PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

Candepres® Plus 16/12,5 mg (tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **CANDEPRES PLUS 16/12,5** tablet contains 16 mg candesartan cilexetil and 12,5 mg hydrochlorothiazide.

Contains sugar (75,850 mg lactose monohydrate per tablet).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

CANDEPRES PLUS 16/12,5 tablets are apricot, mottled, oval biconvex tablets, scored on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CANDEPRES PLUS 16/12,5 is indicated for essential hypertension in patients stabilised on the individual components given at the same dosages.

4.2 Posology and method of administration

Dosage:

The recommended dose of **CANDEPRES PLUS 16/12,5** is 1 tablet once daily.

Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Use in the elderly:

No initial dosage adjustment is necessary in elderly patients.

Use in patients with intravascular volume depletion:

Dose titration of candesartan cilexetil is recommended in patients at risk for hypotension, such as patients with possible volume depletion (an initial dose of candesartan cilexetil of 4 mg may be considered in these patients).

Use in impaired renal function:

CANDEPRES PLUS 16/12,5 should not be used in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Use in impaired hepatic function:

CANDEPRES PLUS 16/12,5 should not be used in patients with moderate to severe hepatic impairment and/or cholestasis.

Children and adolescents (less than 18 years of age):

The safety and efficacy of **CANDEPRES PLUS 16/12,5** have not been established in children.

Method of administration:

Oral use.

CANDEPRES PLUS 16/12,5 should be taken once daily with or without food.

There is no clinically significant interaction between hydrochlorothiazide and food.

4.3 Contraindications

- Hypersensitivity to candesartan cilexetil, hydrochlorothiazide or any of the ingredients of **CANDEPRES PLUS 16/12,5** listed in section 6.1.

- 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.
- Severe hepatic impairment and/or cholestasis.
- Aortic stenosis.
- Concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride (see section 4.5).
- Porphyria.
- **CANDEPRES PLUS 16/12,5** contains hydrochlorothiazide (a thiazide diuretic) and should not be given to patients with Addison's disease.
- Lithium therapy: Concomitant administration with **CANDEPRES PLUS 16/12,5** may lead to toxic blood concentrations of lithium (see section 4.5).
- Pregnancy and lactation (see section 4.6).
- The concomitant use of **CANDEPRES PLUS 16/12,5** with aliskiren-containing products is contraindicated (see section 4.4).
- Refractory hypokalaemia and hypercalcaemia.
- Gout.

4.4 Special warnings and precautions for use

Should a woman become pregnant while receiving CANDEPRES PLUS 16/12,5, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see section 4.3 and section 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 RAAS through the combined use of **CANDEPRES PLUS 16/12,5** and aliskiren is therefore contraindicated (see section 4.3). **CANDEPRES PLUS 16/12,5** should not be used concomitantly with aliskiren (see section 4.3).

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 other medicines that affect this system has been associated with acute hypotension, uraemia, oliguria and acute renal failure. The possibility of similar effects cannot be excluded with **CANDEPRES PLUS 16/12,5**. Excessive blood pressure decrease in patients with ischaemic heart disease or atherosclerotic cerebrovascular disease could result in a myocardial infarction or stroke.

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma but are more likely in patients with such a history. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazide diuretics.

The antihypertensive effect of **CANDEPRES PLUS 16/12,5** may be enhanced by other medicines with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.

Renal impairment:

As with other medicines inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with **CANDEPRES PLUS 16/12,5**.

When **CANDEPRES PLUS 16/12,5** is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium, creatinine and uric acid levels is recommended.

Kidney transplantation:

There is limited clinical evidence regarding **CANDEPRES PLUS 16/12,5** use in patients who have undergone renal transplant.

Renal artery stenosis:

Medicines that affect the renin-angiotensin-aldosterone system (RAAS), including **CANDEPRES PLUS 16/12,5**, 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 **CANDEPRES PLUS 16/12,5** is not recommended until this condition has been corrected.

