Blopress® Tablet
8 mg and 16 mg
Candesartan Cilexetil

COMPOSITION
Blopress tablets 8 mg are round pale pink tablets with a single score line on one sides. Each tablet contains 8 mg candesartan cilexetil.
Blopress tablets 16 mg are round pink tablets with no score. Each tablet contains 16 mg candesartan cilexetil.

PHARMACOLOGICAL ACTIONS
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a significant role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It is also has an important 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 I (AT_1) receptor.

Blopress is a prodrug suitable for oral use. It is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Blopress is an angiotensin II receptor antagonist, selective for AT_1 receptor, with tight binding to and slow dissociation from the receptor. It has no agonist activity.
Candesartan does not inhibit ACE, which convert 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 Blopress with ACE-inhibitor, the incidence of cough was lower in patients receiving Blopress. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hypertension
In hypertension, Blopress causes a dose–dependent, long lasting reduction in arterial blood pressure. The antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected. There is no indication of serious exaggerate first –dose hypotension or rebound effect after cessation of treatment.

Blopress is effective in all grades of hypertension.
After administration of a single dose. Onset of antihypertensive effect generally occurs within 2 hours. With continuous treatment, the maximum reduction in blood pressure with any dose generally attained within 4 weeks and is sustained during long–term treatment. It provides effective and smooth blood pressure reduction over the 24-hr with little difference between maximum and trough effects during the dosing interval.

When Blopress is used together with hydrochlorothiazide, the reduction in blood pressure is additive. Blopress is similarly effective in patients irrespective of age and gender.
Blopress increases renal blood flow and either has no effect on, or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. Blopress has no adverse effect on blood glucose or lipid profile.

Heart failure
Treatment with candesartan cilexetil reduces mortality, reduces hospitalization due to heart failure and improves symptoms in patients with left ventricular systolic dysfunction as shown in the Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) programme.

This multinational, placebo controlled, double-blind study programme in chronic heart failure (CHF) patients with NYHA functional class II to IV consisted of three separate studies: CHARM-Alternative (n=2,028) in patients with LVEF ≤40% not treated with an ACE inhibitor because of intolerance (mainly due to cough, 72%), CHARM-Added (n=2,548) in patients with LVEF ≤40% and treated with an ACE inhibitor, and CHARM-Preserved (n=3,023) in patients with LVEF >40%. Patients on optimal CHF therapy at baseline were

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randomised to placebo or candesartan cilexetil (titrated from 4 mg or 8 mg once daily to 32 mg once daily or the highest tolerated dose, mean dose 24 mg) and followed for a median of 37.7 months. After 6 months of treatment 63% of the patients still taking candesartan cilexetil (89%) were at the target dose of 32 mg.

In CHARM-Alternative, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (hazard ratio (HR) 0.77, 95% CI 0.67-0.89, p<0.001). This corresponds to a relative risk reduction of 23%. Fourteen patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan (HR 0.80, 95% CI 0.70-0.92, p=0.001). Both the mortality and morbidity (CHF hospitalisation) components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.008).

In CHARM-Added, the composite endpoint of cardiovascular mortality or first CHF hospitalisation was significantly reduced with candesartan in comparison with placebo (HR 0.85, 95% CI 0.75-0.96, p=0.011). This corresponds to a relative risk reduction of 15%. Twenty-three patients needed to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure. The composite endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced with candesartan (HR 0.87, 95% CI 0.78-0.98, p=0.021). Both the mortality and morbidity components of these composite endpoints contributed to the favourable effects of candesartan. Treatment with candesartan cilexetil resulted in improved NYHA functional class (p=0.020).

In CHARM-Preserved, no statistically significant reduction was achieved in the composite endpoint of cardiovascular mortality or first CHF hospitalisation (HR 0.89, 95% CI 0.77-1.03, p=0.118). The numerical reduction was attributable to reduced CHF hospitalisation. There was no evidence of effect on mortality in this study.

All-cause mortality was not statistically significant when examined separately in each of the three CHARM studies. However, all-cause mortality was also assessed in pooled populations, CHARM-Alternative and CHARM-Added (HR 0.88, 95% CI 0.79-0.98, p=0.018) and all three studies (HR 0.91, 95% CI 0.83-1.00, p=0.055).

The beneficial effects of candesartan on cardiovascular mortality and CHF hospitalization 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, an d decreases aldosterone levels.

