BLOPRESS® PLUS

Candesartan cilexetil & Hydrochlorothiazide

ACTION

Candesartan cilexetil: is a prodrug, which is rapidly converted to the active drug, candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. Candesartan is an angiotensin II receptor antagonist, selective for AT1 receptors, with tight binding to and slow dissociation from the receptor. It has no agonist activity. Candesartan does not influence ACE or other enzyme systems usually associated with the use of ACE inhibitors. Since there is no effect on the degradation of kinins, or on the metabolism of other substances, such as substance P, angiotensin II receptor antagonists are unlikely to be associated with cough. In controlled clinical trials comparing candesartan cilexetil 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 AT1 receptors results in dose related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

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. Large clinical studies have shown that long-term treatment with hydrochlorothiazide reduces the risk for cardiovascular morbidity and mortality.

Candesartan and hydrochlorothiazide: have additive antihypertensive effects. In hypertensive patients, Blopress Plus causes an effective and long-lasting reduction in arterial blood pressure 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 Blopress Plus onset of the antihypertensive effect generally occurs within 2 hours. With continuous treatment, most of the reduction in blood pressure is attained within four weeks and is sustained during long-term treatment. Blopress Plus once daily provides effective and smooth blood pressure reduction over 24 hours, with little difference between maximum and trough effects during the dosing interval.

In double-blind, randomised studies, the incidence of adverse events, especially cough, was lower during treatment with candesartan cilexetil/hydrochlorothiazide than during treatment with combinations of ACE inhibitors and hydrochlorothiazide. Candesartan cilexetil/hydrochlorothiazide is similarly effective in patients irrespective of age and gender. Currently there are no data on the use of candesartan cilexetil/hydrochlorothiazide in patients with renal disease/nephropathy, reduced left ventricular function/congestive heart failure and post myocardial infarction.

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 0.1 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.

Hydrochlorothiazide: Hydrochlorothiazide is rapidly 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%. The apparent volume of distribution is approximately 0.8 L/kg.

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-labelled candesartan cilexetil, approximately 26% of the dose is excreted in the urine as candesartan and 7% as an inactive metabolite while approximately 66% of the dose is recovered in the faeces as candesartan and 10% as the inactive metabolite. In the elderly (over 65 years) both Cmax and AUC of candesartan are increased in comparison to young subjects. In patients with mild to moderate renal impairment, Cmax and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but the terminal t1/2 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 t1/2 of candesartan was approximately doubled in patients with severe renal impairment. The pharmacokinetics in patients undergoing haemodialysis were similar to those in patients with severe renal impairment. In patients with mild to moderate hepatic impairment, there was a 23% increase in the AUC of candesartan.

Hydrochlorothiazide is not metabolized and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal t1/2 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 h) after administration of hydrochlorothiazide in combination with candesartan cilexetil. No additional accumulation of hydrochlorothiazide occurs after repeated doses of the combination compared to monotherapy. The terminal t1/2 of hydrochlorothiazide is prolonged in patients with renal impairment.

INDICATIONS

Essential hypertension, where monotherapy with candesartan cilexetil or hydrochlorothiazide is not sufficient.

DOSAGE AND ADMINISTRATION

The recommended dose of Blopress Plus 8 mg or 16 mg is one tablet once daily. The dose of candesartan cilexetil should be titrated before switching to Blopress Plus 16 /12.5 mg. When clinically appropriate a direct change from monotherapy to Blopress Plus may be considered. Most of the antihypertensive effect is usually attained within 4 weeks of initiation of treatment.

Blopress Plus should be taken once daily with or without food.

Special population:

- 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: Loop diuretics are preferred to thiazides in this population. Dose titration of candesartan cilexetil is recommended in patients with renal impairment whose creatinine clearance is ≥ 30 ml/min/1.73 m2BSA before treatment with Blopress Plus (the recommended starting dose of candesartan cilexetil is 4 mg in patients with mild to moderate renal impairment).

Blopress Plus should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min/1.73 m2 BSA).

- Use in impaired hepatic function: Dose titration of candesartan cilexetil is recommended in patients with mild to moderate hepatic impairment before treatment with Blopress Plus (the recommended starting dose of candesartan cilexetil is 2 mg in these patients).