Anaesthesia and surgery:

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

Hepatic impairment:

Hydrochlorothiazide should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may

precipitate hepatic coma. There is no clinical experience with **CANDEPRES PLUS 16/12,5** in patients with severe hepatic impairment (see section 4.3).

Hydrochlorothiazide should be avoided in patients with severe hepatic impairment, in whom encephalopathy may be precipitated. Patients with hepatic cirrhosis are also more likely to develop hypokalaemia.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy):

As with other vasodilators, special caution is indicated 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 generally will not respond to antihypertensive medicines acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of **CANDEPRES PLUS 16/12,5** is not recommended in this population.

Electrolyte imbalance:

As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. **CANDEPRES PLUS 16/12,5** can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis).

Hydrochlorothiazide should be used with caution in patients with existing fluid and electrolyte disturbances or who are at risk from changes in fluid and electrolyte balance, such as the elderly.

CANDEPRES PLUS 16/12,5 may decrease urinary calcium excretion and may cause intermittent and slightly increased serum calcium concentrations. Marked hypercalcaemia may be a sign of hidden hyperparathyroidism. **CANDEPRES PLUS 16/12,5** should be discontinued before carrying out tests for parathyroid function.

There is an increased risk of cholecystitis in patients taking hydrochlorothiazide.

Hydrochlorothiazide dose-dependently increases urinary potassium excretion which may result in hypokalaemia. This effect of hydrochlorothiazide seems to be less evident when combined with candesartan cilexetil. The risk for hypokalaemia may be increased in patients with cirrhosis of the liver, in patients experiencing brisk diuresis, in patients with an inadequate oral intake of electrolytes and in patients receiving concomitant therapy with corticosteroids or adrenocorticotropic hormone (ACTH).

Patients with hepatic cirrhosis are also more likely to develop hypokalaemia. Hyponatraemia may occur in patients with severe heart failure who are very oedematous, particularly with large doses of hydrochlorothiazide and restricted salt intake. All patients should be carefully observed for signs of fluid and electrolyte imbalance, especially in the presence of vomiting or during parenteral fluid therapy.

Hydrochlorothiazide should not be given to patients with Addison's disease.

Treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment.

Concomitant use of **CANDEPRES PLUS 16/12,5** and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicines that may increase serum potassium levels

(e.g. heparin sodium, co-trimoxazole also known as trimethoprim/sulfamethoxazole) may lead to increases in serum potassium (see section 4.5). Monitoring of potassium should be undertaken as appropriate (see section 4.3).

Hydrochlorothiazide has been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.

Metabolic and endocrine effects:

Treatment with **CANDEPRES PLUS 16/12,5** may impair glucose tolerance. Dosage adjustment of antidiabetics, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy. Increases in cholesterol and triglyceride levels have been associated with thiazide diuretic therapy. However, at the 12,5 mg dose contained in **CANDEPRES PLUS 16/12,5**, minimal or no effects were reported.

Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Photosensitivity:

Cases of photosensitivity reactions have been reported during use of hydrochlorothiazide (see section 4.8). If a photosensitivity reaction occurs, it is recommended to stop treatment. If re-administration of treatment is essential, it is recommended to protect areas exposed to the sun or to artificial UVA radiation.

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 exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitising actions of hydrochlorothiazide could act as a possible

mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC 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 case of exposure, adequate protection should be advised to the patients in order to minimise the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Hydrochlorothiazide, a sulfonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of medicinal product initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamides or penicillin allergy.

Acute Respiratory Toxicity

Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary oedema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnoea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, **CANDEPRES PLUS 16/12,5** should be withdrawn and appropriate

treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

CANDEPRES PLUS 16/12,5 contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **CANDEPRES PLUS 16/12,5**. **CANDEPRES PLUS 16/12,5** contains lactose monohydrate which may have an effect on the glycaemic control of patients with diabetes mellitus.

