Front Side

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

RANEPRES PLUS 16/12.5 mg
RANEPRES PLUS 32/12.5 mg
RANEPRES PLUS 32/25 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RANEPRES PLUS 16/12.5 mg Tablets
Each tablet contains Candesartan cilexetil 16mg and hydrochlorothiazide 12.5 mg
RANEPRES PLUS 16/12.5 mg contains sugar (lactose monohydrate 65.00 mg)
RANEPRES PLUS 32/12.5 mg Tablets
Each tablet contains Candesartan cilexetil 32 mg and hydrochlorothiazide 12.5 mg
RANEPRES PLUS 32/12.5 mg contains sugar (lactose monohydrate 142.70 mg)
RANEPRES PLUS 32/25 mg Tablets
Each tablet contains Candesartan cilexetil 32 mg and hydrochlorothiazide 25 mg
RANEPRES PLUS 32/25 mg contains sugar (lactose monohydrate 130.00 mg)

Excipients:
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets.
RANEPRES PLUS 16/12.5 mg:
Pink, oval, biconvex, uncoated tablets, debossed with “ML 71” on one side and breakline on both sides.
RANEPRES PLUS 32/12.5 mg:
Yellow, oval, biconvex, uncoated tablets, debossed with "ML 58" on one side and breakline on both sides.
RANEPRES PLUS 32/25 mg:
Pink, oval, biconvex, uncoated tablets, debossed with "ML 57" on one side and breakline on both sides.
The score line of **RANEPRES PLUS 16/12.5 mg, 32/12.5 mg** and **32/25 mg** is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
RANEPRES PLUS 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:
RANEPRES PLUS 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.
Use in the elderly:
No special dosage recommendations.
Use in impaired renal function:
RANEPRES PLUS should not be used in patients with severe renal impairment (creatinine clearance ≤30 ml/min/) (see section 4.3).
Use in impaired hepatic function:
RANEPRES PLUS should not be used in patients with moderate to severe hepatic impairment and/or cholestasis.
Use in children:
The safety and efficacy of **RANEPRES PLUS** have not been established in children.
Method of administration:
Oral use.
RANEPRES PLUS should be taken once daily with or without food.

4.3 Contraindications
- Hypersensitivity to candesartan cilexetil, hydrochlorothiazide or 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)
- 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
- **RANEPRES PLUS** contains a thiazide diuretic in (fixed close) 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 **RANEPRES PLUS** may lead to toxic blood concentrations of lithium (see section 4.5)
- Pregnancy and lactation (see section 4.6).
- The concomitant use of **RANEPRES PLUS** with aliskiren-containing products is contraindication (see section 4.4 & 4.5)
- Concomitant use of fluoroquinolones with ACE inhibitors/ Renin-Angiotensin blockers is contraindicated in patients with moderate to severe renal impairment.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving **RANEPRES PLUS**, 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 angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of **RANEPRES PLUS** and aliskiren is therefore contraindicated (see section 4.3).
RANEPRES PLUS should not be used concomitantly with aliskiren (see section 4.3).

Concomitant use of fluoroquinolones
Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) whether used separately and/or concomitantly.

Warfarin interaction:
Prolongation of INR and bleeding complications with concomitant warfarin therapy may occur.
Lithium toxicity:
Lithium toxicity may occur when **RANEPRES PLUS** is used in combination with lithium therapy (see sections 4.3 and 4.5).

Renal artery stenosis:
RANEPRES PLUS may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. **RANEPRES PLUS** is contraindicated in these conditions (see section 4.3)

Anaesthesia and surgery:
Hypotension may occur during anaesthesia and surgery in patients treated with **RANEPRES PLUS** 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 **RANEPRES PLUS** is not recommended until this condition has been corrected.

Renal impairment/kidney transplantation:
When **RANEPRES PLUS** 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 **RANEPRES PLUS** in this population.
There is no experience regarding the administration of **RANEPRES PLUS** in patients with recent kidney transplantation.
RANEPRES PLUS is contraindicated in patients with severe renal function impairment (creatinine clearance less than 30 ml/min) (see section 4.3)
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.
RANEPRES PLUS can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis).
Marked hypercalcaemia may be a sign of hyperparathyroidism. **RANEPRES PLUS** should be discontinued before carrying out tests for parathyroid function.
Hydrochlorothiazide (a component of **RANEPRES PLUS**) dose -dependently increases 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 **RANEPRES PLUS** 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 **RANEPRES PLUS** 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 **RANEPRES PLUS** 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 **RANEPRES PLUS** 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 oratherosclerotic cerebrovascular disease may result in a myocardial infarction or stroke.

Lactose intolerance:
RANEPRES PLUS 16/12,5 mg contains 65 mg lactose.
RANEPRES PLUS 32/12,5 mg contains 142,70 mg lactose.
RANEPRES PLUS 32/25 mg contains 130 mg lactose.
Lactose is a source of glucose and galactose. If you have one of the rare genetic disorders galactosaemia, or glucose-galactose intolerance or congenital lactase deficiency you must talk to your doctor or pharmacist before taking this medicine.

4.5 Interaction with other medicines and other forms of interaction
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 **RANEPRES PLUS** 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 diuretic, 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-dysrhythmics. Periodic monitoring of serum potassium is recommended when **RANEPRES PLUS** is administered with such medicines.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with **RANEPRES PLUS**. Concomitant use of these medicines is contraindicated (see section 4.3).
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 medicines(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 steroid soradrenocorticotropic 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 medicines, 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 high doses of iodinated contrast media.
There is no clinically significant interaction between hydrochlorothiazide and food.
Dual blockade of the RAAS with ARBs, ACE inhibitors, or aliskiren 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 (see section 4.3 and 4.4).

Concomitant use of fluoroquinolones:
Concomitant use of fluoroquinolones and Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

4.6 Fertility, pregnancy and lactation
Use in pregnancy:
RANEPRES PLUS is contraindicated in pregnancy (see section 4.3).
Should a woman become pregnant while receiving **RANEPRES PLUS** the treatment must be stopped promptly and switched to a different medicine. Should a woman contemplate pregnancy, the doctor should institute alternative medication.
When used in pregnancy during the second and third trimesters, medicines that act directly on the renin-angiotensin system can cause embryonal toxicity, foetal and neonatal injury and death. These medicines pass through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms. Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration in the second and third trim-ester. Cases of defective skull ossification have been observed. Premature and low birth mass can occur.
Women of childbearing age should ensure effective contraception.
Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.
Lactation:
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 **RANEPRES PLUS** is considered essential (see section 4.3).

4.7 Effects on ability to drive and use machines
The effect of **RANEPRES PLUS** 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
The following adverse reactions have been reported in association with the candesartan cilexetil/hydrochlorothiazide combination as contained in **RANEPRES PLUS**:
The overall incidence of adverse events showed no association with dose, age or gender.

