BLOPRESS PLUSâ 16 TABLET
(Candesartan cilexetil 16 mg & Hydrocholorothiazide 12.5 mg)

DESCRIPTION
Light pink, oval, flat tablet with a score and embossing 16/C on both sides. Each tablet contains candesartan cilexetil 16 mg and Hydrochlorothiazide 12.5 mg.

MECHANISM OF ACTIONS
Angiotensin II antagonist + Diuretic
Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin – converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore, independent of the pathways of angiotensin II synthesis.
There is also an AT2 receptor found in many tissues, but AT2 is not known to be associated with cardiovascular homeostasis. Candesartan has much greater affinity (>10.000-fold) for the AT1 receptor than for the AT2 receptor.
Blockade of the renin-angiotensin system with the ACE inhibitor, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalysed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response of bradykinin. Whether this difference has clinical relevancies not yet known. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.
Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of candesartan on blood pressure.
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent in increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist trends reverse the potassium loss associated with these diuretics.
The mechanism of the antihypertensive effects of thiazides is unknown.

INDICATION
Blopress Plus is indicated for the treatment of hypertension which is not controlled on candesartan cilexetil 16 mg or hydrochlorothiazide 12.5 mg in monotherapy.

POSOLOGY
Dosage
One tablet daily, with or without food.

Administration
- Geriatric use
  Before treatment with Blopress plus tablet, the treatment should start with 2 mg of candesartan cilexetil monotherapy for elderly people ≥ 75 years or 4 mg of candesartan cilexetil monotherapy for elderly people < 75 years.

- Patients with renal impairment
  The usual regimen of therapy with Blopress plus may be followed as long as the patients creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Blopress plus is not recommended.

- Patients with hepatic impairment
  Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of Blopress plus.

- Pediatric use
  Safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS
- Hypersensitivity to the active ingredients of Blopress Plus or to sulfonamide derived drugs (hydrochlorothiazide is a sulfonamide derived drug) or to any of excipients.
- Pregnancy and lactation.
- Severe renal impairment (creatinine clearance <30 ml/min/1.73m^2 BSA) or anuria
- Severe hepatic impairment and/or cholestasis.
- Refractory hypokalaemia and hypercalcemia.
- Gout.
- The use of candesartan cilexetil/hydrochlorothiazide in combination with aliskiren-containing medicines in patients with diabetes or moderate to severe renal impairment (GFR<60mL/min/1.73m2).

UNDESIRABLE EFFECTS
Candesartan cilexetil-Hydrochlorothiazide
Blopress plus has been evaluated for safety in more than 2800 patients treated for hypertension. More than 750 of these patients were studied for at least six months and more than 500 patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse events reported with Blopress plus was comparable to placebo. The overall frequency of adverse experiences was not related to dose, age, gender, or race.
In placebo-controlled trials that includes 1089 patients treated with various combinations of candesartan cilexetil (doses of 2-32 mg) and hydrochlorothiazide (doses of 6.25 – 25 mg) and 592 patients treated with placebo, adverse events, whether or not attributed to treatment, occurring in greater than 2% of patients treated with Blopress plus and that were more frequent for Blopress plus than placebo were:
- Respiratory system disorder: upper respiratory tract infections (3.6% vs 3.0%).
- Body as whole: back pain (3.3% vs 2.4%), influenza like symptoms (2.5% vs 1.9%).
- Central / peripheral nervous system: dizziness (2.9% vs 1.2%).
  The frequency of headache was greater than 2% (2.9% in patients treated with Blopress plus was less frequent than the rate in patients treated with placebo (5.2%).

Other adverse events which have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from more than 2800 patients worldwide treated with Blopress plus included:
- Body as whole : inflicted injury, fatigue, pain, peripheral oedema, asthenia.
- Central and peripheral nervous system: vertigo paraesthesia, hypesthesia.
- Respiratory system disorders : bronchitis, sinusitis, pharyngitis, coughing, rhinitis, dyspnea.
- Musculoskeletal system disorders : arthralgia, myalgia, arthrosis, arthritis, leg cramps, sciatica.

