

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cuenca 320 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 320 mg of valsartan

Excipients

Each tablet contains

sorbitol 37.0 mg

lactose 4.3 mg

sodium 1.28 mg (0.06 mmol)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Oblong, coated, scored on one side, greyish-violet film-coated tablets.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

Treatment of essential hypertension.

4.2 Posology and method of administration

Hypertension.

The recommended starting dose of Cuenca is 80 mg once daily. The antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks. In some patients whose blood pressure is not adequately controlled, the dose can be increased to 160 mg and to a maximum of 320 mg.

Cuenca may also be administered with other antihypertensive agents. The addition of a diuretic such as hydrochlorothiazide will decrease blood pressure even further in these patients.

Method of administration

Cuenca may be taken independently of a meal and should be administered with water.

Additional information on special populations

Elderly

No dose adjustment is required in elderly patients.

Renal impairment

No dosage adjustment is required for patients with a creatinine clearance >10 ml/min (see sections 4.4 and 5.2)

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, the dose of valsartan should not exceed 80

mg. Cuenca is contraindicated in patients with severe hepatic impairment and in patients with cholestasis (see sections 4.3, 4.4 and 5.2).

Paediatric patients

Cuenca is not recommended for use in children below the age of 18 years due to a lack of data on safety and efficacy.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Severe hepatic impairment, biliary cirrhosis and cholestasis.
- Second and third trimester of pregnancy (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

Hyperkalaemia

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other agents that may increase potassium levels (heparin, etc.) is not recommended. Monitoring of potassium should be undertaken as appropriate.

Sodium- and/or volume-depleted patients

In severely sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur in rare cases after initiation of therapy with Cuenca. Sodium and/or volume depletion should be corrected before starting treatment with Cuenca, for example by reducing the diuretic dose.

Renal artery stenosis

In patients with bilateral renal artery stenosis or stenosis to a solitary kidney, the safe use of Cuenca has not been established.

Short-term administration of Cuenca to twelve patients with renovascular hypertension secondary to unilateral renal artery stenosis did not induce any significant changes in renal haemodynamics, serum creatinine, or blood urea nitrogen (BUN). However, other agents that affect the renin-angiotensin system may increase blood urea and serum creatinine in patients with unilateral renal artery stenosis, therefore monitoring of renal function is recommended when patients are treated with valsartan.

Kidney transplantation

There is currently no experience on the safe use of Cuenca in patients who have recently undergone kidney transplantation.

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with Cuenca as their renin-angiotensin system is not activated.

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

As with all other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or hypertrophic obstructive cardiomyopathy (HOCM).

Impaired renal function

No dosage adjustment is required for patients with a creatinine clearance >10 ml/min. There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 5.2).

Hepatic impairment

In patients with mild to moderate hepatic impairment without cholestasis, Cuenca should be used with caution (see sections 4.2 and 5.2).

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. Unless continued AIIRAs

therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive 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 (see sections 4.3 and 4.6).

Other conditions with stimulation of the renin-angiotensin system

In patients whose renal function may depend on the activity of the renin-angiotensin system (e.g patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotaemia and in rare cases with acute renal failure and/or death. As valsartan is an angiotensin II antagonist, it cannot be excluded that the use of Cuenca may be associated with impairment of the renal function.

Warning about excipients:

This medicine contains sorbitol. Patients with hereditary problems of fructose intolerance should not take this medicine.

This medicine contains lactose. Patients with hereditary problems of galactose intolerance, the Lapp lactase deficiency (insufficiency observed in certain populations of Lapland) or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 23 mg of sodium per dose; that is, essentially “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concurrent use of ACE inhibitors. Due to the lack of experience with concomitant use of valsartan and lithium, this combination is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels

If a medicinal product that affects potassium levels is considered necessary in combination with valsartan, monitoring of potassium plasma levels is advised.

