

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amlodipine/Valsartan/Hydrochlorothiazide Krka 10 mg/160 mg/25 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg amlodipine (as amlodipine besilate), 160 mg valsartan and 25 mg hydrochlorothiazide. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Brown yellow, oval, biconvex, film-coated tablets, engraved with mark K4 on one side of the tablet, dimensions approximately 13 x 8 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of essential hypertension as substitution therapy in adult patients whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlorothiazide (HCT), taken either as three single-component formulations or as a dual-component and a single-component formulation.

4.2 Posology and method of administration

Posology

The recommended dose of Amlodipine/Valsartan/Hydrochlorothiazide Krka is one tablet per day, to be taken preferably in the morning.

Before switching to Amlodipine/Valsartan/Hydrochlorothiazide Krka patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of Amlodipine/Valsartan/Hydrochlorothiazide Krka should be based on the doses of the individual components of the combination at the time of switching.

The maximum recommended dose of Amlodipine/Valsartan/Hydrochlorothiazide Krka is 10 mg/320 mg/25 mg.

Special populations

Renal impairment

Due to the hydrochlorothiazide component, Amlodipine/Valsartan/Hydrochlorothiazide Krka is contraindicated for use in patients with anuria (see section 4.3) and in patients with severe renal impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²) (see sections 4.3, 4.4 and 5.2).

No adjustment of the initial dose is required for patients with mild to moderate renal impairment (see sections 4.4 and 5.2).

Hepatic impairment

Due to the valsartan component, Amlodipine/Valsartan/Hydrochlorothiazide Krka is contraindicated in patients with severe hepatic impairment (see section 4.3). In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan and therefore Amlodipine/Valsartan/Hydrochlorothiazide Krka is not suitable in this group of patients (see sections 4.3, 4.4 and 5.2). Amlodipine dose recommendations have not been established in patients with mild to moderate hepatic impairment. When switching eligible hypertensive patients (see section 4.1) with hepatic impairment to Amlodipine/Valsartan/Hydrochlorothiazide Krka, the lowest available dose of the amlodipine component should be used.

Heart failure and coronary artery disease

There is limited experience with the use of Amlodipine/Valsartan/Hydrochlorothiazide Krka, particularly at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of Amlodipine/Valsartan/Hydrochlorothiazide Krka, 10 mg/320 mg/25 mg.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of Amlodipine/Valsartan/Hydrochlorothiazide Krka, 10 mg/320 mg/25 mg, since available data in this patient population are limited. When switching eligible elderly hypertensive patients (see section 4.1) to Amlodipine/Valsartan/Hydrochlorothiazide Krka, the lowest available dose of the amlodipine component should be used.

Paediatric population

There is no relevant use of Amlodipine/Valsartan/Hydrochlorothiazide Krka in the paediatric population (patients below age 18 years) for the indication of essential hypertension.

Method of administration

Oral use.

Amlodipine/Valsartan/Hydrochlorothiazide Krka can be taken with or without food.

The tablets should be swallowed whole with some water, at the same time of the day and preferably in the morning.

4.3 Contraindications

- Hypersensitivity to the active substances, to other sulphonamide derivatives, to dihydropyridine derivatives, or to any of the excipients listed in section 6.1.
- Second and third trimesters of pregnancy (see sections 4.4 and 4.6).
- Hepatic impairment, biliary cirrhosis or cholestasis.
- Severe renal impairment (GFR <30 ml/min/1.73 m²), anuria and patients undergoing dialysis.
- Concomitant use of amlodipine/valsartan/HCT with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR <60 ml/min/1.73 m²) (see sections 4.5 and 5.1).
- Refractory hypokalaemia, hyponatraemia, hypercalcaemia, and symptomatic hyperuricaemia.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy and high grade aortic stenosis).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

The safety and efficacy of amlodipine in hypertensive crisis have not been established.

Sodium- and/or volume-depleted patients

Excessive hypotension, including orthostatic hypotension, was seen in 1.7% of patients treated with the maximum dose of amlodipine/valsartan/HCT (10 mg/320 mg/25 mg) compared to 1.8% of valsartan/hydrochlorothiazide (320 mg/25 mg) patients, 0.4% of amlodipine/valsartan (10 mg/320 mg) patients, and 0.2% of hydrochlorothiazide/amlodipine (25 mg/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.

In sodium-depleted and/or volume-depleted patients, such as those receiving high doses of diuretics, symptomatic hypotension may occur after initiation of treatment with amlodipine/valsartan/HCT. Amlodipine/valsartan/HCT should be used only after correction of any pre-existing sodium and/or volume depletion.

If excessive hypotension occurs with amlodipine/valsartan/HCT, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. Treatment can be continued once blood pressure has been stabilised.

Serum electrolyte changes

Amlodipine/valsartan/HCT

In the controlled trial of amlodipine/valsartan/HCT, the counteracting effects of valsartan 320 mg and hydrochlorothiazide 25 mg on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Periodic determination of serum electrolytes and potassium in particular should be performed at appropriate intervals to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medicinal products or history of prior electrolyte imbalances.

Valsartan

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

Hydrochlorothiazide

Treatment with amlodipine/valsartan/HCT should only start after correction of hypokalaemia and any coexisting hypomagnesaemia. Thiazide diuretics can precipitate new onset hypokalaemia or exacerbate pre-existing hypokalaemia. Thiazide diuretics should be administered with caution in patients with conditions involving enhanced potassium loss, for example salt-losing nephropathies and prerenal (cardiogenic) impairment of kidney function. If hypokalaemia develops during hydrochlorothiazide therapy, amlodipine/valsartan/HCT should be discontinued until stable correction of the potassium balance.

