Approved Professional Information for Medicines for Human Use:

CANURETIC

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CANURETIC

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CANURETIC:

Each tablet contains 16 mg candesartan cilexetil and

12,5 mg hydrochlorothiazide.

Contains sugar (lactose monohydrate):

182,1 mg lactose monohydrate per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CANURETIC tablets are white, elliptic biconvex tablets, marked ***CH*** and ***16*** on the same face; and are scored on both faces.

Thickness: 4.3 ± 0.2 mm

Length: 12.0 ± 0.2 mm

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CANURETIC is indicated for essential hypertension in patients stabilised on the individual components given at the same dosages.

4.2 Posology and method of administration

Posology

CANURETIC should be taken once daily and may be taken with or without food.

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

Special populations

Elderly patients

No special dosage recommendations.

Patients with impaired renal function

CANURETIC should not be used in patients with moderate to severe renal impairment (creatinine clearance ≤ 60 mL / min / 1,73 m^2 BSA).

Patients with impaired hepatic function

CANURETIC should not be used in patients with moderate to severe hepatic impairment and / or cholestasis.

Paediatric population

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

Method of administration

CANURETIC should be taken once daily and may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to irbesartan, hydrochlorothiazide or to any of the excipients listed in section 6.1.

- Moderate to severe hepatic impairment and/or cholestasis.
- Gout.
- A history of angioedema related to previous therapy with ACE-inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hereditary or idiopathic angioedema.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Moderate to severe renal function impairment (creatinine clearance < 30 mL / min).
- Bilateral renal artery stenosis.
- Renal artery stenosis in patients with a single kidney.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride.
- Porphyria.
- **CANURETIC** contains a thiazide diuretic in (fixed dose) and therefore should not be given to patients with Addison's disease, This therapy is also contraindicated in patients with severe renal impairment or anuria, and in patients who show hypersensitivity to other sulphonamide-derived medicines.
- Lithium therapy: Concomitant administration with **CANURETIC** may lead to toxic blood concentrations of lithium. (see section 4.5)
- Pregnancy and lactation. (see section 4.6)
- The concomitant use of **CANURETIC** with aliskiren-containing products is contraindicated. (see section 4.4 and 4.5)
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip (see section 4.4).

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **CANURETIC**, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (See section 4.3 and 4.6).

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 ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see Section 4.5).

ACE inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

When **CANURETIC** is used in patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end-stage renal impairment (creatinine clearance ≤ 15 mL / min / 1,73 m^2 BSA). Prolongation of INR and bleeding complications with concomitant warfarin therapy may occur.

Lithium toxicity may occur when **CANURETIC** is used in combination with lithium therapy (see section 4.5).

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma but are more likely in patients with such a history. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

Laboratory findings

Increases in serum uric acid, serum creatinine, serum urea, serum potassium, blood glucose and serum alanine transaminase (ALT) may occur. Decreases in haemoglobin and increases in serum aspartate transaminase (AST) have been observed in patients receiving **CANURETIC.**

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 (HCTZ) exposure has been observed in two epidemiological studies. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking **CANURETIC** should be informed of the risk of NMS C 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 the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

CANURETIC should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip (see section 4.3).

Renal artery stenosis

CANURETIC may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with **CANURETIC** due to blockade of the renin-angiotensin-aldosterone system. This may be severe such that additional intravenous fluids and/or vasopressors are needed.

Intravascular volume depletion

In patients with intravascular volume and/or sodium depletion, symptomatic hypotension may occur. Therefore, the use of **CANURETIC** is not recommended until this condition has been corrected.

Renal impairment / kidney transplantation

When **CANURETIC** is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid levels is recommended. Loop diuretics are preferred to **CANURETIC** in this population.

There is no experience regarding the administration of **CANURETIC** in patients with recent kidney transplantation.

Hepatic impairment

There is no experience in patients with moderate to severe hepatic impairment and/or cholestasis.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis or obstructive hypertrophic cardiomyopathy (see section 4.3)

Electrolyte imbalance

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

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

Marked hypercalcaemia may be a sign of hyperparathyroidism. **CANURETIC** should be discontinued before carrying out tests for parathyroid function.

