PROFESSIONAL INFORMATION FOR ABECARD

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ABECARD 8 tablets

ABECARD 16 tablets

ABECARD 32 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABECARD 8: Each tablet contains 8 mg candesartan cilexetil.
Contains sugar (lactose monohydrate, 129,80 mg).
Contains salt (sodium, 0,35 mg).

ABECARD 16: Each tablet contains 16 mg candesartan cilexetil.
Contains sugar (lactose monohydrate, 121,80 mg).
Contains salt (sodium, 0,35 mg).

ABECARD 32: Each tablet contains 32 mg candesartan cilexetil.
Contains sugar (lactose monohydrate, 243,60 mg).
Contains salt (sodium, 0,70 mg).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ABECARD 8: Round, biconvex, approximately 8 mm in diameter, white to off-white tablets; score line on one side and embossed C/8 on the same side.

ABECARD 16: Round, biconvex, approximately 8 mm in diameter, white to off-white tablets; score line on one side and embossed C/16 on the same side.

ABECARD 32: Round, biconvex, approximately 10,5 mm in diameter, white to off-white tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABECARD is indicated for mild to moderate hypertension. It may either be given as monotherapy, or for enhanced efficacy, in combination with other antihypertensive agents such as thiazide diuretics and dihydropyridine calcium antagonists.

Heart failure:

Treatment with **ABECARD** can reduce mortality, reduce hospitalisation due to heart failure and improve symptoms in patients with impaired left ventricular systolic function (LVEF ≤ 40 %).

4.2 Posology and method of administration

Dosage in hypertension

The recommended initial dose of **ABECARD** is 8 mg once daily.
The usual maintenance dose is 8 to 16 mg once daily.
The maximum antihypertensive effect is attained within 4 weeks.
In some patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 32 mg once daily.

Concomitant therapy

ABECARD may be used as monotherapy or if necessary, concomitantly with other antihypertensive agents, such as thiazide diuretics and dihydropyridine calcium antagonists, e.g. amlodipine.

Special patient populations

Use in elderly (65 years and older):

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

Use in children:

The safety and efficacy of **ABECARD** have not been established in children.

Use in impaired renal function:

No initial dose adjustment is necessary for patients with mild to moderate renal impairment (i.e. creatinine clearance ≥ 30 mL/min per 1,73 m2 BSA). **ABECARD** is contra-indicated in patients with severe renal impairment (< 15-30 mL/min per 1,73 m2 BSA).

Use in hepatic impairment:

No initial dosage adjustment is required in patients with mild to moderate hepatic impairment (see section 4.4).
There is no experience available in patients with severe hepatic impairment and/or cholestasis (see section 4.3).

Use in black patients:

The antihypertensive effect of **ABECARD** may be less in black than non-black (Caucasian, Asian and other) patients. Consequently, up-titration of **ABECARD** 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 **ABECARD** is 4 mg once daily with a target dose of 32 mg once daily. This is achieved by doubling the dose at approximately 2 week intervals, as tolerated by the patient (see section 4.4).

Concomitant therapy

ABECARD may be given concomitantly with other cardiac failure treatment, such as ACE-inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products.

Special patient populations

Elderly (65 years or older):

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

Children:

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

Method of administration:

ABECARD can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to any of the ingredients of **ABECARD**.
- 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 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 **ABECARD** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- Safety and efficacy have not been established in children.
- The concomitant use of **ABECARD** with aliskiren-containing products is contraindicated (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Should a woman become pregnant while taking ABECARD, the treatment must be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and 4.6).

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

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers (ARBs) or aliskiren may increase the risk of hypotension, hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of the RAAS through the combined use of **ABECARD** and aliskiren is therefore contra-indicated (see section 4.3).
ABECARD should not be used concomitantly with aliskiren (see section 4.3).

General

Treatment with medicines that affect the renin-angiotensin-aldosterone system has been associated with acute hypotension, uraemia, oliguria or acute renal failure in patients whose vascular tone and renal function mainly depend on the activity of this system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis).
Excessive blood pressure decrease in patients with ischaemic heart disease or ischaemic cerebrovascular disease could result in myocardial infarction or stroke.

The antihypertensive effect of candesartan, as in **ABECARD**, may be enhanced by other medicines with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.

Hypotension

Hypotension may occur during treatment with **ABECARD** in heart failure patients and in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolaemia should be attempted; a lower dose may also be required (see section 4.2).

Renal artery stenosis

Increases in serum creatinine or blood urea have occurred in patients with unilateral or bilateral renal artery stenosis or stenosis of the artery to a solitary kidney (see section 4.3).

Renal impairment

Changes in renal function may be anticipated in susceptible patients treated with **ABECARD**.
Periodic monitoring of serum potassium and creatinine levels is recommended in hypertensive patients with renal impairment.

There is very limited experience in patients with very severe or end-stage renal impairment (i.e. creatinine clearance < 15 mL/min/1,73 m^2 BSA).

