYPOCART 8/12.5 may be administered in patients whose blood pressure is not optimally controlled with hydrochlorothiazide alone or candesartan cilexetil 8 mg monotherapy.

HYPOCART 16/12.5 may be administered in patients whose blood pressure is not optimally controlled with hydrochlorothiazide alone or candesartan cilexetil 16 mg Monotherapy, or at a lower dose of HYPOCART. Dose titration of candesartan cilexetil is recommended when adding on to hydrochlorothiazide monotherapy.

Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

HYPOCART should not be used to initiate treatment.

Paediatrics

The safety and efficacy of HYPOCART has not been established in children.

Geriatrics

Dose titration of candesartan cilexetil is recommended before treatment with HYPOCART.

Hepatic Impairment

Dose titration of candesartan cilexetil is recommended before treatment with HYPOCART in patients with mild to moderate hepatic impairment.

HYPOCART should not be used in patients with severe hepatic impairment and/or cholestasis.

Renal Impairment

Loop diuretics are preferred to thiazides in this population. Dose titration of candesartan cilexetil is recommended before treatment with HYPOCART in patients with renal impairment whose creatinine clearance is ≥ 30 mL/min/1.73 m² BSA.

HYPOCART should not be used in patients with severe renal impairment

(creatinine clearance <30 mL/min/1.73 m² BSA).

Intravascular Volume Depletion

Patients who are severely volume and/or sodium depleted should have this corrected before being treated with HYPOCART.

OVERDOSAGE

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In two case reports of overdose (160 mg and 432 mg candesartan cilexetil) patient recovery was uneventful.

The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

Management

No specific information is available on the treatment of overdose with HYPOCART. The following measures are, however, suggested in case of overdose.

Administration of activated charcoal with or without gastric lavage. If symptomatic hypotension should occur, symptomatic 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 isotonic saline solution. Serum electrolyte and acid balance should be checked and corrected, if needed. Sympathomimetic drugs may be administered if the abovementioned measures are not sufficient.

Candesartan cannot be removed by haemodialysis. It is not known to what extent hydrochlorothiazide is removed by haemodialysis.

PRESENTATION

HYPOCART 8/12.5 mg tablets are round, biconvex, white to off-white tablets with a score line on one side and embossed CH/8 on the same side.

HYPOCART 16/12.5 mg tablets are round, biconvex, white to off-white tablets with a score line on one side and embossed CH/16 on the same side.

Both presentations are packed in blister packs of 30 or 90 tablets.

Do not halve tablets.

STORAGE CONDITIONS

Store below 25°C.

NAME AND ADDRESS OF SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand

Phone: (09) 835 0660

Fax: (09) 835 0665

MEDICINES CLASSIFICATION

Prescription only medicine

DATE OF PREPARATION

August 2011