System Organ Class	Frequency	Undesirable Effect
Infections and infestations:	Frequent	Nasopharyngitis
Blood and lymphatic system disorders	Less frequent	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders:	Frequent	Dyslipidaemia
	Less frequent	Hyperkalaemia, hyponatraemia
Nervous System	Frequent	Headache, Dizziness
Cardiovascular	Frequent	Tachycardia
Respiratory, thoracic and mediastinal disorders	Frequent	Respiratory infection, Bronchitis, Pharyngitis, sinusitis. Cough
Gastrointestinal	Frequent	Nausea
	Less frequent	Abdominal pain
Hepato-biliary disorders:	Less frequent	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorder	Less frequent	Angioedema, rash, urticaria, pruritus
Musculo-skeletal, connective tissue and bone disorder	Less frequent	Back pain
Renal and urinary disorders:	Less frequent	Renal impairment, including renal failure in susceptible patients
General disorders and administration site conditions	Frequent	Fatigue
Other	Frequent	Influenza-like symptoms, Urinary tract infection, Inflicted injury

Candesartan cilexetil as monotherapy:

System Organ Class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Less frequent	Leukopenia, neutropenia and agranulocytosis
Metabolism and nutrition disorders:	Less frequent	Hyperkalaemia, hyponatraemia
Hepato-biliary disorders:	Less frequent	Increased liver enzymes, abnormal hepatic function or hepatitis
Skin and subcutaneous tissue disorder	Less frequent	Angioedema, rash, urticaria, pruritis
Musculo-skeletal, connective tissue and bone disorder	Less frequent	Back pain
Renal and urinary disorders:	Less frequent	Renal impairment, including renal failure in susceptible patients

Hydrochlorothiazide as monotherapy:

System organ class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Less frequent	Leukopenia, neutropenia/ agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia.
		Decreases in haemoglobin, increases in serum aspartate transaminase (AST) and serum alanine transaminase (ALT)
Immune system disorders	Less frequent	Anaphylactic reaction
Metabolism and nutrition disorders	Frequent	hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hypokalaemia, hyponatraemia)
Psychiatric disorders	Less frequent	Sleep disturbances, depression, restlessness
Nervous system disorders	Frequent	Light-headedness, vertigo
	Less frequent	Paraesthesia
Eye disorders	Less frequent	Transient blurred vision
Cardiac disorders	Less frequent	Cardiac dysrhythmias
Vascular disorders	Less frequent	Postural hypotension Necrotising angitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratory distress including pneumonitis and pulmonary oedema.
Gastrointestinal disorders	Less frequent	Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation. Pancreatitis
Hepato-biliary disorders	Less frequent	Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders	Less frequent	Rash, urticaria, photosensitivity reaction. Toxic epidermal necrolysis, cutaneous lupus erythematous-like reactions, reactivation of cutaneous lupus erythematous.
Musculoskeletal and connective tissue disorders	Less frequent	Muscle spasm.
Renal and urinary disorders	Frequent	Glycosuria
	Less frequent	Renal dysfunction and interstitial nephritis
General disorders and administration site conditions	Frequent	Weakness
	Less frequent	Fever
Investigations	Frequent	Increase in cholesterol and triglycerides
	Less frequent	Increases in urea and serum creatinine

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions 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.
Management:
No specific information is available on the treatment of overdosage with **RANEPRES PLUS**.
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

Category and class: A7.1.3 Other hypotensives.
Angiotensin II receptor blockers (ARBs) and diuretics, candesartan and diuretics
ATC code: C09DA06

5.1 Pharmacodynamic properties
Pharmacodynamic properties:
Candesartan cilexetil:
Candesartan cilexetil is a prodrug. After 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- 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 rennin 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 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 cilexetil and hydrochlorothiazide:
Candesartan and hydrochlorothiazide have additive antihypertensive effects.
In hypertensive patients, **RANEPRES PLUS** 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 **RANEPRES PLUS**, 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
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 litres/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 litres/kg.

Biotransformationand elimination:
Candesartan cilexetil
Candesartan is mainly eliminated unchanged via urine and bile and only to a minorex tent 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 CYP_1A_2, CYP_2A_6, CYP_2C_8, CYP_2C_{19}, CYP_2D_6, CYP_2E, or CYP_3A_4. The terminal half- life ($t_{1/2}$) 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 extent (70 %) via the faeces.
Hydrochlorothiazide:
Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged compound by glomerular filtration and active tubular secretion. The terminal $t_{1/2}$, of hydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral close 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.
Pharmacokinetics in special populations:
Candesartan cilexetil:
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.
In patients with mild (Ccr 60 -90 ml/min) and moderate (Ccr 30-60 ml/min) to severe (Ccr 15-30 ml/m in) 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 $t_{1/2}$ 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 %.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
RANEPRES PLUS 16/12.5 mg and 32/25 mg: Corn starch, carboxymethylcellulose calcium, glycerin/glycerol, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, red ferric oxide, yellow ferric oxide.
RANEPRES PLUS 32/12.5 mg: Corn starch, carboxymethylcellulose calcium, glycerin/glycerol, hydroxy propyl cellulose, lactose monohydrate, magnesium stearate, yellow ferric oxide.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months from the manufacturing date.

6.4 Special precautions for storage
Store at or below 25 °C.
Protect from light and moisture.
Keep the blisters in the carton until required for use.
Keep the HDPE container tightly closed.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container
1) Blister Pack:
Tablets are packed in clear film PVC/PVdC 250 µm/90 with 90 gsm PVDC as the forming material and 25 µm aluminium foil with 6-8 gsm heat seal lacquer as the lidding material, packed in pre-printed carton.
Pack size includes 28 tablets.
2) HDPE container pack:
Tablets are packed in round, white 40 ml or 60 ml HDPE container with 33-400 mm neck finish which are closed with 33 mm child resistant closure with pulp and heat seal liner and packed in outer carton.
Pack size includes 90 tablets.
Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Macleods Pharmaceuticals SA (Pty) Ltd
Office block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext. 12,
Alberton, South Africa.

8. REGISTRATION NUMBER(S)

RANEPRES PLUS 16/12.5 mg: 48/7.1.3/0514
RANEPRES PLUS 32/12.5 mg: 48/7.1.3/0515
RANEPRES PLUS 32/25 mg: 48/7.1.3/0516

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 FEBRUARY 2022

10. DATE OF REVISION OF THE TEXT

--

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS S3

RANEPRES PLUS 16/12.5 mg TABLETS
Candesartan cilexetil 16 mg and Hydrochlorothiazide 12.5 mg
Contains sugar (Lactose monohydrate 65.00 mg)
RANEPRES PLUS 32/12.5 mg TABLETS
Candesartan cilexetil 32 mg and Hydrochlorothiazide 12.5 mg
Contains sugar (Lactose monohydrate 142.70 mg)
RANEPRES PLUS 32/25 mg TABLETS
Candesartan cilexetil 32 mg and Hydrochlorothiazide 25 mg
Contains sugar (Lactose monohydrate 130 mg)

Read all of this leaflet carefully before you start taking RANEPRES PLUS
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care provider.
- **RANEPRES PLUS** have been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet?