INDICATION

- Hypertension
- Treatment of patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction $\leq$ 40%) when ACE-inhibitors are not tolerated.

DOSAGE AND ADMINISTRATION

Dosage in Hypertension :

The recommended dose of Blopress is 4 mg once daily. The dose should be titrated according to response up to 16 mg once daily. The maximum antihypertensive effect is attained within 4 weeks after initiation of treatment.

Use in the Elderly
No dosage adjustment is necessary for patients up to 75 year. In patients > 75 years, an initial dose of 2 mg once daily is recommended. The dose may be titrated up according to response.

Use in patients with impaired renal function
No dosage adjustment is necessary in patients with mild renal impairment. In patients with moderate to severe renal impairment, an initial dose 2 mg once daily is recommended. The dose may be titrated up according to response.

Use in the patient with impaired hepatic function
An initial dose of 2 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be titrated up according to response. There is no experience in patients with severe hepatic impairment.

Concomitant therapy
Blopress may be administered with other antihypertensive agents.

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

Dosage in Heart Failure :
The usual recommended initial dose of Blopress is 4 mg once daily. Up-titration to the target dose of 32 mg once daily or the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks.

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

Concomitant therapy
Blopress can be administered with other heart failure treatment, including ACE-inhibitors, beta-blockers, diuretics and digitalis or a combination of these medicinal products.
The combination of an ACE inhibitor, a potassium – sparing diuretic (e.g. spironolacton) and Blopress is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

Administration :
Blopress should be taken once daily with or without food.

Use in children and adolescents :
The safety and efficacy of Blopress have not been established in children and adolescents (under 18 years).

CONTRAINDICATION
- Hypersensitivity to any component of Blopress
- Pregnancy and lactation
- Severe hepatic impairment and/or cholestasis
- The use of Blopress in combination with alliskiren – containing medicines in patients with diabetes or moderate to severe renal impairment (GFR < 60 ml / min / 1.73 m^2)

UNDESIRABLE EFFECTS
Treatment of Hypertension :
In controlled clinical studies, adverse events were mild and transient and comparable to placebo. The overall incidence of adverse events showed no association with dose or age.
Withdrawals from treatment due to adverse events were similar with candesartan cilexetil (3.1%) and placebo (3.2%).

In a pooled analysis of clinical trial data, the following common (>1/100) adverse reactions with candesartan cilexetil were reported based on an incidence of adverse events with at least 1% higher than the incidence seen with placebo :

Nervous system disorders
Dizziness/vertigo, headache.

Infections and infestations
Respiratory infection.

Laboratory findings
In general, there were no clinically important influences of Blopress on routine laboratory variables. As for other inhibitors of the renin-angiotensin-aldosterone system, small decreases in haemoglobin have been seen. Increases in creatinine, urea or potassium and decrease in sodium have been observed.
Increases in S-GPT were reported as adverse events slightly more often with Blopress than the placebo (1.3% vs 0.5%). No routine monitoring of laboratory variables is usually necessary for patients receiving Blopress. However, in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Treatment of Heart Failure :
The adverse experience profile of Blopress in heart failure patients was consistent with the pharmacology of the drug 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.

Post Marketing (hypertension and heart failure) :
The following adverse reactions have been reported very rarely (<1/10.000) in post marketing experiences :

Blood and lymphatic system disorders
Leukopenia, neutropenia and agranulocytosis.

Metabolism and nutrition disorders
Hyperkalaemia, hyponatremia.

Ear and labyrinth disorders
Tinnitus

Nervous system disorders
Dizziness, headache.

Respiratory, thoracic and mediastinal disorders
Cough

Gastrointestinal disorders
Nausea.

Hepato-biliary disorders
Increased liver enzymes, abnormal hepatic function or hepatitis.

Skin and subcutaneous tissue disorders
Angioedema, rash, urticaria, pruritus.

Musculoskeletal, connective tissue disorders
Rhabdomyolysis, back pain, arthralgia, myalgia.

Renal and urinary disorders
Renal impairment, including renal failure in susceptible patients.

PRECAUTIONS

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with aliskiren-containing medicines.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS) by combining Blopress and aliskiren is not recommended since there is an increased risk of hypotension, hyperkalemia, and changes in renal function.
The use of Blopress with aliskiren is contraindicated in patients with diabetes or moderate to severe renal impairment (GFR < 60 ml / min / 1.73 m^2).