Blopress Plus should not be used in patients with severe hepatic impairment and/or cholestasis.

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

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients or to sulfonamide derived drugs (hydrochlorothiazide is a sulfonamide derived drug).
- Pregnancy and lactation; since there is no experience with the use of Blopress Plus in pregnant women. Blopress Plus should not be used in pregnancy. If pregnancy is detected during treatment, Blopress Plus should be discontinued. 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; Hydrochlorothiazide can reduce the plasma volume as well as the uteroplacental blood flow. It may also cause neonatal thrombocytopenia. 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, Blopress Plus should not be given during breast-feeding.
- Severe renal impairment (creatinine clearance <30 ml/min/1.73 m2 BSA).
- Severe hepatic impairment and/or cholestasis.
- Refractory hypokalaemia and hypercalcaemia.
- Gout.

WARNINGS AND PRECAUTIONS

- Renal impairment/Kidney transplantation: Loop diuretics are preferred to thiazides in this population. When Blopress Plus is used in patients with impaired renal function, a periodic monitoring of potassium, creatinine and uric acid levels is recommended. There is no experience regarding the administration of Blopress Plus in patients with a recent kidney transplantation.
- Renal artery stenosis: Other drugs 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.
- Hepatic impairment: Thiazides 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 Blopress Plus in patients with hepatic impairment.
- Intravascular volume depletion: In patients with intravascular volume and/or sodium depletion symptomatic hypotension may occur, as described for other agents acting on the renin-angiotensin-aldosterone system. Therefore, the use of Blopress Plus is not recommended until this condition has been corrected.
- 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 generally will not respond to antihypertensive drugs acting through inhibition of the renin-angiotensin-aldosterone system. Therefore the use of Blopress Plus is not recommended.
- Electrolyte imbalance: As for any patient receiving diuretic therapy, periodic determination of serum electrolytes should be performed at appropriate intervals. Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypercalcaemia, hypokalaemia, hyponatraemia, hypomagnesaemia and hypochloraemic alkalosis). Thiazide diuretics may decrease the urinary calcium excretion and may cause intermittent and slightly increased serum calcium concentrations. Marked hypercalcaemia may be a sign of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Hydrochlorothiazide does significantly 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). Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of Blopress Plus and potassium-sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Although not documented with Blopress Plus treatment with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia.
- Metabolic and endocrine effects: Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic drugs, 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 Blopress Plus minimal or no effects were reported. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.
- 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 drugs 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 angiotensin- receptor antagonists. As with any antihypertensive agent, 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No drug interactions of clinical significance have been identified for candesartan cilexetil. Compounds which have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide and nifedipine. The bioavailability of candesartan is not affected by food. The antihypertensive effect of Blopress Plus may be enhanced by other antihypertensives. The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other drugs associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates). Based on experience with the use of other drugs that affect the renin-angiotensin-aldosterone system, concomitant use of Blopress Plus and potassium-sparing diuretics, potassium supplements or salt substitutes or other drugs that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when Blopress Plus is administered with such drugs. Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors or hydrochlorothiazide. A similar effect may occur with angiotensin II receptor antagonists and careful monitoring of serum lithium levels is recommended during concomitant use. The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs. The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine. The effect on nondepolarizing skeletal muscle relaxants (e.g. tubocurarine) may be potentiated by hydrochlorothiazide. Thiazide diuretics 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 thiazides. Anticholinergic agents (e.g. atropine, biperiden) may increase the bioavailability of thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate. Thiazide may increase the risk of adverse effects caused by amantadine. Thiazides may reduce the renal excretion of cytotoxic drugs (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

The risk for hypokalaemia may be increased during concomitant use of steroids or adrenocorticotropic hormone (ACTH). Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates or anaesthetics.Treatment with a thiazide diuretic may impair glucose tolerance. Dosage adjustment of antidiabetic drugs, including insulin, may be required. 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. There is no clinically significant interaction between hydrochlorothiazide and food.