1. What **RANEPRES PLUS** is and what it is used for
2. What you need to know before you take **RANEPRES PLUS**
3. How to take **RANEPRES PLUS**
4. Possible side effects
5. How to store **RANEPRES PLUS**
6. Contents of the pack and other information

1. What RANEPRES PLUS is and what it is used for

RANEPRES PLUS is a combination of two medicines candesartan cilexetil and hydrochlorothiazide and is used for the treatment of high blood pressure. Your doctor will usually prescribe **RANEPRES PLUS** once your blood pressure has been stabilised with candesartan and hydrochlorothiazide given as separate medicines.
Your doctor measured your blood pressure and found it to be above the normal range for your age. High blood pressure, if not treated, can damage blood vessels in several organs such as the heart, kidney, the brain and the eyes. In some instances this may lead to heart attacks, heart failure or kidney failure, strokes or blindness. There are usually no symptoms of high blood pressure before damage occurs. Thus measurement of blood pressure is necessary to verify if it is in the normal ranges or not.
High blood pressure can be treated and controlled with medicines such as **RANEPRES PLUS**. Your doctor may have also recommended that you adjust your lifestyle to help to lower your high blood pressure (losing weight, avoiding smoking, reducing alcohol consumption and restricting amount of salt in diet). They may also have encouraged the practice of regular, mild (not strenuous) exercise such as walking and swimming.

2. What you need to know before you take RANEPRES PLUS

Do not take RANEPRES PLUS:
- If you are hypersensitive (allergic) to candesartan or hydrochlorothiazide or any of the ingredients (see “What **RANEPRES PLUS** contains”) or to other sulphonamide derived medicines (hydrochlorothiazide is a sulphonamide derived medicine).
- If you have a history of angioedema (swelling of the throat causing airway obstruction and difficulty breathing as well swelling of the face, lips, tongue) related to previous therapy with high blood pressure medication known as ACE inhibitors or angiotensin receptor blockers or if you have inherited or idiopathic (unknown cause) type angioedema.
- If you have been diagnosed with thickening of the heart muscles.
- If you have kidney disease and have difficulty in producing urine.
- If you have been diagnosed with the narrowing of the arteries in your kidneys.
- If you have been diagnosed with narrowing of the aortic valve in the heart.
- If you are taking medicines (water tablets) such as spironolactone, triamterene, amiloride which increase the amount of potassium in the blood.
- If you have porphyria (a group of rare inherited blood disorders).
- If you have Addison's disease (an uncommon disorder that occurs when your body does not produce enough cortisol, a hormone) you should not take medicines called thiazide diuretics with **RANEPRES PLUS**.
- If you are taking medicines containing lithium.
- If you are or think you may be pregnant, if you are planning to become pregnant, or if you are breastfeeding.
- If you know that you have low levels of potassium or sodium in your blood.
- If you know that you have high levels of calcium in your blood.
- If you know that you have high levels of uric acid in your blood or are experiencing symptoms of gout.
- If you have impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.
- If you have kidney damage and/or taking antibiotic medicines that belong to the class “Fluoroquinolones”(see section Other medicines and **RANEPRES PLUS**)
- **RANEPRES PLUS** should not be given to children.

Warnings and precautions
Take special care with **RANEPRES PLUS**:
There are certain conditions which you may have or have had which require special care before or

RANEPRES PLUS
16/12.5 mg
32/12.5 mg
32/25 mg
PM04001701

400 mm

435 mm

Back Side

while taking **RANEPRES PLUS**. Therefore before taking the medicine you should have told your doctor if you suffer from:

- Excessive vomiting or diarrhoea.
- Kidney problems or have a kidney transplant.
- Before surgery and anaesthesia (even at the dentist's office), tell the doctor or dentist that you are taking **RANEPRES PLUS**, as there may be sudden fall in blood pressure associated with the anaesthesia.
- Heart problems.
- Liver problems.
- High potassium levels in your blood or you use potassium-containing salt substitutes.
- Raised aldosterone levels (you may experience retaining water, increased blood pressure and weakness).
- If you currently taking a medicine that belongs to a group called angiotensin converting enzyme inhibitors (also known as ACE inhibitors). This includes medicines such as captopril, enalapril and perindopril.
- Have high cholesterol or blood fat levels.
- Have systemic lupus erythematosus
- Signs such as excessive thirst, a dry mouth, unusual tiredness or weakness, drowsiness, muscle cramps or pain or abnormally fast beating of the heart.
- If you are taking warfarin (medicine to thin the blood)
- Have diabetes or if you suffer from lactose intolerance.
- If you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren, an ACE inhibitor (e.g. enalapril, lisinopril, ramipril)
- Inform your doctor immediately if you are taking any antibiotic medicines which belong to the group "Fluoroquinolones" e.g. levofloxacin, moxifloxacin, ciprofloxacin). Use of ACE inhibitors / renin-angiotensin receptor blockers, including **RANEPRES PLUS**, together with fluoroquinolones can cause damage to your kidneys.

Other medicines and RANEPRES PLUS
Always tell your healthcare provider if you are taking any other medicine. (This includes complementary or traditional medicines.)
The use of **RANEPRES PLUS** with these medicines may cause undesirable interactions. Please consult your doctor, pharmacist or other healthcare professional for advice.
You should tell your doctor if you are taking the following medicines before starting **RANEPRES PLUS**

- Other medicines used to reduce blood pressure.
- Medicines containing lithium (used for some types of psychiatric illnesses).
- Certain type of pain killers called non-steroidal anti-inflammatory medicines (NSAIDs) including aspirin, ibuprofen, diclofenac and COX-2 inhibitors such as celecoxib.
- Medicines that increase the amount of potassium in your blood. These include potassium supplements or salt substitutes containing potassium.
- Potassium-sparing medicines (e.g. spironolactone triamterene, amiloride), laxatives (e.g. castor oil), corticosteroids (e.g. prednisone), ACTH (a hormone), amphotericin (an antifungal medicine), carbenoxolone (used to treat mouth ulcers), penicillin (an antibiotic), salicylic acid and heparin.
- Other medicines such as digoxin, beta-blockers, diazoxide, atropine (for the heart), alcohol, barbiturates (used as a sedative), narcotics (pain killers), antidiabetic medicines (oral and insulin), cholestyramine and colestipol resins (to lower cholesterol levels), noradrenaline (to treat low blood pressure), muscle relaxants, allopurinol (for gout), calcium and vitamin D supplements, biperiden (for Parkinson's), amantadine (antiviral and Parkinson's), certain cancer medicines, methyldopa (treatment of high blood pressure) and cyclosporine (immunosuppressant)
- Blood pressure lowering medicine containing aliskiren, an ACE inhibitor (e.g. enalapril, lisinopril, ramipril).
- Medicines used to treat infections (antibiotic medicines) which belong to the group fluoroquinolones (e.g. levofloxacin, moxifloxacin, ciprofloxacin)

RANEPRES PLUS with food and drink:
RANEPRES PLUS can be taken with or without food.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before taking this medicine.
RANEPRES PLUS should not be used during pregnancy or if you are breastfeeding (see "Before you take **RANEPRES PLUS**").

