Arkanda®Plus

Candesartan Cilexetil / Hydrochlorothiazide

FORMS AND PRESENTATION

Arkanda® Plus 16/12.5: Tablets: Box of 30.
Arkanda® Plus 32/12.5: Tablets: Box of 30.
Arkanda® Plus 32/25: Tablets: Box of 30.

COMPOSITION

Arkanda® Plus 16/12.5: Each tablet contains Candesartan cilexetil 16mg and Hydrochlorothiazide 12.5mg.
Arkanda® Plus 32/12.5: Each tablet contains Candesartan cilexetil 32mg and Hydrochlorothiazide 12.5mg.
Arkanda® Plus 32/25: Each tablet contains Candesartan cilexetil 32mg and Hydrochlorothiazide 25mg.
Excipients: Lactose monohydrate, maize starch, carmellose calcium, hydroxypropyl cellulose, macrogol, magnesium stearate, iron oxide red (Arkanda® Plus 16/12.5, Arkanda® Plus 32/25), iron oxide yellow (Arkanda® Plus 32/12.5).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmaco-therapeutic group: Angiotensin II antagonists + diuretics, ATC code: C09DA06.
Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension and other cardiovascular disorders. It also has a role in the pathogenesis of organ hypertrophy and end organ 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 (AT_1) receptor.
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 AIIRA, selective for AT_1 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, AIIRAs 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 AT_1 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, Arkanda® Plus results in a dose-dependent 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 Arkanda® 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. Arkanda® 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 a double-blind randomised study, candesartan cilexetil/hydrochlorothiazide 16 mg/12.5 mg once daily reduced blood pressure significantly more, and controlled significantly more patients, than the combination losartan/hydrochlorothiazide 50 mg/12.5 mg once daily.
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.

Pharmacokinetic properties

Absorption and distribution

Candesartan cilexetil

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 a tablet formulation of candesartan cilexetil compared with the same oral solution is approximately 34% with very little variability. 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.

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.

Biotransformation and elimination

Candesartan cilexetil

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 medicinal products whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life ($t_{½}$) of candesartan is approximately 9 hours. There is no accumulation following multiple doses. The half-life of candesartan remains unchanged (approximately 9 h) after administration of candesartan cilexetil in combination with hydrochlorothiazide. No additional accumulation of candesartan occurs after repeated doses of the combination compared to monotherapy.
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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolised and is excreted almost entirely as unchanged drug by glomerular filtration and active tubular secretion. The terminal $t_{½}$ 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.

Special Populations

Candesartan cilexetil

In elderly subjects (over 65 years), C_{max} and AUC of candesartan are increased by approximately 50% and 80%, respectively in comparison to young subjects. However, the blood pressure response and the incidence of adverse events are similar after a given dose of Arkanda® Plus in young and elderly patients.
In patients with mild to moderate renal impairment, C_{max} and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but the terminal $t_{½}$ 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 $t_{½}$ 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 two studies, both including patients with mild to moderate hepatic impairment, there was an increase in the mean AUC of candesartan of approximately 20% in one study and 80% in the other study.

Hydrochlorothiazide

The terminal $t_{½}$ of hydrochlorothiazide is prolonged in patients with renal impairment.

INDICATIONS

Arkanda® Plus is indicated for the treatment of essential hypertension in adult patients whose blood pressure is not optimally controlled with candesartan cilexetil or hydrochlorothiazide monotherapy.

CONTRAINDICATIONS

- Hypersensitivity to the active substances or to any of the excipients or to sulfonamide derived active substances. Hydrochlorothiazide is a sulfonamide derived active substance.
- Second and third trimesters of pregnancy.
- Severe renal impairment (creatinine clearance < 30 ml/min/1.73 m² BSA).
- Severe hepatic impairment and/or cholestasis.
- Refractory hypokalaemia and hypercalcaemia.
- Gout.

PRECAUTIONS

Renal impairment/kidney transplantation

Loop diuretics are preferred to thiazides in this population. When Arkanda® 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 Arkanda® Plus in patients with a recent kidney transplantation.

