1. NAME OF THE MEDICINAL PRODUCT
Candesartan Sandoz 8 mg tablet
Candesartan Sandoz 16 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Candesartan Sandoz 8 mg tablet
Each tablet contains 8 mg of candesartan cilexetil.
Each tablet contains 69.57 mg of lactose monohydrate.

Candesartan Sandoz 16 mg tablet
Each tablet contains 16 mg of candesartan cilexetil.
Each tablet contains 139.14 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet.

Candesartan Sandoz 8 mg tablet
8 mg tablets: pink, mottled, round biconvex tablet, debossed with 8 on one side and scored on the other side.

Candesartan Sandoz 16 mg tablet
16 mg tablets: pink, mottled, round biconvex tablet, debossed with 16 on one side and scored on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Treatment of hypertension.
Treatment of patients with heart failure and impaired left ventricle systolic function (left ventricular ejection fraction ≤ 40%) as add-on therapy to ACE inhibitors or when ACE inhibitors are not tolerated.

4.2 Posology and method of administration
Dosage for Hypertension
Recommended Initial Dose and Usual Maintenance Dose: 8 mg once daily.
The dose may be increased to 16 mg once daily. If blood pressure is not sufficiently controlled after 4 weeks of treatment with 16 mg once daily, the dose may be further increased to a maximum of 32 mg once daily. If blood pressure control is not achieved with this dose, alternative strategies should be considered.

Therapy should be adjusted according to blood pressure response. Most of the antihypertensive effect is attained within 4 weeks of initiation of treatment.

Elderly: No initial dosage adjustment is necessary for elderly patients.

Patients with Intravascular Volume Depletion: An initial dose of 4 mg once daily may be considered in patients at risk for hypotension e.g., patients with possible volume depletion.

Impaired Renal Function: No initial dosage adjustment is necessary in patients with mild to moderate renal impairment (i.e., creatinine clearance ≥ 30 mL/min/1.73 m^2 BSA). In patients with severe renal impairment (i.e., creatinine clearance < 30 mL/min/1.73 m^2 BSA), the clinical experience is limited and a lower initial dose of 4 mg once daily should be considered.

Use in impaired hepatic function
Patients with hepatic impairment: Dose titration is recommended in patients with mild to moderate chronic liver disease, and a lower initial dose of 4 mg should be considered. Candesartan should not be used in patients with severe hepatic impairment and/or cholestasis.

Concomitant Therapy: Addition of a thiazide-type diuretic e.g., hydrochlorothiazide has been shown to have an additive antihypertensive effect with candesartan.

Black Patients: The antihypertensive effect of candesartan is less in black than non-black patients. Consequently, up-titration of candesartan and concomitant therapy may be more frequently needed for blood pressure control in black than non-black patients.

Heart Failure
Usual Recommended Initial Dose: 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.

Special Patient Populations: No initial dose adjustment is necessary for the elderly patients or in patients with intravascular volume depletion, renal impairment or mild to moderate hepatic impairment.

Concomitant Therapy: Candesartan can be administered with other heart failure treatment, including ACE inhibitors, β-blockers, diuretics and digitalis or a combination of these medicinal products.

Children and Adolescents: The safety and efficacy of Candesartan have not been established in children and adolescents (<18 years).

Administration: Should be taken once daily with or without food.

4.3 Contraindications
- Hypersensitivity to candesartan cilexetil or to any of the excipients of candesartan.
- Pregnancy and lactation.
- Severe hepatic impairment and/or cholestasis.
- The concomitant use of Candesartan Sandoz with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).
- Children aged below 1 year.

4.4 Special warnings and precautions for use
Renal impairment
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with Candesartan Sandoz.

When Candesartan Sandoz is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min). In these patients Candesartan Sandoz should be carefully titrated with thorough monitoring of blood pressure.

Evaluation of patients with heart failure should include periodic assessments of renal function, especially in elderly patients 75 years or older, and patients with impaired renal function. During dose titration of Candesartan Sandoz, monitoring of serum creatinine and potassium is recommended. Clinical trials in heart failure did not include patients with serum creatinine >265 μmol/L (>3 mg/dL).