Driving and using machines
Some people may feel tired and dizzy while taking **RANEPRES PLUS**. Caution is advised when operating hazardous machinery, including motor vehicles. It is not always possible to predict to what extent **RANEPRES PLUS** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **RANEPRES PLUS** affects them.

RANEPRES PLUS contains
Lactose: Patients with the rare hereditary conditions of lactose or galactose intolerance should not take **RANEPRES PLUS**.

3. How to take RANEPRES PLUS

- Do not share medicines prescribed for you with any other person.
- Always take **RANEPRES PLUS** exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual dose in adults is:
The usual dose is one tablet per day. Your doctor may increase this dose depending on the blood pressure response. The maximal blood pressure lowering effect should be reached 4 weeks after beginning treatment.
In some patients, such as those with liver problems, kidney problems or those who recently have lost body fluids, e.g., through vomiting or diarrhoea or by using water tablets, the doctor may prescribe a lower starting dose.
RANEPRES PLUS can be taken with or without food.
The tablets should be swallowed with a glass of water. You should try to take your daily dose at about the same time each day.
Your doctor will tell you how long your treatment with **RANEPRES PLUS** will last. Do not stop treatment early. If you have the impression that the effect of **RANEPRES PLUS** is too strong or too weak, tell your doctor or pharmacist.
If you take more RANEPRES PLUS than you should
If you take more than the recommended number of tablets, you are likely to feel light-headed and dizzy.
In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison control centre.

If you forget to take RANEPRES PLUS
Take **RANEPRES PLUS** as prescribed by doctor.
If you forget to take a dose, take it as soon as you remember, and then continue as before.
Do not take a double dose to make up for forgotten individual doses.

If you stop taking RANEPRES PLUS
If you stop taking **RANEPRES PLUS**, your blood pressure may increase again. Therefore do not stop taking **RANEPRES PLUS** without first talking to your doctor.

4. Possible side effects

RANEPRES PLUS can have side effects.
Not all the side effects reported for **RANEPRES PLUS** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **RANEPRES PLUS**, please consult your healthcare provider for advice.
If any of the following happens, stop taking RANEPRES PLUS and tell your doctor immediately or go to the casualty department at your nearest hospital
Symptoms of a severe allergic reaction such as:

- Swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing
- Rash, allergic skin reaction or itching.
- Yellowing of the skin and eyes, also called jaundice.

These are all very serious side effects. If you have them, you may have had a serious reaction to RANEPRES PLUS. You may need urgent medical attention or hospitalization.
Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following side effects:

- Angioedema (swelling in face, tongue, larynx, abdomen or arms and legs), rash, urticaria (hives), pruritus (itching).
- Anaphylactic reaction

Other side effects
Frequent side effects:

- Nasopharyngitis (inflammation of pharynx and nasal cavities)
- Dyslipidaemia (abnormal amounts of lipids e.g. triglycerides, cholesterol or fat phospholipids in the blood)
- Headache, Dizziness, vertigo
- Tachycardia (rapid heartbeats)
- Respiratory infection, Bronchitis, Pharyngitis (sore throat), sinusitis (inflammation of air cavities within passages of the nose), Cough
- Nausea
- Fatigue (weakness)
- Influenza-like symptoms, Urinary tract infection, Inflicted injury.
- Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hypokalaemia, hyponatraemia)
- Glycosuria (excretion of glucose into urine)

Less frequent side effects:

- Leukopenia, neutropenia and agranulocytosis (lowered white blood cells count)
- Hyperkalaemia (elevated potassium concentration in the blood), hyponatraemia (low sodium concentration in blood).
- Abdominal pain
- Increased liver enzymes, abnormal hepatic function or hepatitis
- Back pain
- Renal impairment, including renal failure (loss of kidney function) in susceptible patients, interstitial nephritis
- Thrombocytopaenia, aplastic anaemia, bone marrow depression, haemolytic anaemia.
- Decreases in haemoglobin, increases in serum aspartate transaminase (AST) and serum alanine transaminase (ALT)
- Sleep disturbances, depression, restlessness.
- Paraesthesia (burning and prickling sensation)
- Transient blurred vision
- Cardiac dysrhythmias
- Postural Hypotension (low blood pressure), Necrotising angitis (vasculitis, cutaneous vasculitis)
- Respiratory distress including pneumonitis and pulmonary oedema.
- Anorexia (loss of appetite), gastric irritation, diarrhoea, constipation, Pancreatitis.
- Jaundice (intrahepatic cholestatic jaundice)
- Photosensitivity reaction, Toxic epidermal necrolysis, cutaneous lupus erythematous-like reactions (autoimmune disease affecting the skin), reactivation of cutaneous lupus erythematous.
- Muscle spasm.
- Fever
- Increases in urea and serum creatinine

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects 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. By reporting side effects, you can help provide more information on the safety of **RANEPRES PLUS.**

5. How to store RANEPRES PLUS

Store at or below 25 °C.
Store in the original package.
Keep the blisters and bottle in the carton until required for use.
Store all medicines out of reach of children
Protect from light and moisture.
Do not store in a bathroom.
Do not use after the expiry date stated on the blister / label / carton.
Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of pack and other information

What RANEPRES PLUS contains
RANEPRES PLUS 16/12.5 mg Tablets
The active substances are Candesartan cilexetil 16 mg and Hydrochlorothiazide 12.5 mg
RANEPRES PLUS 32/12.5 mg Tablets
The active substances are Candesartan cilexetil 32 mg and Hydrochlorothiazide 12.5 mg
RANEPRES PLUS 32/25 mg Tablets
The active substances are Candesartan cilexetil 32 mg and Hydrochlorothiazide 25 mg

The other ingredients in **RANEPRES PLUS 16/12.5 mg** and **32/25** mg are Corn starch, carboxymethylcellulose calcium, glycerin/glycerol, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, red ferric oxide, yellow ferric oxide.
The other ingredients in **RANEPRES PLUS 32/12.5 mg** are Corn starch, carboxymethylcellulose calcium, glycerin/glycerol, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, yellow ferric oxide.