Caution required with concomitant use

Non-steroidal anti-inflammatory medicines (NSAIDs), including selective COX-2 inhibitors, acetylsalicylic acid >3 g/day), and non-selective NSAIDs

When angiotensin II antagonists are administered simultaneously with NSAIDs, attenuation of the antihypertensive effect may occur. Furthermore, concomitant use of angiotensin II antagonists and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Others

In drug interaction studies with valsartan, no interactions of clinical significance have been found with valsartan or any of the following substances: cimetidine, warfarin, furosemide, digoxin, atenolol, indometacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

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 anti-hypertensive 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.

AIIRAs therapy exposure 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, hyperkalemia); see also section 5.3 "Preclinical safety data".

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 (see also sections 4.3 and 4.4).

Lactation

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive have been performed. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or weariness may occur.

4.8 Undesirable effects

In controlled clinical studies in patients with hypertension, the overall incidence of adverse reactions (ADRs) was comparable with placebo and is consistent with the pharmacology of valsartan. The incidence of ADRs did not appear to be related to dose or treatment duration and also showed no association with gender, age or race.

The ADRs reported from clinical studies, post-marketing experience and laboratory findings are listed below according to system organ class.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention: Very common ($\geq 1/10$),

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

. Within each frequency grouping, adverse reactions are ranked in order of decreasing seriousness.

For all the ADRs reported from post-marketing experience and laboratory findings, it is not possible to apply any ADR frequency and therefore they are mentioned with a "not known" frequency.

■ Hypertension

Blood and lymphatic system disorders	
Not known	Decrease in haemoglobin, Decrease in haematocrit, Neutropenia, Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Not known	Increase of serum potassium
Ear and labyrinth system disorders	
Uncommon	Vertigo

Vascular disorders	
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Abdominal pain
Hepato-biliary disorders	
Not known	Elevation of liver function values including increase of serum bilirubin
Skin and subcutaneous tissue disorders	
Not known	Angioedema, Rash, Pruritus
Musculoskeletal and connective tissue disorders	
Not known	Myalgia
Renal and urinary disorders	
Not known	Renal failure and impairment, Elevation of serum creatinine
General disorders and administration site conditions	
Uncommon	Fatigue

The safety profile seen in controlled-clinical studies in patients with post-myocardial infarction and/or heart failure varies from the overall safety profile seen in hypertensive patients. This may relate to the patients underlying disease. ADRs that occurred in post-myocardial infarction and/or heart failure patients are listed below:

- Post-myocardial infarction and/or heart failure

Blood and lymphatic system disorders	
Not know	Thrombocytopenia
Immune system disorders	
Not known	Hypersensitivity including serum sickness
Metabolism and nutrition disorders	
Uncommon	Hyperkalaemia
Not known	Increase of serum potassium
Nervous system disorders	
Common	Dizziness, Postural dizziness
Uncommon	Syncope, Headache
Ear and labyrinth system disorders	
Uncommon	Vertigo
Cardiac disorders	
Uncommon	Cardiac failure
Vascular disorders	
Common	Hypotension, Orthostatic hypotension
Not known	Vasculitis
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough
Gastrointestinal disorders	
Uncommon	Nausea, Diarrhoea
Hepato-biliary disorders	
Not known	Elevation of liver function values
Skin and subcutaneous tissue disorders	
Uncommon	Angioedema
Not known	Rash, Pruritis
Musculoskeletal and connective tissue disorders	

Not known	Myalgia
Renal and urinary disorders	
Common	Renal failure and impairment
Uncommon	Acute renal failure, Elevation of serum creatinine
Not known	Increase in Blood Urea Nitrogen
General disorders and administration site conditions	
Uncommon	Asthenia, Fatigue

4.9 Overdose

Symptoms

A Cuenca overdose could possibly cause a marked hypotension that under certain circumstances could lead to depressed level of consciousness, circulatory collapse and/or shock.

Therapy

Therapeutic measures depend on when the medicine was taken, as well as the type and severity of the symptoms. Here restoration of stable circulatory conditions should be the main concern.