Monitoring of patients with heart failure should include periodic assessments of renal function, especially in elderly patients and patients with impaired renal function. During dose titration of **ABECARD**, monitoring of serum creatinine and potassium is recommended.

Kidney transplantation

There is no experience regarding the administration of ABECARD in patients with a recent kidney transplant.

Hepatic impairment

For patients with moderate hepatic impairment, consideration should be given to initiation of ABECARD at a lower dose. No initial dosage adjustment is necessary in patients with mild hepatic impairment (see section 4.2). No information is available on the use of ABECARD in patients with severe hepatic function impairment and/or. cholestasis.

Aortic and mitral valve stenosis (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).

Hyperkalaemia

The concurrent use of **ABECARD** with potassium-sparing diuretics, salt substitutes, potassium supplements or any medicine that may increase potassium in patients, may lead to increases in serum potassium in hypertensive patients.
Since hyperkalaemia may occur, serum potassium concentrations should be monitored in patients with heart failure. Concomitant administration with ACE-inhibitors or a potassium-sparing diuretic is not recommended (see section 4.3 and 4.5).

Concomitant therapy with an ACE inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when **ABECARD** is used in combination with an ACE inhibitor (see section 4.8).

Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and candesartan cilexetil is also not recommended. Use of these combinations should be under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure.

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

Anaesthesia and surgery

Due to blockade of the renin-angiotensin system patients may experience hypotension during anaesthesia and surgery when receiving ABECARD. In case of severe hypotension it may be necessary to administer intravenous fluids and/or vasopressors.

Haemodialysis

During dialysis the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, **ABECARD** should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of **ABECARD** is not recommended in this population.

Excipient warning

ABECARD contains lactose monohydrate.
Patients with the rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take **ABECARD**.
Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.
ABECARD contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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 AAS) 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).

Medicines which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin,digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicines have been identified.

Combinations containing any of the following medicines, depending on the amount present, may also interact with ABECARD:

- Other antihypertensives. The antihypertensive effect of **ABECARD** may be enhanced.
- Potassium-sparing diuretics such as spironolactone, potassium supplements and salt substitutes containing potassium may increase potassium levels. In heart failure patients treated with **ABECARD**, hyperkalaemia may occur especially when taken concomitantly with these medicines (see section 4.3).
- Diuretics. Concurrent use with **ABECARD** may have additive hypotensive effects.
- Lithium. Serum lithium level increases and toxicity have been reported with concomitant use (see section 4.3).
- When angiotensin II receptor antagonists are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur
- As with ACE inhibitors, concomitant use of angiotensin II receptor antagonists and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
- Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy and lactation has not been established (see section 4.3).

Should a woman become pregnant while receiving ABECARD, 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 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 trimester. Cases of defective skull ossification have been observed. Premature and low birth mass can occur.

Women of childbearing age should ensure effective contraception.

Lactation:

ABECARD is distributed into the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, breastfeeding should be discontinued if the use of **ABECARD** is considered essential (see section 4.3).

4.7 Effects on ability to drive and use machines:

The effect of **ABECARD** 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 weakness may occur during treatment.

4.8 Undesirable effects

The following side effects may occur:

System Organ Class	Frequency	Side effects
Infections and infestations	Frequent	Respiratory infection
Immune system disorders	Less frequent	Angioedema
Blood and lymphatic system disorders	Less frequent	Leukopenia, neutropenia, agranulocytosis, thrombocytopenia
Metabolism and nutrition disorders	Frequent	Hyperkalaemia
	Less frequent	Hyponatraemia
Nervous system disorders	Frequent	Headache, dizziness/vertigo
Cardiac disorders	Less frequent	Angina pectoris, myocardial infarction
Vascular disorders	Frequent	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Pharyngitis, rhinitis, upper respiratory tract infection, cough
Gastrointestinal disorders	Less frequent	Nausea
	Frequency unknown	Diarrhoea
Hepato-biliary disorders	Less frequent	Abnormal hepatic function, hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Urticaria, pruritus, rash
Musculoskeletal and connective tissue disorders	Less frequent	Hyperuricaemia or gout, back pain, myalgia, arthralgia
Renal and urinary disorders	Frequent	Impaired renal function
	Less frequent	Renal failure in susceptible patients (see section 4.4)
Investigations	Less frequent	Increases in creatinine, urea and potassium. Decreases in haemoglobin and haematocrit values. Raised liver enzymes values

Laboratory findings:

Small decreases in haemoglobin have been seen. Significant increases in creatinine, urea or potassium and decrease in sodium have been observed. In patients with severe renal impairment, periodic monitoring of serum potassium and creatinine levels should be considered.

Hyperkalaemia and renal impairment are common in patients treated with **ABECARD** for the indication of heart failure. Periodic monitoring of serum creatinine and potassium is recommended (see section 4.4).

Reporting of suspected adverse reactions:

Reporting of 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

Symptoms:

The symptoms of an overdosage of **ABECARD** would be dizziness, hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

Management:

If symptomatic hypotension should occur, supportive 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. **ABECARD** can NOT be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin II antagonists, plain ATC: code C09DA06
A 7.1.3 Other hypotensives.