What RANEPRES PLUS looks like and contents of the pack
RANEPRES PLUS 16/12.5 mg:
Pink, oval, biconvex, uncoated tablets, debossed with "ML 71" on one side and breakline on both sides.
RANEPRES PLUS 32/12.5 mg:
Yellow, oval, biconvex, uncoated tablets, debossed with "ML 58" on one side and breakline on both sides.
RANEPRES PLUS 32/25 mg:
Pink, oval, biconvex, uncoated tablets, debossed with "ML 57" on one side and breakline on both sides.
The score line of **RANEPRES PLUS 16/12.5 mg, 32/12.5 mg** and **32/25 mg** is only to facilitate breaking for ease of swallowing and not to divide into equal doses.
Blister Pack:
Tablets are packed in clear film PVC/PVdC 250 µm/90 with 90 gsm PVdC as the forming material and 25 µm aluminium foil with 6-8 gsm heat seal lacquer as the lidding material, packed in pre-printed carton.
Pack size include 14 or 28 tablets.
HDPE container pack:
Tablets are packed in round, white 40 ml or 60 ml HDPE container with 33-400 mm neck finish which are closed with 33 mm child resistant closure with pulp and heat seal liner and packed in outer carton.
Pack size includes 90 tablets.
Not all packs and pack sizes are necessarily marketed

Holder of Certificate of Registration and Manufacturer
MACLEODS PHARMACEUTICALS SA (PTY) LTD
Office block 1, Bassonia Estate Office Park (East),
1 Cussonia Drive, Bassonia Rock, Ext. 12,
Alberton, South Africa.

This leaflet was last revised in
28 FEBRUARY 2022

Registration number
RANEPRES PLUS 16/12.5 mg: 48/7.1.3/0514
RANEPRES PLUS 32/12.5 mg: 48/7.1.3/0515
RANEPRES PLUS 32/25 mg: 48/7.1.3/0516

Access to the corresponding Professional Information
The corresponding professional information can be accessed at https://www.macleodspharma.com or email macleodsrsa@macleodspharma.com or contact 011 682 1169.

PASIËNTINLIGTINGSTUK

SKEDULERINGSTATUS: S3

RANEPRES PLUS 16/12.5 mg TABLETTE
Kandesartan silieksetil 16 mg en 12,5 mg Hidrochloortiasied
Bevat suiker (65,00 mg Laktosemonohidraat)
RANEPRES PLUS 32/12.5 mg TABLETTE
Kandesartan silieksetil 32 mg en 12,5 mg Hidrochloortiasied
Bevat suiker (142,70 mg Laktosemonohidraat)
RANEPRES PLUS 32/25 mg TABLETTE
Kandesartan silieksetil 32 mg en 25 mg Hidrochloortiasied
Bevat suiker (130 mg Laktosemonohidraat)

Lees hierdie hele inligtingstuk sorgvuldig deur voordat jy RANEPRES PLUS begin neem

- Hou hierdie inligtingstuk. Dit mag nodig wees dat jy dit weer moet lees.
- Vra assblief jou dokter, apteker, verpleegkundige of ander gesondheidsorgverskaffer indien jy verdere vrae het.
- **RANEPRES PLUS** is vir jou persoonlik voorgeskryf, en jy moet nie jou medisyne met ander persone deel nie. Dit mag skadelik vir hulle wees, selfs al is hul simptome dieselfde as joune.

Wat in hierdie inligtingstuk is
1. Wat **RANEPRES PLUS** is en waarvoor dit gebruik word
2. Wat jy behoort te weet voordat jy **RANEPRES PLUS** neem
3. Hoe om **RANEPRES PLUS** te neem
4. Moontlike newe-effekte
5. Hoe om **RANEPRES PLUS** te bewaar
6. Inhoud van die pak en ander inligting

1. Wat RANEPRES PLUS is en waarvoor dit gebruik word

RANEPRES PLUS is 'n kombinasie van twee medisyne kandesartan silieksetil en hidrochloortiasied en word gebruik vir die behandeling van hoë bloeddruk. Jou dokter sal gewoonlik **RANEPRES PLUS** voorskryf sodra jou bloeddruk gestabiliseer het met kandesartan en hidrochloortiasied wat as aparte medisyne gegee is.
Jou dokter het jou bloeddruk gemeet en gevind dat dit bo die normale reikwydte vir jou ouderdom is. Hoë bloeddruk, indien dit nie behandel word nie, kan bloedvate in verskeie organe soos bv. die hart, nier, die brein en die oë beskadig. In sommige gevalle kan dit lei tot hartaanvalle, hartversaking of nierversaking, beroertes of blindheid. Daar is gewoonlik geen simptome van hoë bloeddruk voordat skade voorkom nie. Meting van bloeddruk is dus nodig om te verifieer of dit binne die normale reeks is of nie.
Hoë bloeddruk kan behandel en beheer word met medisyne soos **RANEPRES PLUS**. Jou dokter het moontlik ook aanbeveel dat jy jou leefstyl moet aanpas om te help om jou hoë bloeddruk te verlaag (gewig te verloor, rook te vermy, alkoholverbruik te verminder en die hoeveelheid sout in jou dieet te beperk). Hulle het moontlik ook die beoefening van gereelde, ligte (nie strawwe) oefening soos stap en swem aangemoedig.

2. Wat jy behoort te weet voordat jy RANEPRES PLUS neem

Moet nie RANEPRES PLUS neem nie:

- Indien jy hipersensitief (allergies) is vir kandesartan of hidrochloortiasied of enige van die bestanddele (sien "Wat **RANEPRES PLUS** bevat") of vir ander sulfoonamied afkomstige medisyne (hidrochloortiasied is 'n sulfoonamied afkomstige middel).
- Indien jy 'n geskiedenis van angioëdeem het (swelling van die keel wat lugwegobstruksie en moeilike asemhaling veroorsaak, sowel as swelling van die gesig, lippe, tong) wat verband hou met vorige behandeling met hoë bloeddruk medikasie bekend as AOE inhibeerders of angiotensien reseptorblokkeerders, of indien jy oorerflike of idiopatiese (onbekende oorsaak) tipe angioëdeem het.
- Indien jy gediagnoseer is met verdikking van die hartspiere.
- Indien jy 'n niersiekte het en sukkel om uriene te produseer.
- Indien jy gediagnoseer is met die vernouing van die arterieë in jou niere.
- Indien jy gediagnoseer is met vernouing van die aortaklep in die hart.
- Indien jy medisyne neem (water tablette) soos bv. spironolaktoon, triamtereen, amiloried wat die hoeveelheid kalium in die bloed verhoog.
- Indien jy porfirie het ('n groep seldsame oorgeërfde bloedafwykings).
- Indien jy Addison se siekte het ('n seldsame afwyking wat voorkom wanneer jou liggaam nie genoeg kortisol, 'n hormoon, produseer nie) moet jy nie medisyne wat tiasieddiuretika genoem word saam met **RANEPRES PLUS** neem nie.
- Indien jy medisyne gebruik wat litium bevat.
- Indien jy swanger is of vermoed dat jy dalk swanger kan wees, indien jy beplan om swanger te raak, of indien jy jou baba borsvoed.
- Indien jy weet dat jy lae kalium- of natriumvlakke in jou bloed het.
- Indien jy weet dat jy hoë kalsiumvlakke in jou bloed het.
- Indien jy weet dat jy hoë uriensuurvlakke in jou bloed het of simptome van jig ervaar.
- Indien jy ingekorte nierfunksie het en jy behandel word met 'n bloeddrukverlagende middel wat aliskiren bevat.
- Indien jy nierskade het en/of antibiotiese middels neem wat aan die klas "Fluorokinolone" behoort (sien afdeling Ander medisyne en **RANEPRES PLUS**)
- **RANEPRES PLUS** moet nie aan kinders gegee word nie.

