NEW ZEALAND DATA SHEET

1 PRODUCT NAME

APO-CANDESARTAN HCTZ 16/12.5

APO-CANDESARTAN HCTZ 32/12.5

APO-CANDESARTAN HCTZ 32/25

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 16 mg or 32 mg candesartan cilexetil and 12.5 mg or 25 mg hydrochlorothiazide as the active ingredient.

Excipients with known effect

Sugars as lactose monohydrate.

For the full list of excipients see section **6.1 List of Excipients.**

3 PHARMACEUTICAL FORM

Candesartan HCTZ 16/12.5 tablets

Light pink, oval shape, biconvex, uncoated, mottled tablets debossed with ‘L3’ and ’02’ on either side of breakline on one side and break line on other side.

Candesartan HCTZ 32/12.5 mg tablet

Light yellow, oval biconvex uncoated mottled tablets debossed with 'L3' & '04' on either side of break line on one side & break line on one other side.

Candesartan HCTZ 32/25 mg tablet

Light pink, oval biconvex uncoated mottled tablets debossed with 'L3' & '04' on either side of break line on one side & break line on one other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Candesartan HCTZ is indicated for the treatment of hypertension. Treatment should not be initiated with these fixed dose combinations.

4.2 DOSE AND METHOD OF ADMINISTRATION

APO- candesartan HCTZ are intended for oral administration.

Dosage

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

The recommended dose is 1 tablet once daily. Candesartan HCTZ may be taken with or without food. The tablets should not be divided.

Candesartan HCTZ 16/12.5 may be administered in patients whose blood pressure is not optimally controlled with hydrochlorothiazide alone or candesartan 16 mg monotherapy.

Candesartan HCTZ 32/12.5 or 32/25 may be administered in patients whose blood pressure is not optimally controlled with hydrochlorothiazide alone or candesartan 32 mg monotherapy, or at a lower dose of Candesartan HCTZ. 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.

Candesartan HCTZ should not be used to initiate treatment.

Special patient populations

Paediatrics use

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

Use in the elderly

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

Hepatic Impairment

Dose titration of candesartan cilexetil is recommended before treatment with candesartan HCTZ in patients with mild to moderate chronic liver disease.

Candesartan HCTZ should not be used in patients with severe hepatic impairment and/or cholestasis (see Section **4.3 Contraindications**).

Renal Impairment

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

Candesartan HCTZ should not be used in patients with severe renal impairment (i.e. creatinine clearance < 30 mL/min/1.73 m^2 BSA).

Intravascular Volume Depletion

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

4.3 CONTRAINDICATIONS

- Hypersensitivity to any component of candesartan cilexetil, hydrochlorothiazide or to sulfonamide derived drugs
- Pregnancy and lactation (see section **4.6 Fertility, pregnancy and lactation - Use in pregnancy**).
- Severe renal impairment (creatinine clearance < 30 mL/min/1.73m^2 BSA)
- Severe hepatic impairment and/or cholestasis
- Gout
- The use of Candesartan HCTZ in combination with aliskiren-containing medicines in patients with diabetes mellitus (type I or II) or with moderate to severe renal impairment (GFR< 60 mL/min/1.73m^2).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of Candesartan HCTZ with ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see section **4.5 Interactions with other medicines and other forms of interactions**).

If dual blockade therapy is considered necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy. The use of Candesartan HCTZ with aliskiren is contraindicated in patients with diabetes mellitus (type I or II) or moderate to severe renal impairment (GFR< 60 mL/min/1.73m^2) (see section **4.3 Contraindications**).

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 or 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 adrenocorticotropic hormone (ACTH).

Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of candesartan HCTZ and ACE Inhibitors, aliskiren, potassium sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels may lead to increases in serum potassium.

Non-melanoma skin cancer

An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide exposure has been observed in two epidemiological studies based on Danish National Cancer Registry (see Section **5.1 Pharmacodynamic properties -Clinical Trials**). Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see Section **4.8 Adverse effects (Undesirable effects)**).

Kidney Transplantation

There is limited clinical experience regarding the administration of candesartan HCTZ in patients who have undergone renal 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.

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 candesartan HCTZ only minimal effects were observed. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Hypotension, volume depleted patients

Candesartan HCTZ 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 candesartan HCTZ.

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.

Choroidal effusion, Acute Myopia and Secondary Angle-Closure Glaucoma

Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Angioedema

Angioedema including swelling of the face, lips, throat, tongue and the intestines (see **Section 4.4 Special warnings and precautions for use – intestinal angioedema**) has been reported rarely in patients treated with angiotensin II receptor antagonists. Some of these patients previously experienced angioedema with other medicines, including ACE inhibitors. The risk of developing angioedema is lower for angiotensin II receptor antagonists compared to ACE inhibitors.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see **Section 4.8 Adverse effects (undesirable effects)**). As the risk of angioedema with angiotensin II receptor antagonists is lower compared to ACE inhibitors, the risk of intestinal angioedema is also presumed to be lower.