- Gastrointestinal system disorders : nausea, abdominal pain, diarrhea, dyspepsia, gastritis, gastroenteritis, vomiting.
- Metabolic and nutritional disorders : hyperuricaemia, hyperglycaemia, hypokalaemia, increased BUN, creatinine phosphokinase increased, hyponatremia.
- Urinary system disorder : urinary tract infection, hematuria, cystitis.
- Liver/biliary system disorders : hepatic function abnormal, increased transaminase levels.
- Heart rate and rhythm disorders : tachycardia, palpitation, extrasystoles, bradycardia;
- Psychiatric disorders : depression, insomnia, anxiety.
- Cardiovascular disorders : ECG abnormal.
- Skin and appendages disorders: eczema, sweating increased, pruritus, dermatitis, rash.
- Platelet/bleeding clotting disorders: epistaxis.
- Resistance mechanism disorders: infection, viral infection.
- Vision disorders: conjunctivitis.
- Hearing and vestibular disorders: tinnitus.

Reported events seen less frequently than 0.5% included angina pectoris, myocardial infarction and angioedema.

Postmarketing
Following is a list of ADRs which have been observed in postmarketing and are not included above:
Blood and Lymphatic System Disorders
Leukopenia, neutropenia, agranulocytosis

Metabolism and Nutrition Disorders
Hyponatremia

Skin and Subcutaneous Tissue Disorders
Rash, urticaria

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

Postmarketing of Candesartan cilexetil
Other adverse experiences that have been reported candesartan cilexetil, without regard to causality, were:
- Body as whole : fever.
- Metabolic and nutritional disorders : hypertriglyceridemia, hyperkalemia.
- Psychiatric disorders : somnolence.
- Urinary system disorders : albuminuria.
- Hepato-biliary disorders : hepatitis, Increased liver enzymes, abnormal hepatic function.
- Ear and Labyrinth Disorders : Tinnitus.
- Respiratory, Thoracic and Mediastinal Disorders : Cough.
- Skin and Subcutaneous Tissue Disorders : Angioedema, pruritus.
- Musculoskeletal, Connective Tissue and Bone Disorders : Back pain.

Postmarketing of Hydrochlorothiazide
Other adverse experiences that have been reported with Hydrochlorothiazide, without regard to causality, are listed below:
- Body as whole : weakness, fever.

- Vascular Disorders : hypotension including orthostatic hypotension (may be aggravated by alcohol, barbiturates, narcotics or antihypertensive drugs), postural hypotension.
- Cardiac disorders : cardiac arrhythmias.
- Gastrointestinal Disorders : pancreatitis, sialadenitis, cramping, constipation, gastric irritation, anorexia, loss of appetite, diarrhea, constipation.
- Hepatobiliary Disorders: jaundice (intrahepatic cholestatic jaundice)
- Hematologic : aplastic anemia, agranulocytosis, leukopenia, neutropenia, hemolytic anemia, thrombocytopenia, bone marrow depression.
- Hypersensitivity : anaphylactic reactions, necrotizing angitis (vasculitis and cutaneous vasculitis), photosensitivity, urticarial, purpura.
- Respiratory, thoracic and mediastinal disorders: respiratory distress (including pneumonitis and pulmonary oedema), acute respiratory distress syndrome (ARDS).
- Metabolism and Nutrition Disorders : Hyperglycemia, hyperuricemia, electrolyte imbalance (including hypokalemia), glycosuria.
- Musculoskeletal : muscle spasm.
- Psychiatric Disorders : restlessness, sleep disturbances, depression.
- Nervous System Disorders : light-headedness, paresthesia.
- Renal : renal failure, renal dysfunction, interstitial nephritis.
- Skin : erythema multiforme including Steven-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, alopecia, systemic lupus erythematosus, reactivation of systemic lupus erythematosus, cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus.
- Eye disorders : transient blurred vision, xantopsia, acute myopia, acute angle-closure glaucoma.
- Urogenital : impotence.
- Investigations : Increases in cholesterol and triglycerides, increases in BUN and serum creatinine.

Laboratory test finding

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with the administration of Blopress plus.

Increases in creatinine, Blood Urea Nitrogen or potassium and decreases in sodium have been observed. Minor increases in blood urea nitrogen (BUN) and serum creatinine were observed infrequently. One patient was discontinued from Blopress plus due to increased BUN. No patient was discontinued due to an increase in serum creatinine.

Hemoglobin and hematocrit – small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.2 g/dl and 0.4 volume percent respectively) were observed in patients treated with Blopress plus, but were rarely of clinical importance.

Potassium – a small decrease (mean decrease of 0.1 meq/L) was observed in patients treated with Blopress plus. In placebo-controlled trials, hypokalaemia was reported in 0.4% of patients treated with Blopress plus compared to 1% of patients treated with hydrochlorothiazide or 0.2% of patients treated with placebo.

