Arkanda®

Candesartan Cilexetil

FORMS AND PRESENTATION

Arkanda® 8: Tablets: Box of 30.
Arkanda® 16: Tablets: Box of 30.
Arkanda® 32: Tablets: Box of 30.

COMPOSITION

Arkanda® 8: Each tablet contains Candesartan cilexetil 8mg.
Arkanda® 16: Each tablet contains Candesartan cilexetil 16mg.
Arkanda® 32: Each tablet contains Candesartan cilexetil 32mg.
Excipients: Lactose monohydrate, corn starch, carboxymethylcellulose calcium, hydroxypropyl cellulose, polyethylene glycol, magnesium stearate, iron oxide red.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II antagonists, plain, ATC code: C09CA06.

Mechanism of action

Angiotensin II is the primary vasoactive hormone of the renin-angiotensin-aldosterone system and plays a role in the pathophysiology of hypertension, heart failure and other cardiovascular disorders. It also has a role in the pathogenesis of end-organ hypertrophy and damage. The major physiological effects of angiotensin II, such as vasoconstriction, aldosterone stimulation, regulation of salt and water homeostasis and stimulation of cell growth, are mediated via the type 1 (AT1) receptor.

Candesartan cilexetil is a prodrug suitable for oral use. It is rapidly converted to the active substance, 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.

Pharmacodynamic effects

Candesartan does not inhibit ACE, which converts angiotensin I to angiotensin II and degrades bradykinin. There is no effect on ACE and no potentiation of bradykinin or substance P. In controlled clinical trials comparing candesartan 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 angiotensin II (AT1) receptors results in dose-related increases in plasma renin levels, angiotensin I and angiotensin II levels, and a decrease in plasma aldosterone concentration.

Pharmacokinetic properties

Absorption and distribution

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 mean peak serum concentration (Cmax) is reached 3-4 hours following tablet intake. The candesartan serum concentrations increase linearly with increasing doses in the therapeutic dose range. 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.

The bioavailability of candesartan is not affected by food.

Biotransformation and elimination

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 drugs whose metabolism is dependent upon cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. The terminal half-life of candesartan is approximately 9 hours. There is no accumulation following multiple doses.

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.

Pharmacokinetics in special populations

In the elderly (over 65 years) Cmax 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 Candesartan cilexetil in young and elderly patients.

In patients with mild to moderate renal impairment Cmax and AUC of candesartan increased during repeated dosing by approximately 50% and 70%, respectively, but t½ 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 t½ of candesartan was approximately doubled in patients with severe renal impairment. The AUC of candesartan in patients undergoing hemodialysis was similar to that in patients with severe renal impairment.

Pediatric population

In children aged 1 to <6 years, no clearance data has been collected; therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

In children aged 6 to <17 years, there was no correlation between Cmax and AUC with age. However, the weight seems to significantly correlate with Cmax and AUC. No clearance data has been collected, therefore the possibility of a correlation between clearance and weight/age in this population is unknown.

The pharmacokinetics of candesartan cilexetil have not been investigated in paediatric patients <1 year of age.

INDICATIONS

Arkanda® is indicated for the:

- Treatment of primary hypertension in adults.
- Treatment of hypertension in children and adolescents aged 6 to <18 years.
- The treatment of adult patients with heart failure and impaired left ventricular systolic function (left ventricular ejection fraction ≤ 40%) when Angiotensin Converting Enzyme (ACE)-inhibitors are not tolerated or as add-on therapy to ACE-inhibitors in patients with symptomatic heart failure, despite optimal therapy, when mineralocorticoid receptor antagonists are not tolerated.

CONTRAINDICATIONS

Candesartan cilexetil is contraindicated in the following cases:

- Hypersensitivity to the active substance or to any of the excipients.
- Second and third trimester of pregnancy.
- Severe hepatic impairment and/or cholestasis.
- Children aged below 1 year.
- The concomitant use of Candesartan Cilexetil with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

PRECAUTIONS

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Renal impairment

When candesartan is used in hypertensive patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ <15 ml/min). In these patients, candesartan should be carefully titrated with thorough monitoring of blood pressure.

Use in pediatric patients with renal impairment

Candesartan has not been studied in children with a glomerular filtration rate of less than 30 ml/min/1.73 m^2.

Concomitant therapy with an ACE-inhibitor in heart failure

The risk of adverse reactions, especially hypotension, hyperkalemia and decreased renal function (including acute renal failure), may increase when candesartan is used in combination with an ACE-inhibitor.

A triple combination of an ACE-inhibitor, a mineralocorticoid receptor antagonist, and candesartan is also not recommended.

ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Hemodialysis

During dialysis, the blood pressure may be particularly sensitive to AT1-receptor blockade as a result of reduced plasma volume and activation of the renin-angiotensin-aldosterone system. Therefore, candesartan should be carefully titrated with thorough monitoring of blood pressure in patients on hemodialysis.

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.

Hypotension

Hypotension may occur during treatment with candesartan in heart failure patients. It may also occur in hypertensive patients with intravascular volume depletion such as those receiving high dose diuretics. Caution should be observed when initiating therapy and correction of hypovolemia should be attempted.

