1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MYLACAND PLUS 16/12,5 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each MYLACAND PLUS tablet contains 16 mg candesartan cilexetil and 12,5 mg hydrochlorothiazide.

Contains sugar: Lactose monohydrate 102,94 mg

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Peach colour mottled, round, biconvex tablet debossed with “M” on one side and “CH2” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MYLACAND PLUS is indicated for the treatment of essential hypertension in patients stabilised on the individual components given at the same dosages.

4.2 Posology and method of administration

Posology

- The recommended dose is one MYLACAND PLUS tablet once daily.

- The maximal antihypertensive effect is attained within 4 weeks of initiation of treatment.

Special populations:

Elderly population:

- No special dosage recommendations.

Renal impairment:

- No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1,73 m^2 BSA) (*see section 4.3*).
- MYLACAND PLUS should not be used in patients with moderate to severe renal impairment (i.e. creatinine clearance < 60 ml/min/1,73 m^2 BSA).

Hepatic impairment:

- No dosage adjustment is necessary in patients with mild hepatic impairment.
- MYLACAND PLUS is contraindicated in patients with moderate to severe hepatic impairment and/or cholestasis.

Paediatric population

- The safety and efficacy of MYLACAND PLUS have not been established in children.

Method of administration

- For oral use.
- MYLACAND PLUS should be taken once daily with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance, candesartan cilexetil or hydrochlorothiazide or to any of the excipients of MYLACAND PLUS or to sulphonamide medicines.

- Hereditary or idiopathic angioedema. A history of angioedema related to previous therapy with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs): These patients must never again be given these medicines.
- Hypertrophic obstructive cardiomyopathy (HOCM) (*see section 4.4)*.
- Severe renal function impairment (creatinine clearance less than 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 (*see section 4.5*).
- Porphyria.
- Lithium therapy: Concomitant administration with MYLACAND PLUS may lead to toxic blood concentrations of lithium (*see section 4.5*).
- Pregnancy and lactation (*see section 4.6*).
- Moderate to severe hepatic impairment and/or cholestasis.
- MYLACAND PLUS contains a thiazide diuretic in (fixed dose) and therefore should not be given to patients with Addison's disease.
- Anuria.
- Gout.
- The concomitant use of MYLACAND PLUS with aliskiren-containing products is contraindicated *(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.
- Patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

Pregnancy:

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

Renal impairment:

- When MYLACAND PLUS is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.
- When administering MYLACAND PLUS to patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered. There is very limited experience in patients with very severe or end-stage renal impairment (creatinine clearance < 30 ml/min/1,73 m^2 BSA) (*see section 4.3*).
- Prolongation of INR and bleeding complications with concomitant warfarin therapy may occur.
- Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers 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 ACE inhibitors/renin-angiotensin receptor blockers.

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

- There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) 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 MYLACAND PLUS and aliskiren is therefore contraindicated *(see section 4.3*).

- MYLACAND PLUS should not be used concomitantly with aliskiren (*see section 4.3*).

Renal artery stenosis:

- Medicines that affect the renin-angiotensin-aldosterone system such as MYLACAND PLUS may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (*see section 4.3*).

Intravascular volume depletion:

- In patients with intravascular volume and/or sodium depletion, symptomatic hypotension may occur. Therefore, the use of MYLACAND PLUS is contraindicated until this condition has been corrected.

Kidney transplantation:

- There is no experience regarding the administration of MYLACAND PLUS in patients with recent kidney transplantation.

Hepatic impairment:

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

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy):

- MYLACAND PLUS is contraindicated in patients suffering from haemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy (*see section 4.3*).

Electrolyte imbalance:

- Periodic determination of serum electrolytes should be performed at appropriate intervals.
- Hydrochlorothiazides can cause fluid or electrolyte imbalance.
- Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted.

Hyperkalaemia:

- Concomitant use of MYLACAND PLUS with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicines that may increase potassium levels (e.g. heparin) may lead to increases in serum potassium in hypertensive patients.
- In heart failure patients treated with MYLACAND PLUS**,** hyperkalaemia may occur. During treatment with MYLACAND PLUS in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

Anaesthesia and surgery:

- Hypotension may occur during anaesthesia and surgery in patients treated with MYLACAND PLUS due to blockade of the renin-angiotension system.
- Hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Primary Hyperaldosteronism:

- Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicines acting through inhibition of the renin-angiotensin-

aldosterone system. Therefore, the use of ATACAND PLUS in these patients is not recommended.