Waarskuwings en voorsorgmaatreëls
Neem spesiale sorg met **RANEPRES PLUS**:
Daar is sekere toestande wat jy moontlik het of gehad het, wat spesiale sorg vereis voordat, of terwyl jy **RANEPRES PLUS** neem. Voordat jy dus hierdie medisyne neem, moet jy jou dokter vertel indien jy iy aan:

- Oormatige braking of diaree.
- Nierprobleme of 'n nieroorplanting gehad het.
- Vertel die dokter of tandarts voor 'n operasie en narkose (selfs by die tandarts se praktyk), dat jy **RANEPRES PLUS** gebruik, aangesien daar moontlik 'n skielike daling in bloeddruk kan wees wat verband hou met die narkose.
- Hartprobleme
- Lewerprobleme
- Hoë kaliumvlakke in jou bloed of jy neem kaliumbevattende soutvervangers.
- Verhoogde aldosteroonvlakke (jy kan vogretensie, verhoogde bloeddruk en swakheid ervaar).
- Indien jy tans 'n middel neem wat aan 'n groep bekend as angiotensien omskakelings ensiem inhibeerders (ook bekend as AOE inhibeerders) behoort. Dit sluit medisyne soos kaptopril, enalapril en perindopril in.
- Het hoë cholesterol- of vetvlakke in die bloed.
- Het sistemiese lupus eritemateuses.
- Tekens soos oormatige dors, 'n droë mond, ongewone moegheid of swakheid, lomerigheid, spierkrampe of pyn of abnormaal vinnige hartklop.
- Indien jy warfarien neem (medisyne om die bloed te verdun).
- Het diabetes of as jy aan laktose intoleransie ly.
- Indien jy diabetes of ingekorte nierfunksie het en jy behandel word met 'n bloeddrukverlagende middel wat aliskiren bevat en 'n AOE inhibeerder (bv. enalapril, lisinopril, ramipril).
- Stel jou dokter dadelik in kennis indien jy enige antibiotiese middel neem wat aan die groep "fluorokinolone" behoort, bv. levofloksasien, moksifloksasien, siprofloksasien). Gebruik van AOE inhibeerders/renien angiotensien reseptorblokkeerders, insluitend **RANEPRES PLUS**, saam met fluorokinolone kan skade aan jou niere veroorsaak.

Ander medisyne en RANEPRES PLUS
Vertel altyd vir jou gesondheidsorgverskaffer indien jy enige ander medisyne neem. (Dit sluit komplementêre of tradisionele medisyne in.)
Die gebruik van **RANEPRES PLUS** saam met hierdie medisyne kan ongewenste interaksies veroorsaak. Raadpleeg asseblief jou dokter, apteker of ander professionele gesondheidsorgwerker vir advies.
Jy behoort jou dokter te vertel indien jy die volgende medisyne gebruik, voordat jy met **RANEPRES PLUS** begin.

- Ander medisyne wat gebruik word om bloeddruk te verlaag.
- Litium bevattende medisyne (gebruik vir sommige tipes psigiatriese siektes).
- Sekere tipe pynstillers naamlik nie-steroïed anti-inflammatoriese middels (NSAIM's) insluitend aspirien, ibuprofen, diklofenak en COX-2 inhibeerders soos selekoksib.
- Medisyne wat die hoeveelheid kalium in jou bloed vermeerder. Hierdie sluit kaliumaanvullings of kalium bevattende soutvervangers in.
- Kaliumsparende medisyne (bv. spironolaktoon, triamtereen, amiloried), lakseermiddels (bv. kasterolie), kortikosteroïede (bv. prednisoon), AKTH ('n hormoon), amfoterisien ('n swambestrydende middel), karbenoksoloon (gebruik om mondsere te behandel), penisillien ('n antibiotika), salisielsuur en heparien.
- Ander medisyne soos digoksien, betablokkers, diasoksied, atropien (vir die hart), alkohol, barbiturate (gebruik as kalmeermiddel), verdowingsmiddels (pynstillers), anti-diabetiese medisyne (oraal en insulien), cholestiramien en kolestipol harse (om cholesterolvlakke te verlaag), noradrenalien (om lae bloeddruk te behandel), spierverslappers, allopurinol (vir jig), kalsium- en vitamien D aanvullings, biperiden (vir Parkinson's), amantadien (antiviraal en Parkinson's), sekere kankermedisyne, metieldopa (behandeling van hoë bloeddruk) en siklosporien (immuunonderdrukker)
- Bloeddrukverlagende medisyne wat aliskiren bevat, 'n AOE inhibeerder (bv. enalapril, lisinopril, ramipril).
- Medisyne wat gebruik word om infeksies te behandel (antibiotiese middels) wat aan die groep fluorokinolone behoort (bv. levofloksasien, moksifloksasien, siprofloksasien).

RANEPRES PLUS met voedsel en drank:
RANEPRES PLUS kan met of sonder kos geneem word.

Swangerskap, borsvoeding en fertiliteit
Indien jy swanger is of jou baba borsvoed, vermoed dat jy dalk swanger is of beplan om 'n baba te hê, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer vir advies voordat jy hierdie medisyne gebruik.
RANEPRES PLUS moet nie tydens swangerskap of indien jy borsvoed gebruik word nie (sien "Voordat jy **RANEPRES PLUS** neem").

Bestuur en gebruik van masjinerie
Sommige mense kan moeg en duiselig voel terwyl hulle **RANEPRES PLUS** gebruik. Versigtigheid word aanbeveel wanneer gevaarlike masjinerie, insluitend motorvoertuie hanteer word. Dit is nie altyd moontlik om te voorspel tot watter mate **RANEPRES PLUS** met die daaglikse aktiwiteite van 'n pasiënt kan inmeng nie. Pasiënte moet seker maak dat hulle nie by bogenoemde aktiwiteite betrokke raak nie, totdat hulle bewus is van die mate waartoe **RANEPRES PLUS** hulle affekteer.