Concomitant therapy with an ACE-inhibitor in heart failure
The risk of adverse events, especially hypotension, hyperkalaemia and decreased renal function (including acute renal failure), may increase when Candesartan Sandoz is used in combination with an ACE inhibitor (see section 4.8).
Triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist and candesartan 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

If dual blockade therapy is considered absolutely necessary, this should only occur 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.

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 Candesartan Sandoz should be carefully titrated with thorough monitoring of blood pressure in patients on haemodialysis.

Renal artery stenosis
Medicinal products that affect the renin-angiotensin-aldosterone system, including AIIRAs, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

Kidney transplantation
There is no experience regarding the administration of Candesartan Sandoz in patients with a recent kidney transplantation.

Hypotension
Hypotension may occur during treatment with Candesartan Sandoz in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics.

Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

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. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

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.

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 Candesartan Sandoz is not recommended in this population.

Hyperkalaemia
Concomitant use of Candesartan Sandoz with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products 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 Candesartan Sandoz, hyperkalaemia may occur. Periodic monitoring of

serum potassium is recommended.

The combination of an ACE inhibitor, a potassium-sparing diuretic (e.g. spironolactone) and Candesartan Sandoz is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

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 medicinal products that affect this system has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with AIIRAs. As with any antihypertensive agent, excessive blood pressure decrease in patients with ischaemic cardiopathy or ischaemic cerebrovascular disease could result in a myocardial infarction or stroke.

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

Pregnancy
Angiotensin II antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Use in paediatric patients, including patients with renal impairment
Candesartan has not been studied in children with a glomerular filtration rate less than 30 ml/min/1.73m^2 (see section 4.2).

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), Candesartan Sandoz treatment should be initiated under close medical supervision and a lower starting dose should be considered (see section 4.2).

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).

Special warnings regarding excipients
Candesartan Sandoz contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction
Compounds 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 medicinal products have been identified.

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate (see section 4.4).

Dual blockade of the RAAS with AIIRAs, ACE inhibitors, or aliskiren
There may be dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren 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.

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 AIIRAs. Use of candesartan with lithium is not recommended. If the combination proves necessary, careful monitoring of serum lithium

levels is recommended.

When AIIRAs are administered simultaneously with non-steroidal anti-inflammatory drugs (NSAIDs) (i.e. selective COX-2 inhibitors, acetylsalicylic acid (>3g/day) and non-selective NSAIDs), attenuation of the antihypertensive effect may occur.

As with ACE inhibitors, concomitant use of AIIRAs 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.

Paediatric population
Interaction studies have only been performed in adults.

4.6 Pregnancy and lactation
Pregnancy
The use of candesartan is contraindicated during pregnancy (see Contraindications). Patients receiving candesartan should be made aware of that before contemplating a possibility of becoming pregnant so that they can discuss appropriate options with their treating physician. When pregnancy is diagnosed, treatment with candesartan must be stopped immediately and if appropriate, alternative therapy should be started.

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause foetal and neonatal injury and death. Exposure to angiotensin II receptor antagonist therapy is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Lactation
It is not known whether candesartan is excreted in human milk. However, candesartan is excreted in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, candesartan should not be given during breast-feeding.

4.7 Effects on ability to drive and use machines
No studies on the effects of candesartan 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 Candesartan Sandoz.

4.8 Undesirable effects
Treatment of Hypertension
Adverse events were mild and transient. The overall incidence of adverse events had no association with dose or age.

Adverse reactions commonly (≥1/100) seen were:

Nervous System Disorders:
Dizziness/vertigo, headache.

Infections and Infestations:
Respiratory infection.