Liver functions tests – occasional elevations of liver enzymes and/or serum bilirubin have occurred.

PRECAUTIONS

General

Candesartan cilexetil – Hydrochlorothiazide

In clinical trials of various doses of candesartan cilexetil and hydrochlorothiazide, the incidence of hypertensive patients who developed hypokalaemia (serum 3.5 meq/L) was 2.5% versus 2.1% for placebo; the incidence the hyperkalaemia (serum potassium > 5.7 meq/L) was 0.4% versus 1.0% for placebo. No patients receiving Blopress plus 16-12.5 mg was discontinued due to increases or decreases in serum potassium. Overall, the combination of candesartan cilexetil and hydrochlorothiazide had no clinically significant on serum potassium.

Hydrochlorothiazide
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should performed at appropriate intervals.
All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatraemia, hypochloremic alkalosis, and hypokalaemia.
Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.
Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Hypokalaemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis.
Dilution hyponatraemia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration salts, except in rare instances when the hyponatremia is life – threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricaemia may occur or acute gout may be precipitated in certain patients receiving thiazide therapy.
In diabetic patients dosage adjustment of insulin or oral hypoglycemia agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy.
The antihypertensive effect of the drug may be enhanced in the post-sympathectomy patient.
If progressive renal impairment becomes evident consider with holding or discontinuing diuretic therapy.

Thiazide have been shown to increase the urinary excretion of magnesium, this may result in hypomagnesemia.
Thiazides have been shown to decrease the urinary calcium excretion or may impair glucose tolerance. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinues before carrying out test for parathyroid function.
Increase in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired renal function
Candesartan cilexetil
As a consequence of inhibiting the renin-angiotensin- aldosterone system, changes in renal function may be anticipated in susceptible in individuals treated with candesartan cilexetil. In patients whose renal function may depend upon the activity of the renin-angiotensin-aldosterone system (e.g. patients severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonist has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar result may be anticipated in patients treated with candesartan cilexetil. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan cilexetil in patients with unilateral or

bilateral renal artery stenosis, but similar results may be expected. Renal function may worsen in patients with renal artery stenosis. When candesartan cilexetil/hydrochlorothiazide is used in patients with impaired renal function, a periodic monitoring of serum potassium, creatinine and uric acid levels is recommended.

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. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking candesartan cilexetil/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 minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of candesartan cilexetil/hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC.

Hydrochlorothiazide
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Anaesthesia and surgery
Hypotension may occur during anaesthesia and surgery in patients treated with angiotensin II anatagonists due 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.

WARNINGS

Dual blockade of the renin-angiotensin-aldosterone-system (RAAS) by combining candesartan cilexetil/hydrochlorothiazide and aliskiren is not recommended since there is an increased risk of hypotension, hyperkalaemia and changes in renal function.

Fetal/neonatal/morbidity and mortality
Drugs the act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administrated to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. Post-marketing experience has identified reports of fetal and neonatal toxicity in babies born to women treated with candesartan cilexetil during pregnancy.

Because candesartan cilexetil is a component of Blopress plus, when pregnancy is detected, Blopress plus must be immediately discontinued.

The use drugs that act directly in the renin-angiotensin system during the second and the third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.

Oligohydramnios in the setting has been associated with the fetal limb contractures, craniofacial deformation, and hypoplastic lung development.
Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug.
These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed.
Nonetheless, when patients become pregnant, Blopress plus must be immediately discontinued.

Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potensial hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment.
If oligohydramnios is observed, Blopress plus should be discontinued unless it is considered life saving for the mother.
Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.
Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.
Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Candesartan cilexetil – Hydrochlorothiazide
There was no evidence of teratogenicity or other adverse effects on embryo-fetal development when pregnant mice, rats or rabbits were treated orally with candesartan cilexetil alone or in combination with hydrochlorothiazide. For mice, the maximum dose of candesartan cilexetil was 1000 mg/kg/day (about 150 times the maximum Recommended Daily Human Dose (MRHD).
For rats, the maximum dose of candesartan cilexetil was 100 mg/kg/day (about 31 times the MRHD).
For rabbits, the maximum dose of candesartan cilexetil was 1 mg/kg/day (a maternally toxic dose that is about a half the MRHD).