After an overdose, the patients should receive a sufficient quantity of activated charcoal.

In case of hypotension the patient should be placed in a horizontal position. Salt and plasma replacement preparations should be rapidly administered.

Valsartan cannot be removed by haemodialysis due to its strong plasma-protein bonding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC code: C09CA03

Valsartan is an orally active, potent, and specific angiotensin II (Ang II) receptor antagonist. It acts selectively on the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of Ang II following AT1 receptor blockade with valsartan may stimulate the unblocked AT2 receptor, which appears to counterbalance the effect of the AT1 receptor. Valsartan does not exhibit any partial agonist activity at the AT1 receptor and has much (about 20,000 fold) greater affinity for the AT1 receptor than for the AT2 receptor. Valsartan is not known to bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Valsartan does not inhibit ACE (also known as kininase II) which converts Ang I to Ang II and degrades bradykinin. Since there is no effect on ACE and no potentiation of bradykinin or substance P, angiotensin II antagonists are unlikely to be associated with coughing. In clinical trials where valsartan was compared with an ACE inhibitor, the incidence of dry cough was significantly ($P < 0.05$) less in patients treated with valsartan than in those treated with an ACE inhibitor (2.6% versus 7.9% respectively). In a clinical trial of patients with a history of dry cough during ACE inhibitor therapy, 19.5% of trial subjects receiving valsartan and 19.0% of those receiving a thiazide diuretic experienced cough compared to 68.5% of those treated with an ACE inhibitor ($P < 0.05$).

Hypertension

Administration of Cuenca to patients with hypertension results in reduction of blood pressure without affecting pulse rate.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after dosing. During repeated dosing, the antihypertensive effect is substantially present within 2 weeks, and maximal effects are attained within 4 weeks and persist during long-term therapy. Combined with hydrochlorothiazide, a

significant additional reduction in blood pressure is achieved.

Abrupt withdrawal of Cuenca has not been associated with rebound hypertension or other adverse clinical events.

In hypertensive patients with type 2 diabetes and microalbuminuria, valsartan has been shown to reduce the urinary excretion of albumin. The MARVAL (Micro Albuminuria Reduction with Valsartan) study assessed the reduction in urinary albumin excretion (UAE) with valsartan (80-160 mg/od) versus amlodipine (5-10 mg/od), in 332 type 2 diabetic patients (mean age: 58 years; 265 men) with microalbuminuria (valsartan: 58 µg/min; amlodipine: 55.4 µg/min), normal or high blood pressure and with preserved renal function (blood creatinine <120 µmol/l). At 24 weeks, UAE was reduced (p<0.001) by 42% (-24.2 µg/min; 95% CI: -40.4 to -19.1) with valsartan and approximately 3% (-1.7 µg/min; 95% CI: -5.6 to 14.9) with amlodipine despite similar rates of blood pressure reduction in both groups.

The Cuenca Reduction of Proteinuria (DROP) study further examined the efficacy of valsartan in reducing UAE in 391 hypertensive patients (BP=150/88 mmHg) with type 2 diabetes, albuminuria (mean=102 µg/min; 20-700 µg/min) and preserved renal function (mean serum creatinine = 80 µmol/l). Patients were randomized to one of 3 doses of valsartan (160, 320 and 640 mg/od) and treated for 30 weeks. The purpose of the study was to determine the optimal dose of valsartan for reducing UAE in hypertensive patients with type 2 diabetes. At 30 weeks, the percentage change in UAE was significantly reduced by 36% from baseline with valsartan 160 mg (95% CI: 22 to 47%), and by 44% with valsartan 320 mg (95% CI: 31 to 54%). It was concluded that 160-320 mg of valsartan produced clinically relevant reductions in UAE in hypertensive patients with type 2 diabetes.