Candesartan is a nonpeptide angiotensin II receptor antagonist that selectively blocks the binding of angiotensin II to the AT_1 receptors. Angiotensin II stimulates the adrenal cortex to synthesise and secrete aldosterone, which decreases the excretion of sodium and increases the excretion of potassium. Angiotensin II also acts as a vasoconstrictor in vascular smooth muscle. By blocking the binding of angiotensin II to the AT_1 receptors, candesartan causes vasodilation and decreases the effects of aldosterone. The antagonism of the AT_1 receptors results in dose-related increases in plasma renin levels, angiotensin I and II levels, and a decrease in plasma aldosterone concentration.

Hypertension:

Antihypertensive action is caused by the decreased systemic peripheral resistance.
The heart-rate, stroke volume and cardiac output will not be affected by candesartan.
Candesartan increases renal blood flow and either has no effect on, or increases glomerular filtration rate while renal vascular resistance and filtration fractions are reduced.

Heart failure:

Candesartan decreases pulmonary capillary wedge pressure, systemic vascular resistance and aldosterone levels.
Candesartan increases plasma renin activity and angiotensin II concentration.

5.2 Pharmacokinetic properties

Absorption and distribution

Candesartan cilexetil is an inactive ester prodrug that is completely hydrolysed to the active form, candesartan, during absorption from the gastrointestinal tract. Peak plasma levels are obtained 3 to 4 hours after oral administration.
Candesartan is not affected by food.

Candesartan is highly plasma-protein bound (more than 99 %). The volume of distribution of candesartan is 0,1 litres/kg.
The candesartan serum concentration increases linearly with increasing doses in the therapeutic dose range.

Metabolism and elimination

The terminal elimination half-life is approximately 9 hours.

Elimination after oral administration:

Renal – 33 %
Faecal – 67 %
Candesartan is not removable by haemodialysis.
Elimination of candesartan is primarily as unchanged substance in the urine and, by the biliary route, in the faeces. Minor hepatic metabolism of candesartan occurs by O-deethylation to form an inactive metabolite.
Plasma clearance is about 0,37 mL/min per kg.
Renal clearance is 0,19 mL/min per kg.

Pharmacokinetics in special populations

Elderly patients (65 years and older):

In elderly patients the C_{max} and AUC of candesartan are respectively increased by approximately 50 % and 80 %, compared with young adults.

Renal impairment:

In patients with mild (creatinine clearance 60-90 mL/min), moderate (creatinine clearance 30-60 mL/min) and severe (creatinine clearance 15-30 mL/min) renal impairment, the C_{max} and AUC of candesartan increased during repeated dosing. In patients with severe renal impairment both the t1/2 and AUC of candesartan were approximately double those of persons with normal renal function. No information is available on patients with more severe renal failure, i.e. creatinine clearance below 15 mlL/min.

Hepatic impairment:

A significant increase in the mean AUC of candesartan of respectively 30 % and 145 % was observed in patients with mild hepatic impairment and patients with moderate to severe hepatic impairment. No data are available on patients with cholestasis or severe hepatic impairment.

5.3 Preclinical safety data

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. Candesartan have effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan causes a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit).
Effects on the kidneys (such as interstitial nephritis, tubular distension, basophilic tubules; increased plasma concentrations of urea and creatinine) was induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion.

In normotensive neonatal and juvenile rats, candesartan causes a reduction in body weight and heart weight. As in adult animals, these effects are considered to result from the pharmacological action of candesartan. At the lowest dose of 10 mg/kg exposure to candesartan was between 12 and 78 times the levels found in children aged 1 to < 6 who received candesartan cilexetil at a dose of 0.2 mg/kg and 7 to 54 times those found in children aged 6 to < 17 who received candesartan cilexetil at a dose of 16 mg. The safety margin for the effects on heart weight and the clinical relevance of the finding is unknown.

Foetotoxicity has been observed in late pregnancy.
Data from *in vitro* and *in vivo* mutagenicity testing indicates that candesartan will not exert mutagenic or clastogenic activities under conditions of clinical use.
There was no evidence of carcinogenicity.

The renin-angiotensin-aldosterone system plays a critical role in kidney development in utero.
Renin-angiotensin-aldosterone system blockade has been shown to lead to abnormal kidney development in very young mice.
Administering medicines that act directly on the renin-angiotensin-aldosterone system can alter normal renal development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Maize starch
Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original packaging (in the blisters in the carton) at or below 25 °C.
KEEP MEDICINE OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Packs of 28 or 30 tablets packed in transparent PVC/PVDC/Aluminium blisters in a cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd
2 Waterford Mews
Waterford Place
Century City
7441
Cape Town
South Africa

8. REGISTRATION NUMBERS

ABECARD 8: 46/7.1.3/0231
ABECARD 16: 46/7.1.3/0232
ABECARD 32: 46/7.1.3/0233

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2015

10. DATE OF REVISION OF THE TEXT

To be advised by SAHPRA