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 (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 section 4.4).

The use of candesartan cilexetil with the renin inhibitor aliskiren is not recommended and should be avoided in some patients.

No interactions of clinical significance have been identified for candesartan cilexetil. Compounds which have been investigated in clinical pharmacokinetic studies include warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril. No clinical significant pharmacokinetic interactions with these medicines have been identified.

The bioavailability of candesartan is not affected by food.

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, steroids or adrenocorticotropic hormone (ACTH).

Concomitant use of **CANDEPRES PLUS 16/12,5** and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicines that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when **CANDEPRES PLUS 16/12,5** is administered with such medicines and with the following medicines that could induce *torsades de pointes*:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide),
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide),
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperiodol),
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with **CANDEPRES PLUS 16/12,5**. Use of **CANDEPRES PLUS 16/12,5** with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended (see section 4.3).

When **CANDEPRES PLUS 16/12,5** is administered simultaneously with non-steroidal anti-inflammatory medicines i.e. selective COX-2 inhibitors, acetylsalicylic acid (> 3 g/day) and non-selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), attenuation of the antihypertensive effect may occur.

Concomitant use of **CANDEPRES PLUS 16/12,5** 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. **CANDEPRES PLUS 16/12,5** 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.

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

The use of NSAIDs may also attenuate the hypotensive effect of candesartan.

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect on non-depolarising skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide.

Hydrochlorothiazide may increase serum calcium levels due to decreased excretion. If calcium supplements or Vitamin D must be prescribed, serum calcium levels should be monitored and dosage adjusted accordingly.

The hyperglycaemic effect of beta-blockers and diazoxide may be enhanced by hydrochlorothiazide.

Anticholinergic medicines (e.g. atropine, biperiden) may increase the bioavailability of hydrochlorothiazide by decreasing gastrointestinal 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.

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

The hyponatraemic effect of hydrochlorothiazide may be intensified by concomitant administration of medicines such as furosemide, antidepressants, antipsychotics, antiepileptics etc. Severe hyponatraemia has been reported in patients taking trimethoprim with co-amilozide and hydrochlorothiazide (see section 4.4). Caution is advised in long-term administration of these medicines.

Treatment with a hydrochlorothiazide may impair glucose tolerance. Dosage adjustment of antidiabetic medication, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

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

Hydrochlorothiazide may increase the risk of acute renal insufficiency especially with high doses of iodinated contrast media.

Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Concurrent use of hydrochlorothiazide with diflunisal produces significantly increased plasma concentrations of hydrochlorothiazide. In addition, the hyperuricaemic effect of hydrochlorothiazide is decreased.

Concurrent use of dopamine and **CANDEPRES PLUS 16/12,5** may increase the diuretic effect of either hydrochlorothiazide or dopamine, as a result of dopamine's direct effect on dopaminergic receptors to produce vasodilatation of renal vasculature and increase renal blood flow, dopamine also has a direct natriuretic effect.

There have been isolated reports of haemolytic anaemia in patients receiving concomitant treatment with methyldopa and hydrochlorothiazide.

Dose adjustment of uricosuric medications may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dosage of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

There is no clinically significant interaction between hydrochlorothiazide and food.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established (see section 4.3). When pregnancy is planned or confirmed, **CANDEPRES PLUS 16/12,5** should be discontinued.

Medicines affecting the renin-angiotensin system, such as **CANDEPRES PLUS 16/12,5**, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women.
Women of childbearing age should ensure effective contraception.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with angiotensin II receptor inhibitors, similar risks may exist for this class of medicines.

CANDEPRES PLUS 16/12,5 passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

The use of **CANDEPRES PLUS 16/12,5** during the first trimester of pregnancy has been associated with an increased risk of birth defects, in particular of the cardiovascular and the central nervous system.