5.2 Pharmacokinetic properties

Absorption:

Following oral administration of valsartan alone, peak plasma concentrations of valsartan are reached in 2–4 hours. Mean absolute bioavailability is 23%. Food decreases exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%, although from about 8 h post dosing plasma valsartan concentrations are similar for the fed and fasted groups. This reduction in AUC is not, however, accompanied by a clinically significant reduction in the therapeutic effect, and valsartan can therefore be given either with or without food.

Distribution:

The steady-state volume of distribution of valsartan after intravenous administration is about 17 litres, indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (94–97%), mainly serum albumin.

Biotransformation:

Valsartan is not biotransformed to a high extent as only about 20% of dose is recovered as metabolites. A hydroxy metabolite has been identified in plasma at low concentrations (less than 10% of the valsartan AUC). This metabolite is pharmacologically inactive.

Excretion:

Valsartan shows multiexponential decay kinetics (t_{1/2α} <1 h and t_{1/2β} about 9 h). Valsartan is primarily eliminated by biliary excretion in faeces (about 83% of dose) and renally in urine (about 13% of dose), mainly as unchanged drug. Following intravenous administration, plasma clearance of valsartan is about 2 l/h and its renal clearance is 0.62 l/h (about 30% of total clearance). The half-life of valsartan is 6 hours.

Special populations

Elderly

A somewhat higher systemic exposure to valsartan was observed in some elderly subjects than in young subjects; however, this has not been shown to have any clinical significance.

Impaired renal function

As expected for a compound where renal clearance accounts for only 30% of total plasma clearance, no correlation was seen between renal function and systemic exposure to valsartan. Dose adjustment is therefore not required in patients with renal impairment (creatinine clearance >10 ml/min). There is currently no experience on the safe use in patients with a creatinine clearance <10 ml/min and patients undergoing dialysis, therefore valsartan should be used with caution in these patients (see sections 4.2 and 4.4). Valsartan is highly bound to plasma protein and is unlikely to be

removed by dialysis.

Hepatic impairment

Approximately 70% of the dose absorbed is eliminated in the bile, essentially in the unchanged form. Valsartan does not undergo any noteworthy biotransformation. A doubling of exposure (AUC) was observed in patients with mild to moderate hepatic impairment compared to healthy subjects. However, no correlation was observed between plasma valsartan concentration versus degree of hepatic dysfunction. Cuenca has not been studied in patients with severe hepatic dysfunction (see sections 4.2, 4.3 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

In rats, maternally toxic doses (600 mg/kg/day) during the last days of gestation and lactation led to lower survival, lower weight gain and delayed development (pinna detachment and ear-canal opening) in the offspring (see section 4.6). These doses in rats (600 mg/kg/day) are approximately 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In non-clinical safety studies, high doses of valsartan (200 to 600 mg/kg body weight) caused in rats a reduction of red blood cell parameters (erythrocytes, haemoglobin, haematocrit) and evidence of changes in renal haemodynamics (slightly raised plasma urea, and renal tubular hyperplasia and basophilia in males). These doses in rats (200 and 600 mg/kg/day) are approximately 6 and 18 times the maximum recommended human dose on a mg/m² basis (calculations assume an oral dose of 320 mg/day and a 60-kg patient).

In marmosets at similar doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy which included raised urea and creatinine.

Hypertrophy of the renal juxtaglomerular cells was also seen in both species. All changes were considered to be caused by the pharmacological action of valsartan which produces prolonged hypotension, particularly in marmosets. For therapeutic doses of valsartan in humans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline (E 460)
Silica, colloidal anhydrous (E 551)
Sorbitol (E-420)
Magnesium carbonate (E 504)
Maize starch, pregelatinised
Povidone K-25 (E 1201)
Sodium stearyl fumarate
Sodium lauryl sulphate
Crospovidone Type A (E 1202)

Film coating

Lactose monohydrate
Hypromellose (E 464)
Titanium dioxide (E 171)
Macrogol
Yellow iron oxide (E 172)
Brown iron oxide (E 712)
Indigo carmine aluminium lake (E 132)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

1 year

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium blister.

Pack sizes: 7, 14, 28, 56, 98, 280 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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