BLOPRESS®

candesartan cilexetil

ACTION

Blopress (candesartan cilexetil)-(the parent compound)-rapidly undergoes complete hydrolysis during gastrointestinal absorption to form the active agent candesartan. Candesartan is a highly selective, long lasting and non competitive antagonist specific for AT1 subtype angiotensin II receptor. It binds tightly and dissociate slowly from AT1 receptor, consequently it inhibits angiotensin II-induced vasoconstriction. Candesartan does not bind to or block other hormone receptors or ion channels known to be necessary in cardiovascular regulation. Blopress antihypertensive action is due to decreased systemic peripheral resistance, while heart rate, stroke volume and cardiac output are not affected. Blopress causes a dose-dependent, long-lasting reduction in arterial blood pressure. Blopress is effective in all grades of hypertension. It provides effective and smooth blood pressure reduction over the 24 hours dosing interval, with a trough/peak ratio > 0.8 confirming the once daily dosing. Blopress can be taken as monotherapy or in combination with other antihypertensive drugs, such as thiazide diuretics and calcium antagonists. Blopress is similarly effective in patients regardless of age and gender. Blopress increases renal blood flow and maintains or increases glomerular filtration rate while renal vascular resistance and filtration fraction are reduced. There is no evidence of serious or exaggerated first dose hypotension or rebound effect after cessation of Blopress treatment. Blopress has no adverse effect on blood glucose or lipid profile. Angiotensin II receptor antagonists are generally considered unlikely to cause cough. In controlled clinical trials comparing Blopress with (ACE) inhibitors, the incidence of cough was lower in patients receiving Blopress.

Absorption and distribution: Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis from the gastrointestinal tract to candesartan. The average absolute bioavailability of candesartan is approximately 40% following oral solution of candesartan cilexetil. The mean peak serum concentration (Cmax) is reached in 3-4 hours after oral administration. Candesartan serum concentrations increase in a linear way with increasing doses in the therapeutic dose range. Candesartan is highly bound to plasma proteins (more than 99%). The evident volume of distribution of candesartan is 0.13 L/kg.

The pharmacokinetics of candesartan is not gender related. The area under the serum concentration versus time curve (AUC) of candesartan is not significantly affected by food.

Metabolism and elimination: Candesartan is mainly excreted unchanged in urine and bile. It undergoes minor hepatic metabolism to an inactive metabolite. The terminal half-life of candesartan is approximately 9 hours. Total plasma clearance of candesartan is about 0.37 ml/min/kg, with a renal clearance of about 0.19 ml/min/kg. Following an oral dose of 14C - labeled candesartan cilexetil, approximately 33% of the total radioactivity is recovered in urine and approximately 67% in faeces. In the elderly (over 65 years) both Cmax and AUC of candesartan are increased in comparison to young subjects, however, no dose adjustment is necessary in the elderly. In patients with impaired renal function, increased Cmax, (AUC) and elimination half life of candesartan are observed. However, in patients with mild impaired renal function no dose adjustment is necessary, While in patients with severe impairment of renal function (i.e. creatinine clearance < 30 ml/min/ 1.73 m2 BSA) the clinical experience is limited and a lower initial dose of 4 mg should be considered. In patients with mild to moderate impaired hepatic function no changes in the pharmacokinetics of candesartan were noticed.

INDICATIONS

Blopress is indicated in:

- Essential hypertension, in all grades of hypertension.
- Treatment of heart failure and impaired left ventricular systolic function and as additional therapy to ACE inhibitors or when ACE inhibitors are not tolerated.

DOSAGE AND ADMINISTRATION

The recommended maintenance dose of Blopress is 8 mg or 16 mg once daily. The maximal antihypertensive effect is attained within 4 weeks after initiation of treatment. In patients starting on 8 mg who require further blood pressure reduction, a dose increase to 16 mg is recommended. An initial dose of 16 mg is also well tolerated. Blopress should be taken once daily with or without food; the bioavailability of candesartan is not affected by food. No initial dosage adjustment is necessary for elderly patients. No initial dosage adjustment is necessary in patients with mild impaired renal function (i.e. creatinine clearance ≥ 30 ml/min/1.73 m2 BSA). In patients with severe impaired renal function (i.e. creatinine clearance <30 ml/min/1.73 m2 BSA), the clinical experience is limited and a lower initial dose of 4 mg should be considered. No initial dosage adjustment is necessary in patients with mild to moderate impaired hepatic function. No experience is available to date in patients with severe impaired hepatic function (e.g. cirrhotic patients). 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.