Patients receiving hydrochlorothiazide (HCTZ) as contained in MYLACAND PLUS should take caution with the following:

Non-melanoma skin cancer:

- An increased risk of non-melanoma skin cancer (NMSC) [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] with increasing cumulative dose of hydrochlorothiazide (HCTZ) exposure has been observed in two epidemiological studies. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.
- Patients taking MYLACAND PLUS should be informed of the risk of NMS C and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in the case of exposure, adequate protection should be advised to the patients to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. MYLACAND PLUS should not be used by patients who have had previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and/or lip *(see section 4.3*).
- Patients should also be advised to avoid the use of indoor tanning equipment and to use adequate protection (e.g. a broad spectrum sunscreen with a SPF of 30 or higher, clothing, and a hat) when exposed to sunlight or UV light to minimize the risk of skin cancer.
- Alternatives to MYLACAND PLUS may be considered for patients who are at a particularly high risk for NMSC (e.g. light coloured skin, known personal or family history of skin cancer, ongoing immunosuppressive therapy, etc.).

Endocrine and Metabolism:

- Hydrochlorothiazide (HCTZ) as contained in MYLACAND PLUS, should be carefully observed for clinical signs of fluid and electrolyte imbalance (hyponatremia, hypochloremic alkalosis and hypokalemia).
- Periodic determinations of serum electrolytes, to detect possible electrolyte disturbance, should be performed at appropriate intervals. Warning signs or symptoms of fluid and electrolyte imbalance include dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscle fatigue, hypotension, oliguria, tachycardia and gastrointestinal disturbances such as nausea and vomiting.
- Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy.
- Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g. increased ventricular irritability).
- Any chloride deficit during thiazide therapy is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Appropriate therapy is water restriction rather than administration of salt, except in rare instances, when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
- Hyperuricemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.
- Thiazides may decrease serum PBI (protein bound iodine) levels without signs of thyroid disturbance.

- Thiazides have been shown to increase excretion of magnesium; this may result in hypomagnesemia.
- Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism.
- Treatment with a thiazide diuretic may impair glucose tolerance.

Immune:

- *Hypersensitivity Reactions:* Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma.
- *Systemic Lupus Erythematosus:* The possibility of exacerbation or activation of systemic lupus erythematosus has been reported in patients treated with hydrochlorothiazide as contained in MYLACAND PLUS.

Ophthalmologic:

- Hydrochlorothiazide, a sulfonamide, can cause an idiosyncratic reaction, resulting in choroidal effusion, acute transient myopia and/or acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity, blurred vision or ocular pain and typically occur within hours to weeks of medicine initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.
- Discontinue MYLACAND PLUS as rapidly as possible.

Peri-Operative Considerations:

- Thiazides as contained in MYLACAND PLUS may increase the responsiveness to tubocurarine.

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 has been associated with acute hypotension, uraemia, azotemia, ~~oliguria~~ or rarely, acute renal failure. Excessive blood pressure decreases in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

Lactose warning:

MYLACAND PLUS contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take MYLACAND PLUS.

4.5 Interaction with other medicines and other forms of Interaction

- No interactions of clinical significance have been identified. Medicines which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, digoxin, oral contraceptives (ethinylestradiol/levonorgestrel), glibenclamide, nifedipine.
- Post marketing reports suggest 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 MYLACAND 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 diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivatives).

- Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effect of digoxin and anti-dysrhythmics. Periodic monitoring of serum potassium is recommended when MYLACAND PLUS is administered with such medicines.
- Concurrent use with lithium is a contraindication due to increases to toxic levels
- (*see section 4.3*).
- Diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by non-steroid anti-inflammatory drugs (NSAIDs).
- Hydrochlorothiazide absorption is reduced by colestipol or cholestyramine.
- Effect of non-depolarising skeletal muscle relaxants may be potentiated by hydrochlorothiazide.
- Hydrochlorothiazide may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D is prescribed, serum calcium levels should be monitored, and dosage adjusted accordingly.
- The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by hydrochlorothiazide.
- Anticholinergic medicines (e.g. atropine, biperiden) may increase the bioavailability of hydrochlorothiazide by decreasing gastro-intestinal motility and stomach-emptying rate.
- Hydrochlorothiazide may increase the risk of adverse effects caused by amantadine.
- Hydrochlorothiazide may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
- The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotropic hormone.

- Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.
- Treatment with hydrochlorothiazide 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. epinephrine (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.
- Gout medications (allopurinol, uricosurics, xanthine oxidase inhibitors) (*see section 4.3*)
- **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 & 4.4*).
  - Concomitant use of fluoroquinolones and ACE inhibitors/renin-angiotensin receptor blockers may precipitate acute kidney injury (*see section 4.3*).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

- Women of childbearing age should ensure effective contraception.

Pregnancy

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

- Medicines affecting the renin-angiotensin system, such as MYLACAND PLUS, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
- Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.