Renal artery stenosis

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

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 Arkanda® Plus is not recommended until this condition has been corrected.

Anaesthesia and surgery

Hypotension may occur during anaesthesia and surgery in patients treated with AIIRAs 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.

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.

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 agents acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of Arkanda® Plus is not recommended in this population.

Electrolyte imbalance

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 dose-dependently 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).
Treatment with candesartan cilexetil may cause hyperkalaemia, especially in the presence of heart failure and/or renal impairment. Concomitant use of candesartan cilexetil / hydrochlorothiazide and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate.
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. Dose adjustment of antidiabetic medicinal products, 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. At the doses contained in Arkanda® Plus, only minimal effects were observed. Thiazide diuretics increase serum uric acid concentration and may precipitate gout in susceptible patients.

Photosensitivity

Cases of photosensitivity reactions have been reported during use of thiazide diuretics. If a photosensitivity reaction occurs, it is recommended to stop treatment. If re-administration of treatment is essential, it is recommended to protect areas exposed to the sun or to artificial UVA radiation.

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 medicinal products that affect this system including AIIRAs, has been associated with acute hypotension, azotaemia, oliguria or, rarely, acute renal failure. 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.
Exacerbation or activation of systemic lupus erythaematosus has been reported with the use of thiazide diuretics.

The antihypertensive effect of Arkanda® Plus may be enhanced by other antihypertensives.
This medicinal product contains lactose, as an excipient, and patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles or operating machines, it should be considered that occasionally dizziness or weariness may occur during treatment with Arkanda® Plus.

PREGNANCY AND LACTATION

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs):

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however, a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with AIIRAs, similar risks may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive 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.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia). Should exposure to AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended. Infants whose mothers have taken AIIRAs should be closely observed for hypotension.

Hydrochlorothiazide:

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide its use during the second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension, or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease. Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Lactation

Angiotensin II Receptor Antagonists (AIIRAs):

Because no information is available regarding the use of Arkanda® Plus during breast-feeding, Arkanda® Plus is not recommended and alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide:

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of Arkanda® Plus during breast-feeding is not recommended.

DRUG INTERACTIONS

The potassium depleting effect of hydrochlorothiazide could be expected to be potentiated by other medicinal products associated with potassium loss and hypokalaemia (e.g. other kaliuretic diuretics, laxatives, amphotericin, carbenoxolone, penicillin G sodium, salicylic acid derivates, steroids, ACTH).

Concomitant use of candesartan cilexetil / hydrochlorothiazide and potassium-sparing diuretics, potassium supplements or salt substitutes or other medicinal products that may increase serum potassium levels (e.g. heparin sodium) may lead to increases in serum potassium. Monitoring of potassium should be undertaken as appropriate.

Diuretic-induced hypokalaemia and hypomagnesaemia predisposes to the potential cardiotoxic effects of digitalis glycosides and antiarrhythmics. Periodic monitoring of serum potassium is recommended when Arkanda® Plus is administered with such medicinal products, and with the following medicinal products that could induce torsades de pointes:

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol)
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, ketanserin, mizolastin, pentamidine, sparfloxacine, terfenadine, vincamine IV).

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with Angiotensin Converting Enzyme (ACE) inhibitors or hydrochlorothiazide. A similar effect has also been reported with AIIRAs. Use of candesartan and hydrochlorothiazide 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 (> 3 g/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.

The diuretic, natriuretic and antihypertensive effect of hydrochlorothiazide is blunted by NSAIDs.

The absorption of hydrochlorothiazide is reduced by colestipol or cholestyramine.

The effect of nondepolarising 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 the dose 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 medicinal products (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Postural hypotension may become aggravated by simultaneous intake of alcohol, barbiturates, or anaesthetics.

Treatment with a thiazide diuretic may impair glucose tolerance. Dose adjustment of antidiabetic medicinal products, including insulin, may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

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.

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Concomitant treatment with baclofen, amifostin, tricyclic antidepressants or neuroleptics may lead to enhancement of the antihypertensive effect and may induce hypotension.