Hydrochlorothiazide (a component of **CANURETIC**) dose-dependently increased urinary potassium excretion which may result in hypokalaemia, e.g. in liver cirrhosis, after brisk diuresis, inadequate intake of electrolytes and in patients receiving corticosteroids. Concomitant use of **CANURETIC** and

potassium-sparing diuretics, potassium supplements or salt substitutes or other medicines that may increase potassium levels (e.g. heparin sodium) may lead to increases in serum potassium.

Metabolic and endocrine effects

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

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 medicines that affect this system such as **CANURETIC** has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure as has been observed in post marketing data. Excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease may result in myocardial infarction or stroke.

Excipients: lactose intolerance

CANURETIC contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (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, 4.4 and 5.1).

No medicine interactions of clinical significance have been identified for candesartan cilexetil. Compounds which have formally been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol / levonorgestrel), glibenclamide and nifedipine.

Post marketing report suggests a rare but significant interaction with prolongation of INR and bleeding, with concomitant warfarin therapy.

The bioavailability of candesartan is not affected by food.

The antihypertensive effect of **CANURETIC** may be enhanced by other antihypertensives.

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

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and anti-arrhythmics. Periodic monitoring of serum potassium is recommended when **CANURETIC** is administered with such medicines.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with **CANURETIC**. Careful monitoring of serum lithium levels is recommended during concomitant use.

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

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect on non-depolarizing skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and dosage adjusted accordingly.

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

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

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

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

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

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.

Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required.

Hydrochlorothiazide may cause the arterial response to pressor amines (e.g. adrenaline) to decrease but not enough to exclude a pressor effect.

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

There is no clinically significant interaction between hydrochlorothiazide and food.

4.6 Pregnancy and lactation

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed **CANURETIC** should be discontinued.

Pregnancy

Medicines affecting the renin-angiotensin system, such as **CANURETIC**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
Hydrochlorothiazide can reduce the Plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.
Women of childbearing age should ensure effective contraception.

Breastfeeding

Candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breast-feeding should be discontinued if the use of **CANURETIC** is considered essential

Fertility

No data

4.7 Effects on ability to drive and use machines

The effect of **CANURETIC** on the ability to drive and use machines has not been studied. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Candesartan cilexetil

The following adverse reactions have been reported very rarely (≤ 1/10 000) with candesartan cilexetil in post-marketing experience:

Very rare: ≤ 1/10 000	Blood and lymphatic system disorders:	Leukopenia, neutropenia and agranulocytosis
	Metabolism and nutrition disorders:	Hyperkalaemia, hyponatraemia
	Hepato-biliary disorders:	Increased liver enzymes, abnormal hepatic function or hepatitis
	Skin and subcutaneous tissue disorders:	Angioedema, rash, urticaria, pruritis
	Musculoskeletal, connective tissue and bone disorders:	Back pain
	Renal and urinary disorders:	Renal impairment, including renal failure in susceptible patients

Hydrochlorothiazide:

The following adverse reactions have been reported with hydrochlorothiazide monotherapy, usually in doses of 25 mg or greater. The frequencies used are: Common (≥ 1/100), Uncommon (≥ 1/1 000 and ≤ 1/100) and Rare (≤ 1/1 000).

Common (≥ 1/100)	Metabolism and nutrition disorders:	Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia)
	Nervous system disorders:	Light-headedness, vertigo
	Renal and urinary disorders:	Glycosuria
	General disorders and administration site conditions:	Weakness
	Investigations:	Increases in cholesterol and triglycerides
Uncommon ≥ 1/1 000 and ≤ 1/100)	Vascular disorders:	Postural hypotension
	Gastrointestinal disorders:	Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation
	Skin and subcutaneous tissue disorders:	Rash, urticaria, photosensitivity reactions
	Blood and lymphatic system disorders:	Leukopenia, neutropenia/ agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
	Immune system disorders:	Anaphylactic reactions

