PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RANEPRES PLUS 16/12.5 mg TABLETS

RANEPRES PLUS 32/12.5 mg TABLETS

RANEPRES PLUS 32/25 mg TABLETS

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 PLUS32/12.5 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 lithiumtherapy (see sections 4.3 and 4.5).

Renal artery stenosis:

RANEPRES PLUS may increase blood urea and serum creatinine in patients with bilateralrenal 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 maybe severe such that additional intravenous fluids and/or vasopressors are needed.

Intravascular volume depletion:

In patients with intravascular volume and/or sodium depletion, symptomatic hypotensionmay occur. Therefore, the use of **RANEPRES PLUS** is not recommended until this conditionhas been corrected.

Renal impairment/kidney transplantation:

When **RANEPRES PLUS** is used in patients with impaired renal function, a periodicmonitoring of potassium, creatinine and uric acid levels is recommended. Loop diureticsare preferred to **RANEPRES PLUS** in this population.

There is no experience regarding the administration of **RANEPRES PLUS** in patients withrecent 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/orcholestasis.

Aortic and mitral valve stenosis or obstructive hypertrophic cardiomyopathy:

Special caution is indicated in patients suffering from haemodynamically relevant aortic or mitralvalve 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** shouldbe discontinued before carrying out tests for parathyroid function.

Hydrochlorothiazide (a component of **RANEPRES PLUS**) dose -dependently increasesurinary potassium excretion whichmay result in hypokalaemia, e.g. in liver cirrhosis, afterbrisk diuresis, inadequate intake of electrolytes and in patients receiving corticosteroids.Concomitant use of **RANEPRES PLUS** and potassium-sparing diuretics, potassiumsupplements 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 adjustmentof antidiabetic medicines, including insulin, may be required. Latent diabetes mellitusmay manifest during thiazide therapy. Increases in cholesterol and triglyceride levelshave been associated with hydrochlorothiazidetherapy. At the doses contained in **RANEPRES PLUS** only minimal effects were observed. Hydrochlorothiazide may increaseserum uric acid concentration and may precipitate gout in susceptible patients.

General:

In patients whose vascular tone and renal function depend predominantly on the activity ofthe renin-angiotensin -aldosterone system (e.g. patients with severe congestive heart failureor underlying renal disease, including renal artery stenosis), treatment with medicines thataffect 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 marketingdata. 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. otherkaliuretic diuretic, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acidderivatives*).*

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potentialcardiotoxic effects of digitalis glycosides and anti-dysrhythmics. Periodic monitoring ofserum potassium is recommended when **RANEPRES PLUS** is administered with suchmedicines.

Reversible increases in serum lithium concentrations and toxicity have been reportedduring 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 byNSAIDs.

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. Ifcalcium supplements or Vitamin D must be prescribed, serum calcium levels should bemonitored 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 ofthiazide-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 s oradrenocorticotropic hormone (ACTH).

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

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

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

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with highdoses 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, medicinesthat act directly on the renin-angiotensin system can cause embryonal toxicity,foetal and neonatalinjury 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 bloodflow. 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 beenstudied. When driving vehicles or operating machines, it should be taken into account thatoccasionally 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 **RANEPRESPLUS**:

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	Less frequent	Leukopenia, neutropenia and

disorders		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 subcutaneoustissue 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, cutaneousvasculitis)

Respiratory, thoracic and mediastinal disorders	Less frequent	Respiratorydistress includingpneumonitis 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. Toxicepidermal 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.

4.9Overdose

Symptoms:

Based on pharmacological considerations, the main manifestation of an overdose ofcandesartan cilexetil is likely to be symptomatic hypotension and dizziness. In single casereports 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 andelectrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventriculararrhythmias, 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 symptomatichypotension should occur, symptomatic treatment should be instituted and vital signs monitored.

Candesartan is not removed by haemodialysis. It is not known to what extenthydrochlorothiazide is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 7.1.3 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 gastrointestinaltract. 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, aldosteronestimulation, regulation of salt and water homeostasis and stimulation of cell growth, aremediated via the type I (AT_1) receptor.

The antagonism of the AT_1 receptors results in dose-related increases in plasma reninlevels, angiotensin I and angiotensin II level s, and a decrease in plasma aldosteroneconcentration.

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

Hydrochlorothiazide:

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in ·the distal kidneytubules, and promotes the excretion of sodium, chloride and water. The renal excretion ofpotassium and magnesium increases dose-dependently, while calcium is reabsorbed to agreater extent. Hydrochlorothiazide decreases plasma volume and extracellular fluid andreduces cardiac output and blood pressure. During long-term therapy, reduced peripheralresistance 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 noclinically significant effect on the pharmacokinetics of either medicine

Absorption and distribution.

Candesartan cilexetil:

Following oral administration candesartan cilexetil is converted to the active medicinecandesartan. The mean peak serum concentration (C_{max}) is reached 3-4 hours followingtablet intake. No gender-related differences in the pharmacokinetics of candesartan havebeen observed. The area under the serum concentration versus time curve (AUC) ofcandesartan 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 absolutebioavailability of approximately 70 %. Concomitant intake of food increases the absorptionby approximately 15%. The bioavailability may decrease in patients with cardiac failureand pronounced oedema.

The plasma protein binding of hydrochlorothiazide is approximately 60 %. The apparentvolume 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 studiesindicate no effect on CYP2C9 and CYP3A4. Based on in vitro data, no interaction wouldbe expected to occur in vivo with medicines whose metabolism is dependent uponcytochrome P450 isoenzymes CYP_1A_2, CYP_2A_6, CYP_2C_9, CYP_2C_{19}, CYP_2D_6, CYP_2E_1 orCYP_3A_4. The terminal half- life ($t_{1/2}$) of candesartan is approximately 9 hours. There is noaccumulation following multiple doses. The halt-life of candesartan remains unchanged(approximately 9 hours) after administration of candesartan cilexetil in combination withhydrochlorothiazide. No accumulation of candesartan occurs after repeated doses of thecombination compared to monotherapy.

Total plasma clearance of candesartan is about 0,37 ml/min/kg, with a renal clearanceof about 0,19 ml/min/kg. Following an oral dose of ^{14}C-labelled candesartan cilexetil, theactive candesartan, and its inactive metabolites are excreted via the urine (30 %) and to alarger extent (70 %) via the faeces.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchangedcompound by glomerular filtration and active tubular secretion. The terminal $t_{1/2}$, ofhydrochlorothiazide is approximately 8 hours. Approximately 70% of an oral close iseliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remainsunchanged (approximately 8 hours) after

administration of hydrochlorothiazide incombination with candesartan cilexetil. No accumulation of hydrochlorothiazide occursafter 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 byapproximately 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) tosevere (Ccr 15-30 ml/m in) renal impairment, C_{max} and AUC of candesartan increasedduring repeated dosing. In patients with mild to moderate renal impairment AUC wasapproximately 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, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, red ferric oxide,yellow ferric oxide.

RANEPRES PLUS 32/12.5 mg: Corn starch, carboxymethylcellulose calcium, glycerin/glycerol,hydroxypropyl 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

To be advised.