Oligohydramnios as well as hypotension, oliguria and anuria in newborns, have been reported after administration of candesartan, such as contained in **CANDEPRES PLUS 16/12,5** in the second and third trimester.

Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3 and section 4.4).

Candesartan and other angiotensin II receptor antagonists are contraindicated in all trimesters of pregnancy; they have been associated with foetal toxicity and intra-uterine or neonatal death.

Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia.
Hydrochlorothiazide can cross the placenta and there have been reports of neonatal jaundice, thrombocytopenia, and electrolyte imbalances after maternal use. Reductions in maternal blood volume could also adversely affect placental perfusion.

Based on the above information, **CANDEPRES PLUS 16/12,5** is contraindicated in pregnancy. If pregnancy is detected during treatment, **CANDEPRES PLUS 16/12,5** should be discontinued (see section 4.4).

Breastfeeding

It is not known whether candesartan is excreted in human milk. However, candesartan is excreted in the milk of lactating rats.

Hydrochlorothiazide passes into mother's milk. Because of the potential for adverse effects on the nursing infant, **CANDEPRES PLUS 16/12,5** is contraindicated during breastfeeding.

Effects on ability to drive and use machines

No studies on the effects of **CANDEPRES PLUS 16/12,5** on the ability to drive and use machines have been performed. However, it should be taken into account that occasionally dizziness or weariness may occur during treatment with **CANDEPRES PLUS 16/12,5**.

4.8 Undesirable effects

Candesartan cilexetil:

Infections and infestations:

Frequent: Respiratory infection

Blood and lymphatic system disorders:

Less frequent: Leukopenia, neutropenia, agranulocytosis, thrombocytopenia

Metabolism and nutrition disorders:

Less frequent: Hyperkalaemia, hyponatraemia

Nervous system disorders:

Frequent: Dizziness/vertigo, headache

Frequency unknown: Fatigue

Cardiac disorders:

Frequency unknown: Angina pectoris, myocardial infarction

Vascular disorders:

Frequent: Hypotension

Respiratory, thoracic and mediastinal disorders:

Less frequent: Cough, pharyngitis, rhinitis

Gastrointestinal disorders:

Less frequent: Nausea

Frequency unknown: Diarrhoea, gastrointestinal disturbances

Hepatobiliary disorders:

Less frequent: Increased liver enzymes, abnormal hepatic function, hepatitis

Skin and subcutaneous tissue disorders:

Less frequent: Angioedema, rash, urticaria, pruritus

Musculoskeletal and connective tissue disorders:

Less frequent: Back pain, arthralgia, myalgia, rhabdomyolysis

Frequency unknown: Hyperuricaemia, gout

Renal and urinary disorders:

Less frequent: Renal impairment, including renal failure in susceptible patients (see section 4.4)

Hydrochlorothiazide:

Neoplasms benign, malignant and unspecified (incl. cysts and polyps):

Frequency unknown: Non-melanoma skin cancer (Basal cell carcinoma and squamous cell carcinoma)

Blood and lymphatic system disorders:

Less frequent: Thrombocytopenia sometimes with purpura, agranulocytosis, leukopenia, haemolytic anaemia, bone marrow failure

Frequency unknown: Neutropenia, aplastic anaemia

Immune system disorders:

Less frequent: Hypersensitivity reactions

Metabolism and nutrition disorders:

Frequent: Hypokalaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia

Less frequent: Hypercalcaemia, hyperglycaemia, glycosuria and worsening of diabetic metabolic state, hypochloraemic alkalosis

Psychiatric disorders:

Less frequent: Sleep disturbances, depression and restlessness

Nervous system disorders:

Frequent: Light-headedness, vertigo

Less frequent: Paraesthesia, headache, dizziness

Eye disorders:

Less frequent: Visual impairment

Frequency unknown: Transient blurred vision, yellow vision, acute angle-closure glaucoma, choroidal effusion

Cardiac disorders:

Less frequent: Cardiac arrhythmias

Vascular disorders:

Frequent: Postural hypotension

Frequency unknown: Necrotising angiitis (vasculitis, cutaneous vasculitis)

Respiratory, thoracic and mediastinal disorders:

Less frequent: Respiratory distress (including pneumonitis and pulmonary oedema), Acute respiratory distress syndrome (ARDS) (see section 4.4)

Gastrointestinal disorders:

Frequent: Loss of appetite, mild nausea, vomiting

Less frequent: Anorexia, gastrointestinal discomfort, diarrhoea, constipation, pancreatitis

Frequency unknown: Sialadenitis

Hepatobiliary disorders:

Less frequent: Intrahepatic cholestasis or jaundice

Skin and subcutaneous tissue disorders:

Frequent: Urticaria and other forms of rash

Less frequent: Photosensitisation, toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus

Frequency unknown: Erythema multiforme

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Muscle spasm, gout

Renal and urinary disorders:

Frequent: Glycosuria

Less frequent: Renal dysfunction and interstitial nephritis

Frequency unknown: Acute renal failure

Reproductive system and breast disorders:

Frequent: Impotence

Less frequent: Decreased sexual ability

General disorders and administrative site conditions:

Frequent: Asthenia

Frequency unknown: Pyrexia

Investigations:

Frequent: Increases in cholesterol and triglycerides

Frequency unknown: Increases in blood urea and serum creatinine

Description of selected adverse reactions

Non-melanoma skin cancer: based on available data from epidemiological studies, cumulative dose dependent association between hydrochlorothiazide and NMSC has been observed (see also sections 4.4 and 5.1).

Candesartan cilexetil and hydrochlorothiazide:

Metabolism and nutrition disorders:

Frequency unknown: Electrolyte imbalance

Nervous system disorders:

Frequent: Dizziness, vertigo, light-headedness

Cardiac disorders:

Frequency unknown: Angina, myocardial infarction

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Upper respiratory tract infection

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.

Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

Symptoms:

Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg candesartan cilexetil) in an adult patient, recovery was uneventful.

The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

Management:

No specific information is available on the treatment of overdosage with **CANDEPRES PLUS 16/12,5**. 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. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of isotonic saline solution. Serum electrolyte and acid balance should be checked and corrected, if needed. Sympathomimetic medicines may be administered if the above mentioned measures are not sufficient.

Candesartan cannot be removed by haemodialysis. It is not known to what extent hydrochlorothiazide is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.7.1.3 Other hypotensives

5.1 Pharmacodynamic properties

Candesartan cilexetil:

Mechanism of action

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end organ hypertrophy and damage. 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 1 (AT_1) receptor.

Pharmacodynamic effects

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. 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.

Candesartan does not inhibit Angiotensin Converting Enzyme (ACE), which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan with ACE inhibitors, the incidence of cough was lower in patients receiving candesartan cilexetil. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation. The antagonism of the angiotensin II (AT_1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Clinical efficacy and safety

Hypertension

In hypertension, candesartan causes a dose-dependent, long-lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral

resistance, 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 candesartan cilexetil, onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure with any dose is generally attained within four weeks and is sustained during long-term treatment. According to a meta-analysis, the average additional effect of a dose increase from 16 mg to 32 mg once daily was small. Taking into account the inter-individual variability, a more than average effect can be expected in some patients. Candesartan cilexetil once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval. The antihypertensive effect and tolerability of candesartan and losartan were compared in two randomised, double-blind studies in a total of 1 268 patients with mild to moderate hypertension. The trough blood pressure reduction (systolic/diastolic) was 13,1/10,5 mm Hg with candesartan cilexetil 32 mg once daily and 10,0/8,7 mm Hg with losartan potassium 100 mg once daily (difference in blood pressure reduction 3,1/1,8 mm Hg, $p < 0,0001$/$p < 0,0001$).