Laboratory Findings:
In general, there were no clinically important influences of candesartan on routine laboratory variables. As for other inhibitors of renin-angiotensin-aldosterone system, small decreases in haemoglobin have been seen. Increases in creatinine, urea or potassium and decrease in sodium have been observed. In patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Treatment of Heart Failure
The adverse experience profile of candesartan in heart failure patients was consistent with the pharmacology of candesartan cilexetil and the health status of the patients.

Adverse reactions commonly (≥1/100, <1/10) seen were:

Vascular Disorders:
Hypotension.

Metabolism and Nutrition Disorders:
Hyperkalaemia.

Renal and Urinary Disorders:
Renal impairment.

Laboratory Findings:
Increases in creatinine, urea and potassium. Periodic monitoring of serum creatinine and potassium is recommended.

The following adverse reactions have been reported very rarely (<1/10,000).

Blood and Lymphatic System Disorders:
Leukopenia, neutropenia and agranulocytosis.

Metabolism and Nutrition Disorders:
Hyperkalaemia, hyponatraemia.

Nervous System Disorders:
Dizziness, headache.

Gastrointestinal Disorders:
Nausea.

Hepatobiliary Disorders:
Increased liver enzymes, abnormal hepatic function or hepatitis.

Skin and Subcutaneous Tissue Disorders:
Angioedema, rash, urticaria, pruritus.

Musculoskeletal, Connective Tissue and Bone Disorders:
Back pain, arthralgia, myalgia.

Renal and Urinary Disorders:
Renal impairment, including renal failure in susceptible patients.

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

Management
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 medicinal products may be administered if the above-mentioned measures are not sufficient.

Candesartan cilexetil is not removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

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 (AT1) receptor.

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 AIIRA, selective for AT1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity.

Candesartan does not inhibit 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. Comparing candesartan cilexetil with ACE inhibitors, the incidence of cough may be 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 (AT1) receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

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.

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.

Medicinal products 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.

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. There is currently no data on the effect of candesartan on the progression to diabetic nephropathy.

Heart Failure
The beneficial effects of candesartan were consistent irrespective of age, gender and concomitant medication. Candesartan was effective also in patients taking both beta-blockers and ACE inhibitors at the same time, and the benefit was obtained whether or not patients were taking ACE inhibitors at the target dose recommended by treatment guidelines.

In patients with CHF and depressed left ventricular systolic function (left ventricular ejection fraction, LVEF $\leq$ 40%), candesartan decreases systemic vascular resistance and pulmonary capillary wedge pressure, increases plasma renin activity and angiotensin II concentration, and decreases aldosterone levels.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)
ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

5.2 Pharmacokinetic properties
Absorption and distribution

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 3-4 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.

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 drugs 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.

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.

Pharmacokinetics in special populations
In the elderly (over 65 years) C_{max} and AUC of candesartan may be increased in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar in young and elderly patients.

In patients with mild to moderate renal impairment C_{max} and AUC of candesartan may be increased during repeated dosing, but $t_{1/2}$ was not altered, compared to patients with normal renal function. The terminal $t_{1/2}$ 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.

There is no experience in patients with severe hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize starch
Povidone K-30
Carrageenan
Croscarmellose sodium
Magnesium stearate
Iron oxide, red (E172) (only for 8 and 16 mg tablets)
Titanium dioxide (E171) (only for 8 and 16 mg tablets)

6.2 Shelf life
2 years.

6.3 Special precautions for storage
Do not store above 30°C.
Store in the original package in order to protect from moisture.

6.4 Dosage forms and packaging available

Candesartan Sandoz 8 mg and 16 mg tablets are available in pack size of 30's, 60's and 90's.
These tablets are packed in Al/Al blister and the blisters are packed in an outer carton folding box.

Not all pack sizes are marketed.

7. PRODUCT REGISTRATION HOLDER

Sandoz Products Malaysia Sdn. Bhd.
Unit 1202, Level 12, Uptown 1,
No. 1, Jalan SS21/ 58, Damansara Uptown,
47400 Petaling Jaya Selangor, Malaysia.

8. DATE OF REVISION OF THE TEXT

Mar 2024