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), candesartan treatment should be initiated under close medical supervision and a lower starting dose should be considered.

Anesthesia and surgery

Hypotension may occur during anesthesia and surgery in patients treated with angiotensin II antagonists due to blockade of the renin-angiotensin system. Very rarely, hypotension may be severe such that it may warrant the use of intravenous fluids and/or vasopressors.

Aortic and mitral valve stenosis (obstructive hypertrophic cardiomyopathy)

As with other vasodilators, special caution is indicated in patients suffering from hemodynamically relevant aortic or mitral valve stenosis, or obstructive hypertrophic cardiomyopathy.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism will not generally respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin-aldosterone system. Therefore, the use of candesartan is not recommended in this population.

Hyperkalemia

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

The combination of an ACE-inhibitor, a potassium-sparing diuretic (e.g. spironolac.tone), and candesartan is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

General

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure or underlying renal disease, including renal artery stenosis), treatment with other medicinal products that affect this system has been associated with acute hypotension, azotemia, oliguria or, rarely, acute renal failure. The possibility of similar effects cannot be excluded with AIIRAs. As with any antihypertensive agent, excessive blood pressure decreases in patients with ischemic cardiopathy or ischemic cerebrovascular disease could result in a myocardial infarction or stroke.

The antihypertensive effect of candesartan may be enhanced by other medicinal products with blood pressure lowering properties, whether prescribed as an antihypertensive or prescribed for other indications.

Candesartan Cilexetil contains lactose monohydrate

Patients with rare hereditary problems of galactose intolerance, 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 of candesartan on the ability to drive and use machines have been performed. However, it should be taken into account that occasionally, dizziness or weariness may occur during treatment with candesartan.

PREGNANCY AND LACTATION

Pregnancy

The use of AIIRAs is not recommended during the first trimester of pregnancy. The use of AIIRAs is contraindicated during the second and third trimesters of pregnancy. It is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia).

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.

Breast-feeding

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

DRUG INTERACTIONS

Compounds that have been investigated in clinical pharmacokinetic studies include hydrochlorothiazide, warfarin, digoxin, oral contraceptives (i.e. ethinylestradiol/levonorgestrel), glibenclamide, nifedipine and enalapril. No clinically significant pharmacokinetic interactions with these medicines have been identified.

Concomitant use of potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium, or other medicinal products (e.g. heparin) may increase potassium levels. Monitoring of potassium should be undertaken as appropriate.

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE-inhibitors. A similar effect may occur with AIIRAs. The use of candesartan 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 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.

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers, or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Pediatric population

Interaction studies have only been performed in adults.

ADVERSE EFFECTS

Treatment of hypertension

In controlled clinical studies, adverse reactions were mild and transient. The overall incidence of adverse events showed no association with dose or age. Withdrawals from treatment due to adverse events were similar with candesartan cilexetil and placebo.

Below are presented the adverse reactions from clinical trials and post-marketing experiences by system organ class.

The frequencies used are: very common (≥ 1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data):

Infections and infestations: respiratory infection (common).

Blood and lymphatic system disorders: leucopenia, neutropenia, and agranulocytosis (very rare)

Metabolism and nutrition disorders: hyperkalemia, hyponatremia (very rare).

Nervous system disorders: dizziness/vertigo, headache (common).

Respiratory, thoracic, and mediastinal disorders: cough (very rare).

Gastrointestinal disorders: nausea (very rare); diarrhea (not known).

Hepatobiliary disorders: increased liver enzymes, abnormal hepatic function, or hepatitis (very rare).

Skin and subcutaneous tissue disorders: angioedema, rash, urticaria, pruritus (very rare).

Musculoskeletal and connective tissue disorders: back pain, arthralgia, myalgia (very rare).

Renal and urinary disorders: renal impairment, including renal failure in susceptible patients (very rare).

Laboratory findings: in patients with renal impairment, periodic monitoring of serum potassium and creatinine levels is recommended.

Pediatric population

The safety of candesartan cilexetil was monitored in hypertensive children and adolescents, aged 6 to <18 years old. In nearly all different system organ classes, the frequency of adverse events in children are within common/uncommon range. Whilst the nature and severity of the adverse events are similar to those in adults (see above), the frequency of all adverse events are higher in children and adolescents, particularly in:

• Headache, dizziness and upper respiratory tract infection, are “very common” in children and common in adults.

• Cough is “very common” in children and very rare in adults.

• Rash is “common” in children and “very rare” in adults.

• Hyperkalemia, hyponatremia and abnormal liver function are uncommon in children and very rare in adults.

• Sinus arrhythmia, nasopharyngitis, and pyrexia are “common” and oropharyngeal pain is “very common” in children; but none are reported in adults. However, these are temporary and widespread childhood illnesses.

The overall safety profile for candesartan cilexetil in pediatric patients does not differ significantly from the safety profile in adults.