Breastfeeding

- Candesartan as contained in MYLACAND PLUS is excreted in breast milk.
- Hydrochlorothiazide passes into mother's milk. The safety during lactation has not been established (*see section 4.3*).

4.7 Effects on ability to drive and use machines

MYLACAND PLUS may cause dizziness or weariness and have no or negligible effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. **Tabulated list of adverse reactions**

Body System	**Undesirable effect**		
	Candesartan cilexetil/hydrochlorothiazide:	**Candesartan cilexetil**	**Hydrochlorothiazide**
Infections and Infestations: Frequent: Less frequent:	 Nasopharyngitis, bronchitis	Respiratory infection	
Blood and the lymphatic system disorders: Less frequent:			

		Leukopenia, neutropenia, agranulocytosis	Leukopenia, neutropenia, agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia
Immune system disorders: Less frequent:		 Angioedema	 Anaphylactic reactions
Metabolism and nutrition disorders: Frequent: Less frequent:	 Dyslipidaemia	 Hyperkalaemia Hyponatraemia	 Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia), gout, hypochloraemic alkalosis
Psychiatric disorders: Less frequent:			 Sleep disturbances, depression, restlessness
Nervous system disorders: Frequent: Less frequent:	 Dizziness, headache	 Dizziness/vertigo, headache	 Light-headedness, vertigo, headache Paraesthesia
Eye disorders: Less frequent:			 Transient blurred vision, yellow vision
Cardiac disorders: Less frequent: Frequency unknown:	 Tachycardia		 Cardiac dysrhythmias
Vascular disorders:			

Frequent: Less frequent:		Hypotension	 Postural hypotension, necrotising angitis (vasculitis, cutaneous vasculitis)
Respiratory, thoracic and mediastinal disorders: Less frequent:	 Respiratory infection, bronchitis, pharyngitis. sinusitis, cough		 Respiratory distress (including pneumonitis and pulmonary oedema)
Gastrointestinal disorders: Less frequent:	 Abdominal pain, nausea	 Nausea	 Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation, pancreatitis
Hepato-biliary disorders: Less frequent:		 Increased liver enzymes, abnormal hepatic function or hepatitis	 Jaundice (intrahepatic cholestatic jaundice)
Skin and subcutaneous tissue disorders: Less frequent: Frequency not known:		 Rash, urticaria, pruritus	 Rash, urticaria, photosensitivity reactions, toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus <u>Non-melanoma skin cancer</u>

Musculoskeletal, connective tissue and bone disorders: Less frequent:	Back pain	Back pain, arthralgia, myalgia	Muscle spasm
Renal and urinary disorders: Frequent: Less frequent:		 Renal impairment, including renal failure in susceptible patients (*see section 4.4*) **Laboratory findings:** In patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended ((*see section 4.4*)	 Glycosuria Renal dysfunction and interstitial nephritis
General disorders and administrative site conditions: Frequent: Less frequent:	 Influenza-like symptoms, urinary tract infection, inflicted injury, fatigue		 Weakness Fever
Investigations: Frequent: Less frequent:			Increases in cholesterol and triglycerides Increases in urea and serum creatinine

Description of selected adverse reactions

Laboratory findings:

Increases in serum uric acid, serum creatinine, serum urea, serum potassium, blood glucose and serum alanine transaminase (ALT) may occur. Decreases in haemoglobin and

increases in serum aspartate transaminase (AST) have been observed in patients receiving candesartan plus hydrochlorothiazide, as in MYLACAND PLUS.

In patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended (*see section 4.4*).

Post-marketing Adverse Reactions:

Candesartan cilexetil

- Angioedema, (involving swelling of the face, lips and/or tongue) has been reported rarely in patients treated with candesartan cilexetil.
- In other post-marketing experience, renal impairment, including renal failure in susceptible patients, has been observed (see Renal Impairment).
- Very rare cases of abnormal hepatic function or hepatitis have also been reported.
- Other adverse events reported for candesartan cilexetil where a causal relationship could not be established include very rare cases of leukopenia, neutropenia and agranulocytosis.
- Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide

Potentially serious clinical adverse events have been reported to occur with hydrochlorothiazide, such as:

- **Blood and lymphatic system disorders:** aplastic anemia; hemolytic anemia; leukopenia; neutropenia/agranulocytosis; thrombocytopenia.
- **Eye Disorders:** acute angle-closure glaucoma; acute myopia; choroidal effusion.
- **Endocrine and Metabolism:** hypokalemia.
- **Gastrointestinal disorders:** pancreatitis.
- **Hepatobiliary disorders:** jaundice (intrahepatic cholestatic jaundice).