When candesartan cilexetil is used together with hydrochlorothiazide, the reduction in blood pressure is additive. An increased antihypertensive effect is also seen when candesartan cilexetil is combined with amlodipine or felodipine.

Medicines that block the renin-angiotensin-aldosterone system have less pronounced antihypertensive effect in black patients (usually a low-renin population) than in non-black patients. This is also the case for candesartan. In an open label clinical experience trial in 5 156 patients with diastolic hypertension, the blood pressure reduction during candesartan treatment was significantly less in black than non-black patients (14,4/10,3 mm Hg vs 19,0/12,7 mm Hg, $p < 0,0001$/$p < 0,0001$).

Candesartan increases renal blood flow and either has no effect on or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. In a 3-month clinical study in hypertensive patients with type 2 diabetes mellitus and microalbuminuria, antihypertensive treatment with candesartan cilexetil reduced urinary albumin excretion (albumin/creatinine ratio, mean 30 %, 95 % CI 15to 42 %). There is currently no data on the effect of candesartan on the progression to diabetic nephropathy.

The effects of candesartan cilexetil 8 to 16 mg (mean dose 12 mg), once daily, on cardiovascular morbidity and mortality were evaluated in a randomised clinical trial with 4 937 elderly patients (aged 70 to 89 years; 21 % aged 80 or above) with mild to moderate hypertension followed for a mean of 3,7 years (Study on Cognition and Prognosis in the Elderly). Patients received candesartan cilexetil or placebo with other antihypertensive treatment added as needed. The blood pressure was reduced from 166/90 to 145/80 mm Hg in the candesartan group, and from 167/90 to 149/82 mm Hg in the control group. There was no statistically significant difference in the primary endpoint, major cardiovascular events (cardiovascular mortality, non-fatal stroke and non-fatal myocardial infarction). There were 26,7 events per 1 000 patient-years in the candesartan group versus 30,0 events per 1 000 patient-years in the control group (relative risk 0,89, 95 % CI 0,75 to 1,06, p = 0,19).

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.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and non-melanoma skin cancer has been observed. One study included a population comprised of 71 533 cases of BCC and of 8 629 cases of SCC matched to 1 430 833 and 172 462 population controls, respectively. High hydrochlorothiazide use (≥ 50 000 mg cumulative) was associated with an adjusted Odds Ratio (OR) of 1,29 (95 % CI: 1,23 to 1,35) for BCC and 3,98 (95 % CI: 3,68 to 4,31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to hydrochlorothiazide: 633 cases of lip-cancer were matched with 63 067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2,1 (95 % CI: 1,7 to 2,6) increasing to OR 3,9 (3,0 to 4,9) for high use (~ 25 000 mg) and OR 7,7 (5,7 to 10,5) for the highest cumulative dose (~ 100 000 mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Absorption and distribution:

Candesartan cilexetil:

Following oral administration candesartan cilexetil is converted to the active substance candesartan. The absolute bioavailability of candesartan is approximately 40 % after an oral solution of candesartan cilexetil. The relative bioavailability of the tablet formulation compared with the same oral solution is approximately 34 % with very little variability. The estimated absolute bioavailability of the tablet is therefore 14 %. The mean peak serum concentration (C_{max}) is reached 3 to 4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. No gender related differences in the pharmacokinetics of candesartan have been observed. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Candesartan is highly bound to plasma protein (more than 99 %). The apparent volume of distribution of candesartan is 0,1 L/kg.

The bioavailability of candesartan is not affected by food.

Hydrochlorothiazide:

Hydrochlorothiazide is absorbed from the gastrointestinal tract with an absolute bioavailability of approximately 70 %. Concomitant intake of food increases the absorption by approximately 15 %. The bioavailability may decrease in patients with cardiac failure and pronounced oedema.

The plasma protein binding of hydrochlorothiazide is approximately 60 % and the plasma half-life ($t_{½}$) is ~ 2,5. The apparent volume of distribution is approximately 0,8 L/kg.