Patients with intestinal angioedema can present with non-specific gastrointestinal symptoms such as abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is suspected, the angiotensin II receptor antagonist should be discontinued, and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Use in 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 candesartan HCTZ in patients with hepatic impairment. Use in patients with severe hepatic impairment is contraindicated. Caution is advised in patients with mild to moderate hepatic impairment.

Use in renal impairment

As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with candesartan HCTZ (see section **4.3 Contraindications**). Periodic monitoring of serum potassium, creatinine and uric acid levels is recommended. Loop diuretics are preferred to thiazides in this population.

Use in the elderly

For dosage recommendations for use of candesartan HCTZ in elderly patients (please see section **4.2 Dose and method of administration**). **Section 4.4 Special warnings and precautions for use - Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics, and 5.2 Pharmacokinetic properties - Pharmacokinetics in special populations.**

Paediatric use

Safety and efficacy have not been established in children.

Effects on laboratory tests

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The antihypertensive effect of candesartan HCTZ may be enhanced by other antihypertensives.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Clinical trial data has shown that dual blockade of the RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections **4.3 Contraindications** and **4.4 Special warnings and precautions for use**).

Candesartan Cilexetil

Compounds which have been investigated include hydrochlorothiazide, warfarin, digoxin (see Hydrochlorothiazide below), oral contraceptives (i.e. ethinyloestradiol/levonorgestrel), glibenclamide and nifedipine. No pharmacokinetic interactions of clinical significance were identified in these studies.

The antihypertensive effect of angiotensin II receptor antagonists (AIIRAs), including candesartan, maybe attenuated by NSAIDs, including COX-2 inhibitors and acetylsalicylic acid.

As with ACE inhibitors, concomitant use of AIIRAs 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 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.

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, opioids and anaesthetics

Potentiation 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 candesartan HCTZ is administered with such drugs.

Calcium salts and Vitamin D

Thiazide diuretics may increase the serum calcium concentration due to decreased excretion. If calcium or Vitamin D 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. Candesartan HCTZ 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 (AIIRAs) 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-angiotensin-aldosterone system, concomitant use of candesartan HCTZ and potassium sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels (e.g. heparin sodium, trimethoprim/sulfamethoxazole) 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 adrenocorticotropic 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.

Ciclosporin

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

4.6 FERTILITY, PREGNANCY AND LACTATION

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

The use of candesartan HCTZ is contraindicated during pregnancy (see Section **4.3 Contraindications**). Patients receiving candesartan HCTZ should be made aware of that before contemplating a possibility of becoming pregnant so that they can discuss appropriate options with their treating physician. When pregnancy is diagnosed, treatment with candesartan HCTZ must be stopped immediately and if appropriate, alternative therapy should be started.

The use of drugs that act directly on the renin-angiotensin system has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Exposure to angiotensin II receptor antagonist therapy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during pregnancy may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

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 candesartan HCTZ is considered essential.

4.7 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse events were mild and transient in controlled clinical studies with various doses of candesartan cilexetil/hydrochlorothiazide (candesartan cilexetil up to 32 mg and hydrochlorothiazide up to 25 mg). The overall incidence of adverse events showed no association with age or gender. 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 ≥ 1% during treatment with candesartan cilexetil/hydrochlorothiazide up to 16/12.5 mg in double-blind placebo-controlled trials are presented in Table 1.

Table 1:

	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
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 ≥ 1% of the patients during 8-week randomised treatment with candesartan cilexetil/hydrochlorothiazide 32/12.5 mg and 32/25 mg in double-blind clinical trials are presented in Table 2.

Table 2:

	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
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 ≥ 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, intestinal angioedema and renal impairment, including renal failure in susceptible patients (see section **4.4 Special warnings and precautions for use)**. 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, choroidal effusion, acute myopia and acute angle-closure glaucoma.

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.

The following adverse reactions have been reported post-marketing with hydrochlorothiazide, regardless of causality:

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Frequency “not known”: Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma) (see **sections 4.4 Special warnings and precautions for use** and **5.1 Pharmacodynamic properties-Clinical trials**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://nzphvc.otago.nz/reporting/ and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

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 overdosage with candesartan HCTZ. The following measures are, however, suggested in case of overdosage.

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.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone 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, candesartan HCTZ 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 candesartan HCTZ, onset of the antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment.

Candesartan HCTZ 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 candesartan HCTZ.

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.

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 candesartan cilexetil/hydrochlorothiazide 32/12.5 mg and 32/25 mg combinations produced overall mean blood pressure reductions of 13/9 mmHg and 16/10 mmHg, respectively. This study also demonstrated that the 32/25 mg combination was significantly more effective than the 32/12.5 mg combination.