- **Immune system disorders:** anaphylactic reactions; photosensitivity reactions.

  Musculoskeletal and connective tissue disorders: cutaneous lupus erythematosus; systemic lupus erythematosus.
- **Respiratory, thoracic and mediastinal disorders:** respiratory distress (including pneumonitis and pulmonary edema).
- **Renal and urinary disorders:** interstitial nephritis; renal dysfunction.
- **Skin and subcutaneous tissue disorders**: toxic epidermal necrolysis.
- **Vascular disorders:** necrotising angitis (vasculitis).

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 on the SAHPRA website at: https://medsafety.sahpra.org.za/#download1, via email at: adr@sahpra.org.za or via telephone at: 0125010311.

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Symptoms:

- Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness.
- The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

Treatment:

- No specific information is available on the treatment of overdosage with MYLACAND PLUS. The following measures are, however, suggested in case of overdosage.
- When indicated, induction of vomiting or gastric lavage 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 ACTION

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines – other hypotensives

Pharmacotherapeutic group:

Angiotensin II receptor blockers (ARBs), other combinations ATC code: C09DX06.

Candesartan cilexetil:

It is a prodrug. Candesartan cilexetil is an angiotensin II receptor antagonist, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

After oral administration it is converted to the active, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract.

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 angiotensin AT1 receptors results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

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

Hydrochlorothiazide:

Hydrochlorothiazide inhibits the active reabsorption of sodium, mainly in the distal kidney tubules and promotes the excretion of sodium, chloride and water. The renal excretion of potassium and magnesium increases dose-dependently, while calcium is reabsorbed to a greater 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 cilexetil and hydrochlorothiazide have additive blood pressure lowering properties.

5.2 Pharmacokinetic properties

Absorption and distribution:

Candesartan cilexetil:

After oral administration, candesartan cilexetil is converted to the active, candesartan. The mean peak serum concentration (C_{max}) is reached 3 to 4 hours after tablet intake.

The serum concentration increases linearly with increasing doses in the therapeutic dosage range.

The area under the serum concentration versus time curve (AUC) of is not significantly affected by food. It 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 gastro-intestinal tract, with an absolute bioavailability of about 70 %. When taken with food the absorption increases 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.

Metabolism and elimination:

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

The half-life of candesartan remains unchanged (approximately 9 hours) after administration of candesartan cilexetil in combination with hydrochlorothiazide.

Based on *in vitro* data, no interaction would be expected to occur *in vivo* with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.

The total plasma clearance of candesartan is about 0,37 ml/min/kg, with renal clearance of about 0,19 ml/min/kg. After an oral dose of ^{14}C-labelled candesartan cilexetil, the active candesartan and its inactive metabolite are excreted via the urine (30 %) and to a larger extent (70 %) via the faeces.

Hydrochlorothiazide:

It is not metabolised and is excreted almost entirely unchanged by glomerular filtration and active tubular secretion. The terminal half-life of hydrochlorothiazide is about 8 hours. About 70 % of an oral dose is eliminated in the urine within 48 hours. The half-life remains unchanged (about 8 hours) after administration in combination with candesartan cilexetil. No accumulation 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/min) renal impairment, C_{max} and AUC of candesartan increased during repeated dosing. In patients with mild to moderate renal impairment AUC was approximately doubled, while in severe renal impairment the AUC was further increased. The $t_{½}$ and AUC 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 half-life is prolonged in patients with renal impairment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose calcium, glyceryl monostearate, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, maize starch, methylene chloride, {colourants: iron oxide red, iron oxide yellow}

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in a dry place.

Protect from light and moisture.

Keep in the original container until required for use.

Keep the container well closed.

6.5 Nature and contents of container

Cold form blister pack (in pack size: 7, 10, 14, 15, 28, 30, 50, 56, 60, 84, 90, 98, 100 tablets) comprises of cold form laminate (aluminium foil laminated to oriented polyamide on

one side and to PVC on the other side i.e. OPA/AI/PVC) on one side and hard tempered aluminium foil on the other side. Suitable number of cold form blister packs are placed in a triple laminated pouch with desiccant which is then inserted into a carton.

HDPE bottle pack (in pack size: 30 and 90 tablets) comprises of white opaque HDPE bottle with white opaque screw cap, with absorbent cotton and desiccant, which is then inserted into a carton.

PVC-AI blister pack (in pack size: 30 tablets) comprises of clear, transparent PVC film on one side and hard tempered aluminium foil coated with VMCH heat seal lacquer on the other side.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Mylan (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

8 REGISTRATION NUMBER(S)

45/7.1.3/0394

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 June 2013

10 DATE OF REVISION OF TEXT

11 November 2022