ADVERSE EFFECTS

Like all medicines, Arkanda® Plus can cause side effects, although not everybody gets them. Some of the side effects of Arkanda® Plus are caused by candesartan cilexetil and some are caused by hydrochlorothiazide.

The adverse reactions are presented below by system organ class.

Blood and lymphatic system disorders: leukopenia, neutropenia, and agranulocytosis; thrombocytopenia, bone marrow depression and aplasia, haemolytic anemia.

Metabolism and nutrition disorders: hyperglycaemia, hyperuricaemia, electrolyte imbalance (including hyponatremia and hypokalaemia); hyperkalemia, hyponatremia.

Nervous system disorders: lightheadedness, dizziness/vertigo, headache; paresthesias.

Respiratory, thoracic, and mediastinal disorders: cough, respiratory distress (including pneumonitis and pulmonary oedema); acute respiratory distress syndrome (ARDS).

Gastrointestinal disorders: nausea; anorexia, loss of appetite, gastric irritation, diarrhea, constipation; pancreatitis.

Hepatobiliary disorders: jaundice (intrahepatic cholestatic jaundice); elevated liver enzymes, liver function abnormalities, or hepatitis.

Skin and subcutaneous tissue disorders: angioedema, rash, urticaria, pruritus; hives, photosensitivity reactions; toxic epidermal necrolysis; systemic lupus erythematosus, cutaneous lupus erythematosus.

Musculoskeletal and connective tissue disorders: muscle spasm; back pain, arthralgia, myalgia.

Infections and infestations: respiratory infection.

Renal and urinary disorders: impaired renal function, including cases of renal failure in patients at risk.

Benign, malignant, and unspecified tumors (including cysts and polyps): non-melanoma skin cancer (basal cell carcinoma, squamous cell carcinoma).

Immune system disorders: anaphylactic reactions.

Psychiatric disorders: sleep disturbances, depression, restlessness.

Eye conditions: temporary blurred vision; acute myopia, acute angle-closure glaucoma, choroidal effusion.

Heart conditions: arrythmias.

Vascular disorders: orthostatic hypotension; necrotizing angiitis (vasculitis, cutaneous vasculitis).

Kidney and urinary disorders: glycosuria; renal dysfunction and interstitial nephritis.

General disorders and administration site conditions: weakness; fever.

DOSAGE AND ADMINISTRATION

Posology

The recommended dose of Arkanda® Plus is one tablet once daily.

The usual recommended starting dose of candesartan cilexetil is 16 mg once daily when it is used as monotherapy in patients who are not volume depleted. Candesartan cilexetil can be administered once or twice daily with total daily doses ranging from 8 mg to 32 mg. Patients requiring further reduction in blood pressure should be titrated to 32 mg. Doses larger than 32 mg do not appear to have a greater blood pressure-lowering effect.

Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily.

To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Patients with Renal Impairment:

The usual regimens of therapy with Arkanda® Plus may be followed as long as the patient's creatinine clearance is > 30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so Arkanda® Plus is not recommended.

Patients with Hepatic Impairment:

The usual regimens of therapy with Arkanda® Plus may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of candesartan cilexetil at a lower dose, such as 8 mg. If a lower starting dose is selected for candesartan cilexetil, Arkanda® Plus is not recommended for initial titration because the appropriate initial starting dose of candesartan cilexetil cannot be given.

Thiazide diuretics should be used with caution in patients with hepatic impairment; therefore, care should be exercised with dosing of Arkanda® Plus.

Method of administration

For oral use

Arkanda® Plus may be administered with other antihypertensive agents.

Arkanda® Plus may be given with or without food.

OVERDOSAGE

Limited data are available regarding overdosage with candesartan cilexetil in humans. The most likely manifestations of overdosage with candesartan cilexetil would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be initiated.

For hydrochlorothiazide, the most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremia, hyponatremia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias.

Candesartan cannot be removed by hemodialysis. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of Revision: September 2024.

Marketing Authorization Holder and Manufacturer

Benta S.A.L – Lebanon

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