1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

MYLACAND 8 mg (tablets)

MYLACAND 16 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each MYLACAND 8 mg tablet contains 8 mg candesartan cilexetil.

Contains sugar: Lactose 48,472 mg

Each MYLACAND 16 mg tablet contains 16 mg candesartan cilexetil.

Contains sugar: Lactose 96,945 mg

For full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

MYLACAND 8 mg:

Pink mottled, capsule shaped, biconvex tablet debossed with “M” and “8” on either side of the break line on one side and plain on the other side.

MYLACAND 16 mg:

Pink mottled, capsule shaped, biconvex tablet debossed with “M” and “16” on either side of the break line on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- MYLACAND is indicated for the treatment of mild to moderate hypertension.
- MYLACAND can be used as monotherapy or in combination with other antihypertensive agents such as thiazide diuretics and dihydropyride calcium antagonists for enhanced efficacy.
- Heart failure: Treatment with MYLACAND reduces mortality, reduces hospitalisation due to heart failure, and improves symptoms in patients with left ventricular systolic dysfunction (LVEF ≤ 40 %).

4.2 Posology and method of administration

Posology

Dosage in hypertension:

- The recommended initial dose is MYLACAND 8 mg once daily.
- The usual maintenance dose is 8 mg to 16 mg once daily.

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

Some patients may receive an additional benefit by increasing the dose to 32 mg once daily.

Concomitant therapy:

- MYLACAND can be used as monotherapy or in combination with other antihypertensive agents, such as thiazide diuretics and dihydropyridine calcium antagonists, e.g. amlodipine, for enhanced efficacy.

- MYLACAND can be administered with other heart failure treatment, including ACE inhibitors, beta-blockers, and digoxin or a combination of these medicines (*see section 5.1*).

Use in black patients:

- The antihypertensive effect of MYLACAND is less in black than non-black (Caucasian, Asian and other) patients.
- Consequently, up titration of MYLACAND and concomitant therapy (such as thiazide diuretics) may be more frequently needed for blood pressure control in black than non-black patients.

Dosage in heart failure:

- The usual recommended initial dose of MYLACAND is 4 mg once daily.
- Up titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks (*see section 4.4*).

Special populations:

Elderly population:

- No initial dosage adjustment is necessary for elderly patients with normal renal and hepatic function.

Renal impairment:

- No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 ml/min/1,73m^2 BSA).
- In patients with severe renal impairment (i.e. creatinine clearance < 30 ml/min/1,73m^2 BSA), MYLACAND is contraindicted (*see section 4.3*).

Hepatic Impairment:

- No initial dosage adjustment is necessary in patients with mild to moderate hepatic impairment. There is no experience available in patients with severe hepatic impairment and/or cholestasis (*see section 4.3*).
- A lower initial dose of 4 mg should be considered.

Paediatric population

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

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance, candesartan cilexetil or to any of the excipients of MYLACAND.
- 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) (*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 may lead to toxic blood concentrations of lithium (*see section 4.5*).
- Pregnancy and lactation (*see section 4.6*).
- Severe hepatic impairment and/or cholestasis (*see section 4.2 sub-header 'Hepatic Impairment').*
- The concomitant use of MYLACAND 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.

4.4 Special warnings and precautions for use

Renal impairment:

Changes in renal function may be anticipated in susceptible patients treated with MYLACAND**.**

When administering MYLACAND 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 m2 BSA) (*see section 4.3)*.

Evaluation of patients with heart failure should include periodic assessments of renal function. During dose titration of MYLACAND, monitoring of serum creatinine and potassium is recommended.

Pregnancy:

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

In post-menarche patients the possibility of pregnancy should be evaluated on a regular basis. Appropriate information should be given and/or action taken to prevent the risk of exposure during pregnancy (*see sections 4.3 and 4.6*).

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 and aliskiren is therefore contraindicated *(see section 4.3*).

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

Hypotension:

Hypotension may occur during treatment with MYLACAND in heart failure patients.

It may also occur in hypertensive patients with intravascular volume depletion. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted.

Haemodialysis*:*

During dialysis the blood pressure may be particularly sensitive to AT_1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, candesartan as contained in MYLACAND should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis:

MYLACAND 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*).

Kidney transplantation:

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

Hepatic impairment:

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

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy):

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

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 candesartan is not recommended in this population.

Hyperkalaemia:

Concomitant use of MYLACAND with 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. Monitoring of potassium should be undertaken as appropriate.

In heart failure patients treated with MYLACAND**,** hyperkalaemia may occur. During treatment with MYLACAND in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors.

Anaesthesia and surgery:

Hypotension may occur during anaesthesia and surgery in patients treated with MYLACAND**,** 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.

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, azotaemia uraemia, 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 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.

4.5 Interaction with other medicines and other forms of Interaction

- No interactions of clinical significance have been identified.
- Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, digoxin, oral contraceptives (ethinylestradiol/levonorgestrel), glibenclamide, nifedipine.
- Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicines (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate (*see section 4.4*).

- Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with MYLACAND (*see section 4.3*)**.**
- The antihypertensive effect of MYLACAND may be enhanced by other antihypertensive medicines. When MYLACAND is administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.
- The bioavailability of candesartan is not affected by food.
- Post marketing reports suggest a rare but significant interaction with increase of INR and bleeding with concomitant warfarin therapy.
- **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 should be discontinued.

Medicines affecting the renin-angiotensin system, such as MYLACAND, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.

Breastfeeding

Candesartan is excreted in breast milk. Because of the potential for adverse effects on the breastfed infant, breastfeeding should be discontinued if the use of MYLACAND is considered essential (*see section 4.3*).

4.7 Effects on ability to drive and use machines

The effect of MYLACAND 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 dizziness or weariness may occur during treatment.

4.8 Undesirable effects

MYLACAND can have side effects.

a. Summary of the safety profile

Treatment of Heart Failure:

The adverse experience profile of candesartan cilexetil in heart failure patients was consistent with the pharmacology of the substance and the health status of the patients. The most frequently reported adverse reactions were hyperkalaemia, hypotension and renal impairment. These events were more frequent in patients over 70 years of age, diabetics, or subjects who received other medicines.

b. Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Frequency not known**
Infections and Infestations:	Respiratory infection		
Blood and the lymphatic system disorders:		Leucopenia, neutropenia and agranulocytosis	
Metabolism and nutrition disorders:		Hyponatraemia, hyperkalaemia	
Nervous system disorders:	Dizziness/vertigo, headache		
Vascular disorders:	Hypotension		
Respiratory, thoracic and mediastinal disorders:		Cough	

Gastro-intestinal disorders:		Nausea	Diarrhoea
Hepato-biliary disorders:		Increased liver enzymes, abnormal hepatic function or hepatitis	
Skin and subcutaneous tissue disorders:		Rash, urticaria, pruritus, angioedema	
Musculo-skeletal, connective tissue and bone disorders:		Back pain, arthralgia, myalgia	
Renal and urinary disorders:		Renal impairment, including renal failure in susceptible patients (*see section 4.4*).	

Description of selected adverse reactions

Laboratory findings:

Small decreases in haemoglobin have been seen in patients with renal impairment. Periodic monitoring of serum potassium and creatinine levels is recommended.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare 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

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 is likely to be symptomatic hypotension and dizziness.

Treatment:

If symptomatic hypotension should occur, symptomatic treatment should be instituted, and vital signs monitored.

The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution.

Sympathomimetic medicines may be administered if the above-mentioned measures are not sufficient.

Note: Candesartan is not removed by haemodialysis.

1.3.1.1 Professional Information for medicines for human use

5 PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

A 7.1.3 Vascular medicines – other hypotensives

Pharmacotherapeutic group:

Agents acting on the renin-angiotensin system, Angiotensin II antagonists, plain, ATC code: C09CA06.

Pharmacodynamic effects:

Candesartan is an angiotensin II receptor antagonist, selective for AT_1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity. It is a prodrug. 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 II (AT_1) receptors results in dose related increases in plasma renin activity, angiotensin I and angiotensin II concentrations, and a decrease in plasma aldosterone concentration.

5.2 Pharmacokinetic properties

Absorption and distribution:

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

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

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.

Biotransformation and elimination:

Candesartan is mainly eliminated unchanged via urine and bile and only to a minor extent eliminated by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4. Based on *in* vitro data, no interaction would be expected to occur *in vivo* with medicines whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4.The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

The total plasma clearance of candesartan is about 0,37 ml/min/kg, with 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 metabolite are excreted via the urine (30 %) and to a larger extent (70 %) via the faeces.

Pharmacokinetics in special populations:

In the elderly (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. 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).

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose calcium, glycerol monostearate, hydroxypropyl cellulose, iron lactose, oxide red, magnesium stearate, maize starch.

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

MYLACAND 8 mg and 16 mg:

Cold form blister pack comprises of cold form laminate (aluminium foil laminated to oriented polyamide on one side and to PVC on the other side i.e. OPA/Al/PVC) on one side and hard tempered aluminium foil on the other side.

Blister packs are packed in a triple laminated pouch with dessicant between the blister pack and triple laminated pouch and sealed.

Pouch is placed in a carton.

The HDPE bottle pack comprises with a white opaque HDPE bottle with a white opaque screw cap with induction sealing liner with absorbent cotton and dessicant in 30's and 90's.

The HDPE bottle is placed in a carton.

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

Viatris South Africa (Pty) Ltd

4 Brewery Street, Isando

Johannesburg,

1609

8 REGISTRATION NUMBER(S)

MYLACAND 8 mg: 45/7.1.3/0301

MYLACAND 16 mg: 45/7.1.3/0302

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 October 2013

10 DATE OF REVISION OF TEXT

19 December 2023