RANEPRES PLUS bevat
Laktose: Pasiënte met die seldsame oorerflike probleem van laktose- of galaktose-intoleransie, moet nie **RANEPRES PLUS** gebruik nie.

3. Hoe om RANEPRES PLUS te neem

- Moet nie medisyne wat vir jou voorgeskryf is met enige ander persoon deel nie.
- Neem altyd **RANEPRES PLUS** presies soos jou dokter jou beveel het. Vra jou dokter of apteker indien jy nie seker is nie.

Die gewone dosis in volwassenes is:
Die gewone dosis is een tablet per dag. Jou dokter kan hierdie dosis verhoog afhangende van die bloeddruk reaksie. Die maksimale bloeddruk verlagende effek moet binne 4 weke na die aanvang van behandeling bereik word.
In sommige pasiënte, soos diegene met lewerprobleme, nierprobleme of diegene wat onlangs liggaamsvloeistowwe verloor het, bv. deur braking of diaree of deur water tablette te gebruik, kan die dokter 'n laer aanvangsdosering voorskryf.
RANEPRES PLUS kan met of sonder kos geneem word.
Die tablette moet met 'n glas water gesluk word. Jy moet probeer om jou daaglikse dosis op ongeveer dieselfde tyd elke dag te neem.
Jou dokter sal vir jou sê hoe lank jou behandeling met **RANEPRES PLUS** sal duur. Moet nie met die behandeling vroeër ophou nie. Indien jy onder die indruk is dat die effek van **RANEPRES PLUS** te sterk of te swak is, praat met jou dokter of apteker.

Indien jy meer RANEPRES PLUS geneem het as wat jy behoort te neem
Indien jy meer as die aanbevole aantal tablette neem, sal jy waarskynlik lighoofdig en duiselig voel. In die geval van 'n oordosering, raadpleeg jou dokter of apteker. Indien nie een beskikbaar is nie, kontak die naaste hospitaal of gifbeheersentrum.

Indien jy vergeet om RANEPRES PLUS te neem
Neem **RANEPRES PLUS** soos deur die dokter voorgeskryf.
Indien jy vergeet om 'n dosis te neem, neem dit sodra jy daarvan onthou, en gaan dan voort soos voorheen.
Moet nie 'n dubbele dosis neem om vir vergete individuele dosisse op te maak nie.

Indien jy ophou om RANEPRES PLUS te neem
Indien jy ophou om **RANEPRES PLUS** te neem, kan jou bloeddruk weer styg. Moet dus nie ophou om **RANEPRES PLUS** te neem sonder om dit eers met jou dokter te bespreek nie.

4. Moontlike newe-effekte

RANEPRES PLUS kan newe-effekte hê.
Nie alle newe-effekte wat vir **RANEPRES PLUS** aangemeld is, is in hierdie inligtingstuk ingesluit nie. Sou jou algemene gesondheid versleg of indien jy enige ongewenste effekte ervaar terwyl jy **RANEPRES PLUS** neem, raadpleeg asseblief jou gesondheidsorgverskaffer vir advies.
Indien enige van die volgende gebeur, staak RANEPRES PLUS se gebruik en vertel onmiddellik jou dokter daarvan of gaan na die ongevalle afdeling van jou naaste hospitaal.
Simptome van 'n ernstige allergiese reaksie soos:

- Swelling van hande, voete, enkels, gesig, lippe en mond of keel, wat probleme kan veroorsaak om te sluk of asem te haal
- Uitslag, allergiese velreaksie of jeuk.
- Vergeling van die vel en oë, ook bekend as geelsug.

Al hierdie newe-effekte is baie ernstig. Indien jy dit ervaar, het jy moontlik 'n ernstige reaksie op RANEPRES PLUS gehad. Jy mag dringende mediese aandag of hospitalisasie benodig.
Lig jou dokter onmiddellik in of gaan na die ongevalle afdeling van jou naaste hospitaal indien jy enige van die volgende newe-effekte waarneem:

- Angioëdeem (swelling in gesig, tong, larinks, buik of arms en bene), uitslag, urtikaria (galbulte), pruritus (jeuk).
- Anafilaktiese reaksie.

Ander newe-effekte
Gereelde newe-effekte:

- Nasofaringitis (ontsteking van farinks en neusholtes)
- Dislipidemie (abnormale hoeveelhede van lipiede, bv. trigliseriede, cholesterol of vetfosfolipiede in die bloed)
- Hoofpyn, duiseligheid, vertigo.
- Tagikardie (vinnige hartklop)
- Respiratoriese infeksie, brongitis, faringitis (seer keel), sinusitis (ontsteking van lugholtes binne gange van die neus), hoes
- Naarheid
- Moegheid (swakheid)
- Griepagtige simptome, urienweginfeksie, besering opgedoen.
- Hiperglukemie, hiper-urisemie, elektrolietwanbalans (insluitend bloedkaliumgebrek, bloednatriumtekort)
- Glukosurie (uitskeiding van glukose in uriene)

Minder gereelde newe-effekte:

- Leukopenie, neutropenie en agranulositose (verlaagde witbloedseltelling)
- Hiperkalemie (verhoogde kaliumkonsentrasie in die bloed), hiponatremie (lae natriumkonsentrasie in bloed).
- Abdominale pyn
- Verhoogde lewerensieme, abnormale lewerfunksie of hepatitis
- Rugpyn
- Nierinkorting, insluitend nierversaking (verlies van nierfunksie) in vatbare pasiënte, interstisiële nefritis
- Trombositopenie, aplastiese anemie, beenmurgonderdrukking, hemolitiese anemie.
- Afnames in hemoglobien, verhogings in serum aspartaat transaminase (AST) en serum alanien transaminase (ALT)
- Slaapversteurings, depressie, rusteloosheid.
- Parestesie (brandende en prikkelende sensasie)
- Verbygaande dowwe visie
- Kardiale disritmie
- Posturale hipotensie (lae bloeddruk), nekrotiserende angiïtis (vaskulitis, kutaneuse vaskulitis)
- Respiratoriese infeksies insluitend longontsteking en pulmonêre edeem.
- Anoreksie (verlies aan eetlus), maagirritasie, diaree, hardlywigheid, pankreatitis.
- Geelsug (intrahepatiese cholestatiese geelsug)
- Fotosensitiwiteitsreaksie, toksiese epidermale nekrolise, kutaneuse lupus eritemateuse tipe reaksies (outoïmmuun siekte wat die vel affekteer), heraktivering van kutaneuse lupus eritemateuse.
- Spierspasma.
- Koors
- Toenames in ureum en serumkreatinien

Indien jy enige newe-effekte waarneem wat nie in hierdie inligtingstuk genoem word nie, lig asseblief jou dokter of apteker in.