SIDE EFFECTS

In controlled clinical studies with candesartan cilexetil/hydrochlorothiazide adverse events were mild and transient. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil/hydrochlorothiazide (3.3%) and placebo (2.7%). In a pooled analysis of clinical trial data, the following common (>1/100) adverse reactions with candesartan cilexetil/hydrochlorothiazide were reported based on an incidence of adverse events with candesartan cilexetil/hydrochlorothiazide at least 1% higher than the incidence seen with placebo:

Nervous system disorders: Dizziness/vertigo.

Candesartan cilexetil:

The following adverse reactions have been reported very rarely (<1/10,000) with candesartan cilexetil in post marketing experience:

- Blood and lymphatic system disorders: Leukopenia, neutropenia and agranulocytosis.
- Metabolism and nutrition disorders: Hyperkalaemia and hyponatraemia.
- Nervous system disorders: Dizziness, headache.
- 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 and bone disorders: Back pain, arthralgia, myalgia.
- Renal and urinary disorders: Renal impairment, including renal failure in susceptible patients.

Hydrochlorothiazide:

The following adverse reactions have been reported with hydrochlorothiazide monotherapy, usually with doses of 25mg or greater. The frequencies used are:

Common (>1/100), uncommon (>1/1000 and <1/100) and rare (<1/1000).

- Blood and lymphatic system disorders: Rare: Leucopenia, neutropenia/agranulocytosis, thrombocytopenia, aplastic anaemia, bone marrow depression, haemolytic anaemia.
- Immune system disorders: Rare: Anaphylactic reactions.
- Metabolism and nutrition disorders: Common: Hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatraemia and hypokalaemia).
- Psychiatric disorders: Rare: Sleep disturbances, depression, restlessness.
- Nervous system disorders: Common: Light-headedness, vertigo. Rare: Paraesthesia.
- Eye disorders: Rare: Transient blurred vision.
- Cardiac disorders: Rare: Cardiac arrhythmias.
- Vascular disorders: Uncommon: Postural hypotension. Rare: Necrotising angitis (vasculitis, cutaneous vasculitis).
- Respiratory, thoracic and mediastinal disorders: Rare: Respiratory distress (including pneumonitis and pulmonary oedema).
- Gastrointestinal disorders: Uncommon: Anorexia, loss of appetite, gastric irritation, diarrhoea, constipation. Rare: Pancreatitis.
- Hepatobiliary disorders: Rare: Jaundice (intrahepatic cholestatic jaundice).
- Skin and subcutaneous tissue disorders: Uncommon: Rash, urticaria, photosensitivity reactions. Rare: Toxic epidermal necrolysis, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
- Musculoskeletal and connective tissue disorders: Rare: Muscle spasm.
- Renal and urinary disorders: Common: Glycosuria. Rare: Renal dysfunction and interstitial nephritis.
- General disorders and administration site conditions: Common: Weakness. Rare: Fever.
- Investigations: Common: Increases in cholesterol and triglycerides. Rare: Increases in BUN and serum creatinine.
- Laboratory findings: Increases in serum uric acid, blood glucose and serum ALAT (SGPT) were reported as adverse events slightly more often with candesartan cilexetil/hydrochlorothiazide (crude rates 1.1%, 1.0% and 0.9%, respectively) than with placebo (0.4%, 0.2% and 0%, respectively). Minor decreases in haemoglobin and increases in serum ASAT (SGOT) have been observed in single patients receiving candesartan cilexetil/hydrochlorothiazide. Increases in creatinine, urea or potassium and decrease in sodium have been observed.

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) 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 Blopress Plus 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 drugs 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.

STORAGE

Store below 30°C.

PRESENTATIONS

Tablets

BLOPRESS 8 PLUS: Candesartan cilexetil 8 mg and 12.5 mg hydrochlorothiazide/tablet

BLOPRESS 16 PLUS: Candesartan cilexetil 16 mg and 12.5 mg hydrochlorothiazide/tablet

Excipients: lactose, carmellose calcium, hydroxypropylcellulose, magnesium stevarate, maize starch, polyethylene glycol 8000, red iron oxide in Blopress 16 plus only.

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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APM

Keep medicament out of reach of children

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