Treatment of heart failure

The most reported adverse reactions were hyperkalemia, hypotension, and renal impairment. These events were more common in patients over 70 years of age, diabetics, or subjects who received other medicinal products which affect the renin-angiotensin-aldosterone system, in particular, an ACE-inhibitor and/or spironolactone.

Below are presented the adverse reactions from clinical trials and post-marketing experiences by system organ class.

Blood and lymphatic system disorders: leucopenia, neutropenia and agranulocytosis (very rare).

Metabolism and nutrition disorders: hyperkalemia (common); hyponatremia (very rare).

Nervous system disorders: dizziness, headache (very rare).

Vascular disorders: hypotension (common).

Respiratory, thoracic, and mediastinal disorders: cough (very rare).

Gastrointestinal disorders: nausea (very rare); diarrhea (not known).

Hepatobiliary disorders: increased liver enzymes, abnormal hepatic function, or hepatitis (very rare).

Skin and subcutaneous tissue disorders: angioedema, rash, urticaria, pruritus (very rare).

Musculoskeletal and connective tissue disorders: back pain, arthralgia, myalgia (very rare).

Renal and urinary disorders: renal impairment, including renal failure in susceptible patients (common).

Laboratory findings: periodic monitoring of serum creatinine and potassium is recommended.

DOSAGE AND ADMINISTRATION

Posology in hypertension

The recommended initial dose and usual maintenance dose of Arkanda® is 8 mg once daily. Most of the antihypertensive effect is attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 16 mg once daily and to a maximum of 32 mg once daily. Therapy should be adjusted according to blood pressure response.

Arkanda® may also be administered with other antihypertensive agents. The addition of hydrochlorothiazide has been shown to have an additive antihypertensive effect with various doses of candesartan.

Elderly population

No initial dose adjustment is necessary for elderly patients.

Patients with intravascular volume depletion

An initial dose of 4 mg may be considered in patients at risk for hypotension, such as patients with possible volume depletion.

Renal impairment

The starting dose is 4 mg in patients with renal impairment, including patients on hemodialysis. The dose should be titrated according to the response. There is limited experience in patients with very severe or end-stage renal impairment ($Cl_{creatinine}$ < 15 ml/min).

Hepatic impairment

An initial dose of 4 mg once daily is recommended in patients with mild to moderate hepatic impairment. The dose may be adjusted according to the response. Arkanda® is contraindicated in patients with severe hepatic impairment and/or cholestasis.

Pediatric population

Children and adolescents aged 6 to <18 years:

The recommended starting dose is 4 mg once daily.

• For patients weighing < 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to a maximum of 8 mg once daily.

• For patients weighing ≥ 50 kg: In patients whose blood pressure is not adequately controlled, the dose can be increased to 8 mg once daily and then to 16 mg once daily if needed.

Doses above 32 mg have not been studied in pediatric patients. Most of the antihypertensive effect is attained within 4 weeks.

For children with possible intravascular volume depletion (e.g. patients treated with diuretics, particularly those with impaired renal function), candesartan treatment should be initiated under close medical supervision and a lower starting dose than the general starting dose above should be considered. Candesartan has not been studied in children with a glomerular filtration rate of less than 30 ml/min/1.73 m^2.

Children aged below 1 year to <6 years

• The safety and efficacy in children aged 1 to <6 years of age have not been established. No recommendation on a posology can be made.

• Candesartan is contraindicated in children aged below 1 year.

Posology in heart failure

The usual recommended initial dose of candesartan is 4 mg once daily. Up-titration to the target dose of 32 mg once daily (maximum dose) or to the highest tolerated dose is done by doubling the dose at intervals of at least 2 weeks. Evaluation of patients with heart failure should always comprise assessment of renal function including monitoring of serum creatinine and potassium. Arkanda® can be administered with other heart failure treatments, including ACE-inhibitors, beta-blockers, diuretics, and digitalis or a combination of these medicinal products. Arkanda® may be co-administered with an ACE-inhibitor in patients with symptomatic heart failure despite optimal standard heart failure therapy when mineralocorticoid receptor antagonists are not tolerated.

The combination of an ACE-inhibitor, a potassium-sparing diuretic, and candesartan is not recommended and should be considered only after careful evaluation of the potential benefits and risks.

Special patient populations

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

Pediatric population

The safety and efficacy of candesartan in children aged between birth and 18 years have not been established in the treatment of heart failure. No data are available.

Method of administration

Oral use.

Arkanda® should be taken once daily with or without food.

OVERDOSAGE

Symptoms

Based on pharmacological considerations, the main manifestation of an overdose is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg candesartan cilexetil) in an adult patient recovery was uneventful.

Management

If symptomatic hypotension should occur, symptomatic treatment should be instituted, and vital signs monitored. The patient should be placed supine with the legs elevated. If this is not sufficient, plasma volume should be increased by infusion of, for example, isotonic saline solution. Sympathomimetic medicinal products may be administered if the above-mentioned measures are not sufficient.

Candesartan is not removed by hemodialysis.

STORAGE CONDITIONS

Store below 25°C.

Keep in original pack in intact conditions.

Date of Revision: April 2023.

Marketing Authorization Holder and Manufacturer

Benta S.A.L

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