CONTRAINDICATIONS

Blopress is contraindicated in patients who are hypersensitive to any of its components. Since there is no experience with the use of Blopress in pregnant women, Blopress should not be used in pregnancy. If pregnancy is detected during treatment, Blopress should be discontinued immediately. The use of angiotensin converting enzyme inhibitors (ACEI) during the second and third trimesters of pregnancy has been associated with

foetal and neonatal injury. Animal studies with candesartan cilexetil have demonstrated late foetal and neonatal injury in the kidney. 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, breast feeding should be discontinued if the use of Blopress is considered essential.

WARNINGS

- Intravascular volume depletion: In patients with intravascular volume depletion (such as those receiving high dose diuretics) symptomatic hypotension may occur, hence, this condition should be corrected before administration of candesartan cilexetil.
- Renal artery stenosis: Other drugs that affect the renin-angiotensin-aldosterone system, i.e. angiotensin converting enzyme inhibitors (ACEI) have been associated with increased blood urea and serum creatinine in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney. Although not proved, probably this may occur also with angiotensin II receptor antagonists such as candesartan cilexetil.

PRECAUTIONS

Concomitant administration of Blopress with potassium-sparing diuretics may theoretically result in increased serum potassium levels. If co-administration is considered necessary, caution is advised. Physician should know if patient is receiving Blopress because of possible hypotension during anesthesia and surgery in patients treated with angiotensin-II antagonists.

DRUG INTERACTIONS

No drug interactions of clinical significance have been found. Compounds investigated in clinical studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgrstrel), glibenclamide, nifidipine and enalapril.
The antihypertensive effect of Blopress may be enhanced by other antihypertensives. Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other drugs that may increase potassium levels (e.g. heparin) may lead to increase in serum potassium. Since lithium toxicity has been reported, careful monitoring of serum lithium levels is recommended during concomitant administration of Lithium and Blopress tablets, since lithium reabsorption at renal tubule is increased.

SIDE EFFECTS

The safety and tolerability of Blopress (candesartan cilexetil) was shown to be comparable to that of placebo in double-blind clinical studies. Blopress was well tolerated and adverse events were mild and transient and showed no association with dose, age or gender. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil and placebo.
Adverse events reported were: dizziness/vertigo, headache, back pain, and respiratory tract infection. Causal relationship of these adverse events to Blopress has not been established.Generally, there were no important clinical influences of Blopress on routine laboratory variables. In post marketing surveillance, very rare cases (<1/10000), were reported slightly more often with Candesartan Cilexetil than with placebo including increases in liver enzymes, hepatitis, leucopenia, neutropenia, agranulocytosis, rash, urticaria, angioedema and hyponatremia, but no routine monitoring of laboratory variables is usually necessary for patients receiving Candesartan Cilexetil.

OVERDOSAGE

Based on pharmacological considerations, the main result of an overdose is likely to be hypotension.

MANAGEMENT OF OVERDOSAGE

If symptomatic hypotension occurred, symptomatic treatment should be given and supervision of vital signs monitored. The patient should be placed supine with head down position. If this is not enough, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic drugs may be administered if the above mentioned measures are not sufficient. Candesartan is unlikely to be removed by haemodialysis.

STORAGE CONDITIONS

Store below 30° C.

PRESENTATION

Tablets:

Blopress 4 mg:	candesartan cilexetil 4 mg
Blopress 8 mg:	candesartan cilexetil 8 mg
Blopress 16 mg:	candesartan cilexetil 16 mg

Excipients: lactose, maize starch, carmellose calcium, hydroxypropylcellulose, polyethylene glycol 8000, red iron oxide, magnesium stearate.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

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Keep medicament out of reach of children
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