Biotransformation and elimination:

Candesartan cilexetil:

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 ($t_{½}$) 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.

There is an increase in AUC (15 to 18 %) and C_{max} (23 to 24 %) of candesartan when given together with hydrochlorothiazide. No additional accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.

Total plasma clearance of candesartan is about 0,37 ml/min/kg, with a renal clearance of about 0,19 mL/min/kg. The renal elimination of candesartan is both by glomerular filtration and active tubular secretion. Following an oral dose of ^{14}C-labelled candesartan cilexetil, approximately 26 % of the dose is excreted in the urine as candesartan and 7 % as an inactive metabolite, while approximately 56 % of the dose is recovered in the faeces as candesartan and 10 % as the inactive metabolite.

Hydrochlorothiazide:

Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged substance by glomerular filtration and active tubular secretion. The terminal $t_{½}$ of hydrochlorothiazide is approximately 8 hours. Approximately 70 % of an oral dose is eliminated in the urine within 48 hours. The half-life of hydrochlorothiazide remains unchanged (approximately 8 hours) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No additional accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy.

Pharmacokinetics in special populations:

Candesartan cilexetil:

In elderly patients (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 to moderate renal impairment, C_{max} and AUC of candesartan increased during repeated dosing by approximately 50 % and 70 %, respectively, but $t_{½}$ was not altered, compared to patients with normal renal function. The corresponding changes in patients with

severe renal impairment were approximately 50 % and 110 %, respectively. The terminal $t_{½}$ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing haemodialysis was similar to that in patients with severe renal impairment.

In two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20 % in one study and 80 % in the other study (see section 4.2). There is no experience in patients with severe hepatic impairment.

Hydrochlorothiazide:

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal impairment. The mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed. Hydrochlorothiazide is contraindicated in patients with severe renal impairment (see section 4.3).

5.3 Preclinical safety data

Candesartan cilexetil:

There was no evidence of abnormal systemic or target organ toxicity at clinically relevant doses. In preclinical safety studies candesartan had effects on the kidneys and on red cell parameters at high doses in mice, rats, dogs and monkeys. Candesartan caused 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) were induced by candesartan which could be secondary to the hypotensive effect leading to alterations of renal perfusion. Furthermore, candesartan induced hyperplasia/hypertrophy of the juxtaglomerular cells. These changes were considered to be caused by the pharmacological action of candesartan. For therapeutic doses of candesartan in humans, the hyperplasia/hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

In preclinical studies in normotensive neonatal and juvenile rats, candesartan caused 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. As a no observed effect level was not identified in these studies, 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 (see section 4.6).

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.

Hydrochlorothiazide:

Not available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carrageenan

Corn Starch

Croscarmellose Sodium

Ferric Oxide Red (E172)

Ferric Oxide Yellow (E172)

Lactose Monohydrate

Magnesium Stearate

Povidone K30

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package.

6.5 Nature and contents of container

CANDEPRES PLUS 16/12,5 tablets are packed as 30 tablets in:

Aluminium/aluminium blisters (hard foil: silver aluminium foil, coated with a polyester lacquer (matte outer side), polyurethane primer and LDPE layer (glossy inner side) and soft foil: silver (outer)/blue (inner) aluminium foil, with a desiccant, coated with oriented polyamide (matte outer side), LDPE layer with a desiccant and HDPE layer (blue inner side)). Each blister strip contains ten tablets with three blister strips packed into a cardboard carton.

or

White, round, high density polyethylene (HDPE) bottles closed with white, round, polypropylene (PP) cap - child resistant closure (CRC), fitted with an induction heat seal liner.

Not all packs may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

Marketed by: Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Streets, Woodstock, Cape Town, 8001

8. REGISTRATION NUMBER

44/7.1.3/0555

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 October 2013

10. DATE OF REVISION OF THE TEXT

29 August 2022

[1]Company Reg. No.: 1990/001979/07