In two 8 week clinical studies (randomised, double-blind, placebo controlled, parallel group) including 275 and 1524 randomised patients respectively, the candesartan cilexetil/hydrochlorothiazide combinations 32/12.5 mg and 32/25 mg 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.

Non-melanoma skin cancer (NMSC):

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide (HCTZ) and NMSC has been observed. One study included a population comprised of 71,553 cases of basal cell carcinoma (BCC) and of 8,629 cases of squamous cell carcinoma (SCC) matched to 1,430,883 and 172,462 population controls, respectively. High HCTZ use (≥50,000 mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use (~25,000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100,000 mg). (see Sections **4.4 Special warnings and precautions for use** and Section **4.8 Adverse effects (Undesirable effects)**).

5.2 PHARMACOKINETIC PROPERTIES

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 Excretion

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 ^{14}C-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 candesartan HCTZ 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.

5.3 PRECLINICAL SAFETY DATA

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*.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- carmellose calcium
- maize starch
- macrogol 8000
- hyprolose
- magnesium stearate
- Pigment Blend PB-24880 Pink (16/12.5 mg and 32/25 mg tablets only) and
- iron oxide yellow in the 32/12.5 mg tablets only

The tablets are gluten free.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. See Section 4.5. Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

24 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

APO-candesartan HCTZ 16/12.5 tablets

Blister pack (Alu-Alu) of 7 and 30 tablets (AUST R 210565).

APO-candesartan HCTZ 32/12.5 mg tablet

Blister pack (Alu-Alu) of 30 tablets (AUST R 210566).

APO-candesartan HCTZ 32/25 mg tablet

Blister pack (Alu-Alu) of 7 and 30 tablets (AUST R 210567).

APO and APOTEX are registered trademarks of Apotex Inc.

Not all strengths or pack sizes may be available.

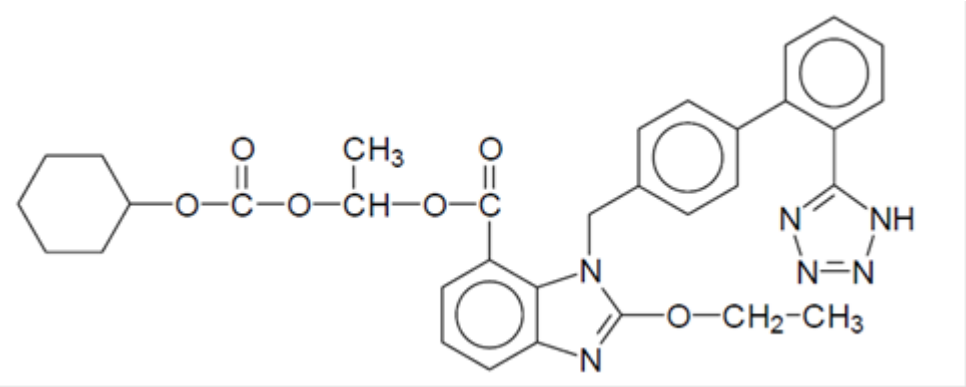
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Candesartan is a white to off white powder and is practically insoluble in water. Hydrochlorothiazide is a sulfonamide derived drug. It is a white, or almost white crystalline powder and is very slightly soluble in water.

Chemical structure - Candesartan



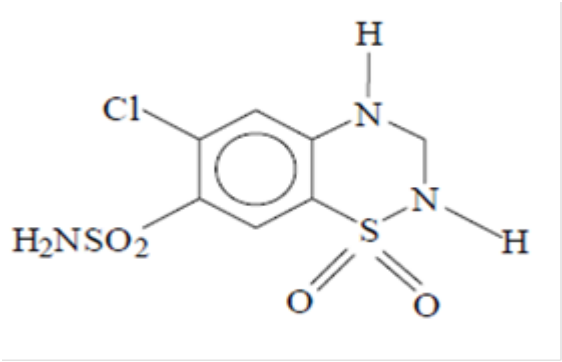
Chemical Name: (±)-1-(cyclohexyloxycarbonyl-oxy) ethyl 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl] methyl]-1H-benzimadozole-7-carboxylate

Molecular Formula: $C_{33}H_{34}N_6O_6$

Molecular Weight: 610.67

CAS number 145040-37-5

Chemical structure - Hydrochlorothiazide



Chemical Name: 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide 1, 1-dioxide.

Molecular Formula: $C_7H_8N_3S_2O_4Cl$

Molecular Weight: 297.75

CAS number 58-93-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine

8 SPONSOR

Arrotex Pharmaceuticals (NZ) Limited
C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street,
Wellington 6011, New Zealand

Phone +64 9 918 5100

9 DATE OF FIRST APPROVAL

5 September 2022

10 DATE OF REVISION OF THE TEXT

21 October 2025

Summary table of changes

Section Changed	Summary of new information
4.4	Addition of Angioedema and Intestinal angioedema sections
4.4	Addition of Intestinal angioedema
4.9	Update to National Poisons Centre information