Rare (≤ 1/1 000)	Psychiatric disorders:	Sleep disturbances, depression, restlessness
	Nervous system disorders:	Paraesthesia
	Eye disorders:	Transient blurred vision
	Cardiac disorders:	Cardiac arrhythmias
	Vascular disorders:	Necrotising angiitis (vasculitis, cutaneous vasculitis)
	Respiratory, thoracic and mediastinal disorders:	Respiratory distress (including pneumonitis and pulmonary oedema
	Gastrointestinal disorders:	Pancreatitis
	Hepato-biliary disorders:	Jaundice (intrahepatic cholestatic jaundice)
	Skin and subcutaneous tissue disorders:	Toxic epidermal necrolysis, cutaneous disorders: lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus
	Musculoskeletal and connective tissue disorders:	Muscle spasm
	Renal and urinary disorders:	Renal dysfunction and interstitial nephritis
	General disorders and administration site conditions:	Fever
	Investigations:	Increases in urea and serum creatinine

Description of Selected Adverse Reactions

Non-melanoma skin cancer: (see section 4.3 and 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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 single case reports of overdose (up to 672 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.

Treatment

No specific information is available on the treatment of overdosage with **CANURETIC**.

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

When indicated, induction of vomiting should be considered. If symptomatic hypotension should occur, symptomatic treatment should be instituted and vital signs monitored.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 7.1.3 Other hypotensives

Pharmaco-therapeutic group: Angiotensin II antagonists + diuretics,

ATC code: C09DA06

Candesartan cilexetil

Candesartan cilexetil is a prodrug. Alter oral administration it is converted to the active medicine, 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.

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 I (AT_1) receptor.

The antagonism of the AT_1 receptors results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide

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 extend. 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 cilexetil and hydrochlorothiazide

Candesartan and hydrochlorothiazide have additive antihypertensive effects.
In hypertensive patients, **CANURETIC** results in a dose-dependent and sustained reduction in arterial blood pressure without 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 **CANURETIC**, onset of the antihypertensive effect generally

begins within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within 4 weeks and is sustained during long-term treatment.

5.2 Pharmacokinetic properties

Concomitant administration of candesartan cilexetil and hydrochlorothiazide has no clinically significant effect on the pharmacokinetics of either medicine product.

Absorption and distribution

Candesartan cilexetil

Following oral administration, candesartan cilexetil is converted to the active medicine candesartan. The mean peak serum concentration (C_{MAX}) is reached 3 - 4 hours following tablet intake. No gender-related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 99 %). The apparent volume of distribution 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.

Biotransformation

Candesartan cilexetil

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extend eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in vitro* data, no interaction would be expected to occur *in vivo* with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life ($T_{½}$) of candesartan is approximately 9 hours. There is no accumulation following multiple doses. The half-life of candesartan remains unchanged (approximately 9 hours) 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. Following an oral dose of ^{14}C-labelled candesartan cilexetil, the active candesartan, and its inactive metabolites are excreted via the urine (30 %) and to a larger extend (70 %) via the faeces.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged compound by glomerular filtration and active tabular secretion. The terminal $t_{½}$ 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 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Special population

Candesartan cilexetil

In patients with mild (Ccr 60-90 mL/min) and moderate (Ccr 30-60 mL/min) to severe (Ccr 15-30 mL/min) renal impairment, C_{MAX} and AUC of candesartan increased during repeated

dosing. In patients with mild to moderate renal impairment AUC was approximately doubled, while in severe renal impairment the AUC was further increased. The terminal $t_{½}$ of candesartan in patients with severe renal impairment was approximately doubled compared to patients with normal renal function. Candesartan has not been studied in patients with more severe renal failure (Ccr ≤ 15 mL/min).

Candesartan is not eliminated by haemodialysis in severe renal impairment.

In patients with mild hepatic impairment, there was an increase in the AUC of candesartan, of approximately 30 %. In patients with moderate hepatic impairment, the increase in the AUC of candesartan was approximately 145 %.

In elderly subjects (over 65 years), C_{MAX} and AUC of candesartan are increased by approximately 50 % and 80 %, respectively in comparison to young adults.

Hydrochlorothiazide

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

5.3 Preclinical safety data

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium carmellose

Hydroxypropyl cellulose (viscosity type 10)

Magnesium stearate

Pre-gelatinized maize starch

Sodium docusate

Sodium lauryl sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 Months

6.4 Special precautions for storage

Store at or below 25 ºC.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC / PVDC aluminium blister packages of 28 or 30 tablets in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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2193

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8. REGISTRATION NUMBER

49/7.1.3/0054

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04 August 2022

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02 February 2023