Aanmelding van newe-effekte
Indien jy newe-effekte kry praat met jou dokter of apteker of verpleegkundige. Dit sluit enige moontlike newe-effekte in wat nie in hierdie inligtingstuk genoem is nie. Jy kan ook newe-effekte aan SAHPRA rapporteer via die "**6.04 Adverse Drug Reaction Reporting Form**", wat aanlyn gevind kan word onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte aan te meld kan jy help om meer inligting beskikbaar te stel aangaande die veiligheid van **RANEPRES PLUS**.

5. Hoe om RANEPRES PLUS te bewaar

Bewaar by of benede 25 °C.
Bewaar in die oorspronklike verpakking
Hou die stulpstroke en bottel in die buitenste karton totdat dit benodig word vir gebruik.
Bewaar alle medisyne buite bereik van kinders.
Beskerm teen lig en vog.
Moet nie in 'n badkamer bêre nie.
Moet nie gebruik na die vervaldatum wat op die stulpstrook/etiket/karton aangebring is nie.
Neem alle ongebruikte medisyne terug na jou apteker.
Moet nie ongebruikte medisyne in afvoerpype of rioolstelsels (bv. toilette) gooi nie.

6. Inhoud van die pak en ander inligting

Wat RANEPRES PLUS bevat
RANEPRES PLUS 16/12.5 mg Tablette
Die aktiewe bestanddele is 16 mg Kandesartan silieksetil en 12,5 mg Hidrochloortiasied
RANEPRES PLUS 32/12.5 mg Tablette
Die aktiewe bestanddele is 32 mg Kandesartan silieksetil en 12,5 mg Hidrochloortiasied
RANEPRES PLUS 32/25 mg Tablette
Die aktiewe bestanddele is 32 mg Kandesartan silieksetil en 25 mg Hidrochloortiasied

Die ander bestanddele in **RANEPRES PLUS 16/12,5 mg** en **32/25 mg** is mieliestysel, kalsiumkarboksimetielsellulose, gliserien/gliserol, hidroksipropielsellulose, laktosemonohidraat, magnesiumstearaat, rooi ysteroksied, geel ysteroksied.
Die ander bestanddele in **RANEPRES PLUS 32/12,5 mg** is mieliestysel, kalsiumkarboksimetielsellulose, gliserien/gliserol, hidroksipropielsellulose, laktosemonohidraat, magnesiumstearaat, geel ysteroksied.

Hoe RANEPRES PLUS lyk en inhoud van die pak
RANEPRES PLUS 16/12.5 mg:
Pienk, ovaal, bikonvekse, onbedekte tablette, met "ML 71" ingeprent op die een kant en breeklyn op beide kante.
RANEPRES PLUS 32/12.5 mg:
Geel, ovaal, bikonvekse, onbedekte tablette, met "ML 58" ingeprent op die een kant en breeklyn op beide kante.
RANEPRES PLUS 32/25 mg:
Pienk, ovaal, bikonvekse, onbedekte tablette, met "ML 57" ingeprent op die een kant en breeklyn op beide kante.
Die breeklyn van **RANEPRES PLUS 16/12,5 mg, 32/12,5 mg en 32/25 mg** is slegs om die breek van die tablet te fasiliteer om sodoende sluk te vergemaklik en nie om in gelyke dosisse te verdeel nie.
Stulpverpakking:
Tablette word verpak in deursigtige film PVC/PVdC 250 µm/90 met 90 gsm PVdC as die vormingsmateriaal en 25 µm aluminiumfoelie met 6-8 gsm hitteseëllak as die dekmateriaal, verpak in voorafgedrukte karton.
Verpakkingsgroottes sluit 14 of 28 tablette in.
HDPE houer verpakking:
Tablette word in 40 ml of 60 ml wit ronde HDPE houer met 33-400 mm nek afwerking verpak, wat met 33 mm kinderbestande sluiting met pulp en hitteseëlvoering toegemaak is, en in buitenste karton verpak is.
Verkpakkingsgroottes sluit 90 tablette in.
Nie alle verpakkings en verpakkingsgroottes word noodwendig bemark nie.

Houer van die Registrasiesertifikaat en Vervaardiger
MACLEODS PHARMACEUTICALS SA (Edms) Bpk
Kantoorblok 1, Bassonia Estate Kantoorpark (Oos),
Cussonia Weg 1, Bassonia Rock, Uitbr. 12,
Alberton, Suid Afrika

Hierdie inligtingstuk was hersien in
28 Februarie 2022

Registrasienommers
RANEPRES PLUS 16/12,5 mg: 48/7.1.3/0514
RANEPRES PLUS 32/12,5 mg: 48/7.1.3/0515
RANEPRES PLUS 32/25 mg: 48/7.1.3/0516

Toegang tot die ooreenstemmende professionele inligting
Die ooreenstemmende professionele inligting kan verkry word by https://www.macleodspharma.com of stuur 'n e-pos na macleodsrsa@macleodspharma.com of kontak 011 682 1169.

400 mm

435 mm

PACKAGING RESEARCH & DEVELOPMENT

Restricted Circulation

(Front Page)

ARTWORK / PRINTPROOF APPROVAL FORM

1. Product: RANEPRES PLUS 16/12.5 mg /32/12.5 mg/32/25 mg (Candesartan cilexetil and hydrochlorothiazide tablets 16/12.5 mg /32/12.5 mg/32/25 mg)					
2. Country: South Africa		3. Packaging component: Package Insert & Patient Information Leaflet			
4. No. of Colours: 1 Colour		5. Pantone Shade No.: Black			
6. Specification: 40 gsm bible paper					
7. Machine Layout No.: NA		8. Dimensions: 435 (L) x 400 (W) mm			
9. Design / Style: Booklet		10. Item code No.: PM04001701			
11. Artwork has been made: Actual Size		12. Pharma code No.: 32228 mini			
13. Barcode/NDC No: NA		14. Supersedes Item code No: NA			
15. Revision no: 00		16. A/W File name: E:\ANDA Regulatory\South Africa\Candesartan+HCTZ Tablets\Private Market\01\Candesartan HCTZ leaflet - PM04001701.cdr			
Approved By:		17. Location: Daman (Unit 2)			
PRD	M.A. HOLDER	RAD	QC	PRODN	QA
	Vanita Rajool Digitally signed by Vanita Rajool DN: cn=Vanita Rajool, o=Macleods Pharmaceuticals SA (Pty) Ltd., ou=Responsible Pharmacist, email=vanitar@macleodspharmac om, c=ZA Date: 2022.11.11 11:18:12 +02'00'				

Note: 1. To follow overleaf checklist for approval of Artwork / Print proof.

Instructions to Vendor :

1. Before processing, please ensure First pull out / Commercial supply should match with approved Artwork with respect to Design, Size, Fonts & Text.
2. Print proof to represent full printing area with Station Numbers.

FRM/CQA/021/04-01

Reason for revision :	Item code	Artwork Release Date	Artwork Implementation Date
1) New Artwork for South Africa	PM04001701		