In each of these studies, hydrochlorothiazide was tested at the same dose level (10 mg/kg/day, about 4,8 and 15 times the MRHD in mouse, rats, rabbit respectively). There was no evidence of harm to the rat or mouse fetus embryo in studies which hydrochlorothiazide was administered alone to pregnant rat or mouse at doses of up to 1000 and 3000 mg/kg/day, respectively.

Thiazides cross the placental barrier and appear in cord blood. There is risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in volume and salt-depleted patients
Based in adverse events reported from all clinical trials of Blopress plus, excessive reduction of blood pressure was rarely seen patients with uncomplicated hypertension treated with candesartan cilexetil and hydrochlorothiazide (0.4%). Initiation of antihypertensive therapy may cause symptomatic hypotension in patients with intravascular volume-or sodium- depletion, e.q. in patients treated vigorously with diuretics or in patients on dialysis. These conditions should

corrected prior to administration of Blopress plus, or the treatment should start under close medical supervision.

If hypotension occurs, the patient should placed in the supine position and, if necessary, given an intravenous infusion or normal saline. A transient hypotensive response is not a contraindication to further treatment which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide
Impaired hepatic function
Thiazide diuretics 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.

Hypersensitive reaction
Hypersensitive 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.

Systemic lupus erythematosus
Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.

Lithium Interaction
Lithium generally should not be given with thiazides.

Acute Respiratory Toxicity
Very rare severe cases of acute respiratory toxicity, including acute respiratory distress syndrome (ARDS) have been reported after taking hydrochlorothiazide. Pulmonary edema typically develops within minutes to hours after hydrochlorothiazide intake. At the onset, symptoms include dyspnea, fever, pulmonary deterioration and hypotension. If diagnosis of ARDS is suspected, candesartan cilexetil/hydrochlorothiazide should be withdrawn and appropriate treatment given. Hydrochlorothiazide should not be administered to patients who previously experienced ARDS following hydrochlorothiazide intake.

Nursing mothers
It is not known whether candesartan is secreted in human milk, but candesartan has been shown to be present in rat milk. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking in account the importance of the drug to the mother.

DRUG INTERACTIONS
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 the use of a single RAAS acting agent.

Candesartan cilexetil
No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers. Because candesartan is not significantly metabolized by the

cytochrome P450/system and at therapeutic concentration has no effects on P450 enzymes, interactions with drugs that inhibit or rare metabolized by those enzymes would not be expected.

Hydrochlorothiazide
When administrated concurrently the following drugs may interact with thiazide diuretics: alcohol, barbiturate, or narcotics-potentiation of orthostatic hypotension may occur.
Antidiabetic drugs (oral agents and insulin) – dosage adjustment of the antidiabetic drug may be required other antihypertensive drugs – additive effect or potentiation.

Cholestyramine and colestipol resins – absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43% respectively.

Costicosteroid ACTH-intensified electrolyte depletion, particularly hypokalaemia.

Pressor amines (e.g, norepinephrine)-possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine)-possible increased responsiveness to the muscle relaxant.

Lithium – generally should not be given with diuretic agents reduce the renal clearance of lithium and add high risk of lithium toxicity. Refer to the package insert for lithium preparation before use of such preparations with Blopress plus.

Non-steroidal anti-inflammatory drugs – in some patients the administration of a non steroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium – sparing and thiazide diuretics.
Therefore when Blopress plus and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of diuretic is obtained.

Overdose
Symptoms
Based on pharmacological considerations, the main manifestation of an overdose of candesartan cilexetil is likely to be symptomatic hypotension and dizziness. In two cases reports of overdose (160 and 432 mg candesartan cilexetil) patient recovery was uneventful.

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

Management
So 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 sign monitored.
The patient should be placed supine with legs elevated. If it is not sufficient, plasma volume should be increased by infusion 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 hemodialysis. It is not known to what extend hydrochlorothiazide is removed by hemodialysis.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
The effect of candesartan cilexetil/hydrochlorothiazide on the ability to drive and use machines has not been studied, but based on its pharmacodynamic properties candesartan cilexetil/hydrochlorothizide is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during the treatment of hypertension.

EXCIPIENTS
Lactose monohydrate, polyethylene glycol 8000, iron oxide red cl 77491, carmellose calcium, magnesium stearate, corn starch, hyprolose.

STORAGE
Store below 25ºC, protect from light.

PACKAGE
Box 14 tablets (2 blisters @ 7 tablets)

REGISTRATION NO.
DKL1825103610A1

ON MEDICAL PRESCPRITION ONLY
HARUS DENGAN RESEP DOKTER

Takeda

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