Renal impairment
As with other agents inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible patients treated with Blopress.
When Blopress 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 Blopress 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 Blopress, 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, hyperkalemia and renal function impairment (including acute renal failure), may increase when Blopress is used in combination with an ACE inhibitor. Patients with such treatment should be monitored regularly and carefully.

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

Renal artery stenosis
Renal function may worsen in patients with renal artery stenosis.
Other medicinal products that affect the renin-angiotensin-aldosterone system, i.e.angiotensin converting enzyme (ACE) inhibitors, may increase blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. A similar effect may be anticipated with angiotensin II receptor antagonists.

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

Hypotension
Hypotension may occur during treatment with Blopress in heart failure patients. As described for other agents acting on the renin-angiotensin-aldosterone system, 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 Blopress is not recommended.

Hyperkalaemia
Co-administration with potassium – sparing diuretics may result in increased potassium level.
Based on experience with the use of other medicinal products that affect the renin-angiotensin-aldosterone system, concomitant use of Blopress 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 increase in serum potassium in hypertensive patients.

In heart failure patients treated with Blopress, hyperkalaemia may occur. During treatment with Blopress in patients with heart failure, periodic monitoring of serum potassium is recommended, especially when taken concomitantly with ACE inhibitors and potassium-sparing diuretics such as spironolactone.

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

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, oluguria or, rarely, acure renal failure. The possibility of similar effects cannot be excluded with angiotensin II receptor antagonists. 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. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

INTERACTIONS
No drug interactions of clinical significance have been identified.

Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril.

Candesartan is eliminated only to a minor extent by hepatic metabolism (CYP2C9). Available interaction studies indicate no effect on CYP2C9 and CYP3A4 but the effect on other cytochrome P450 isoenzymes is presently unknown.

The antihypertensive effect of Blopress may be enhanced by other antihypertensives.

Based on experiences with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of potassium-sparing diuretics, potassium supplements, salts substitutes containing potassium, or other drugs that may increase potassium levels (e.g. heparin) may lead to increase in serum potassium.

Lithium
Reversible increase in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. A similar effect may occur with angiotensin II receptor antagonists and careful monitoring of serum lithium levels is recommended during concomitant use.

NSAIDs
As with other antihypertensive agents, the antihypertensive effect of candesartan may be attenuated by non-steroidal anti-inflammatory drugs such as indomethacin, selective COX-2 inhibitors, acetylsalicylic acid dan non-selective NSAIDs.

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 older and volume-depleted patients.
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)
Dual blockade of the RAAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

The bioavailability of candesartan is not affected by food.

OVERDOSAGE
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 legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, e.g. isotonic saline solution. Sympathomimetic drugs may be administered if the previously-mentioned measures are not sufficient.

Blopress is not removed by haemodialysis.

USE IN PREGNANCY AND LACTATION
Use in pregnancy
There are very limited data from the use of Blopress in pregnant woman. These data are insufficient to allow conclusions about potential risk for the foetus when used during the first trimester. In humans, foetal renal perfusion, which is dependent upon the development of the renin-angiotensin-aldosterone system, begins in the second trimester. Thus, risk to the foetus increases if Blopress is administered during the second or third trimesters of pregnancy. When used in pregnancy during the second and third trimesters, medicinal products that acts directly on the renin-angiotensin system can cause foetal and neonatal injury (hypotension, renal dysfunction, oliguria and/or anuria, oligohydramnios, skull hypoplasia, intrauterine growth retardation) and death. Cases of lung hypoplasia, facial abnormalities and limb contractures have also been described.

Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. The mechanism is believed to be pharmacologically mediated through effects on the renin-angiotensin-aldosterone system.
Based on the above information, Blopress should not be used in pregnancy. If pregnancy is detected during treatment, Blopress should be discontinued.

Use in 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, Blopress should not be given during breast-feeding.

Effects on ability to drive and use Machines
The effect of candesartan on the ability to drive and use machines has not been studied but based on its pharmacodynamic properties is unlikely to affect this ability. When driving vehicles or operating machines it should be taken into account that dizziness or weariness may occur during treatment.

STORAGE
Store at below 30^{o}C and protect from light.

SHELF LIFE
3 years.

PACKAGE
Box 14 Tablets (2 Blisters @ 7 Tablets)

REGISTRATION NUMBER
8 mg, DKL9825101910A1
16 mg, DKL9825101910B1

ON MEDICAL PRESCRIPTION ONLY

Manufactured by PT . TAKEDA INDONESIA, Bekasi Indonesia
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