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroemic alkalosis or exacerbate pre-existing hyponatraemia. Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed. Treatment with hydrochlorothiazide should only be started after correction of pre-existing hyponatraemia. In case severe or rapid hyponatraemia develops during amlodipine/valsartan/HCT therapy, the treatment should be discontinued until normalisation of natraemia.

All patients receiving thiazide diuretics should be periodically monitored for imbalances in electrolytes, particularly potassium, sodium and magnesium.

Renal impairment

Thiazide diuretics may precipitate azotaemia in patients with chronic kidney disease. When amlodipine/valsartan/HCT is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. Amlodipine/valsartan/HCT is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3).

No dose adjustment of amlodipine/valsartan/HCT is required for patients with mild to moderate renal impairment (GFR \geq 30 ml/min/1.73 m²).

Renal artery stenosis

Amlodipine/valsartan/HCT should be used with caution to treat hypertension in patients with unilateral or bilateral renal artery stenosis or stenosis to a solitary kidney since blood urea and serum creatinine may increase in such patients.

Kidney transplantation

To date there is no experience of the safe use of amlodipine/valsartan/HCT in patients who have had a recent kidney transplantation.

Hepatic impairment

Valsartan is mostly eliminated unchanged via the bile. The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dose recommendations have not been established. In patients with mild to moderate hepatic impairment without cholestasis, the maximum recommended dose is 80 mg valsartan, and therefore, amlodipine/valsartan/HCT is not suitable in this group of patients (see sections 4.2, 4.3 and 5.2).

Angioedema

Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue, has been reported in patients treated with valsartan. Some of these patients previously experienced

angioedema with other medicinal products including ACE inhibitors. Amlodipine/valsartan/HCT should be discontinued immediately in patients who develop angioedema and should not be re-administered.

Heart failure and coronary artery disease/post-myocardial infarction

As a consequence of the inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotaemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with valsartan. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

In a long-term, placebo-controlled study (PRAISE-2) of amlodipine in patients with NYHA (New York Heart Association Classification) III and IV heart failure of non-ischaemic aetiology, amlodipine was associated with increased reports of pulmonary oedema despite no significant difference in the incidence of worsening heart failure as compared to placebo.

Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Caution is advised in patients with heart failure and coronary artery disease, particularly at the maximum dose of amlodipine/valsartan/HCT, 10 mg/320 mg/25 mg, since available data in these patient populations is limited.

Aortic and mitral valve stenosis

As with all other vasodilators, special caution is indicated in patients with mitral stenosis or significant aortic stenosis that is not high grade.

Pregnancy

Angiotensin II Receptor Antagonists (AIIRAs) should not be initiated during pregnancy. 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 (see sections 4.3 and 4.6).

Primary hyperaldosteronism

Patients with primary hyperaldosteronism should not be treated with the angiotensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, amlodipine/valsartan/HCT is not recommended in this population.

Systemic lupus erythematosus

Thiazide diuretics, including hydrochlorothiazide, have been reported to exacerbate or activate systemic lupus erythematosus.

Other metabolic disturbances

Thiazide diuretics, including hydrochlorothiazide, may alter glucose tolerance and raise serum levels of cholesterol, triglycerides and uric acid. In diabetic patients dosage adjustments of insulin or oral hypoglycaemic agents may be required.

Due to the hydrochlorothiazide component, amlodipine/valsartan/HCT is contraindicated in symptomatic hyperuricaemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Amlodipine/valsartan/HCT is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. Amlodipine/valsartan/HCT should be discontinued if hypercalcaemia develops during treatment. Serum levels of calcium should be periodically monitored during treatment with thiazides. Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with amlodipine/valsartan/HCT, it is recommended to stop the treatment. If a readministration of the diuretic is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Choroidal effusion, acute myopia and secondary angle-closure glaucoma

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

General

Caution should be exercised in patients who have shown prior hypersensitivity to other angiotensin II receptor antagonists. Hypersensitivity reactions to hydrochlorothiazide are more likely in patients with allergy and asthma.

Elderly (age 65 years or over)

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of amlodipine/valsartan/HCT, 10 mg/320 mg/25 mg, since available data in this patient population are limited.

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

There is evidence that the concomitant use of ACE inhibitors, ARBs or aliskiren increases the risk of hypotension, hyperkalaemia and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is therefore not recommended (see sections 4.5 and 5.1).

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 ARBs should not be used concomitantly in patients with diabetic nephropathy.

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 (HCTZ) exposure has been observed in two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of HCTZ could act as a possible mechanism for NMSC.

Patients taking HCTZ 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 HCTZ may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Acute Respiratory Toxicity

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

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

No formal interaction studies with other medicinal products have been performed with amlodipine/valsartan/HCT. Thus, only information on interactions with other medicinal products that are known for the individual active substances is provided in this section.

However, it is important to take into account that amlodipine/valsartan/HCT may increase the hypotensive effect of other antihypertensive agents.

Concomitant use not recommended

Amlodipine/valsartan/HCT individual component	Known interactions	Effect of the interaction with other medicinal products
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	with the following agents	
Valsartan and HCT	Lithium	Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, angiotensin II receptor antagonists including valsartan or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with amlodipine/valsartan/HCT. Therefore careful monitoring of serum lithium concentrations is recommended during concomitant use.
Valsartan	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, frequent monitoring of potassium plasma levels is advised.
Amlodipine	Grapefruit or grapefruit juice	Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients, resulting in increased blood pressure lowering effects.

Caution required with concomitant use

Amlodipine/valsartan/HCT individual component	Known interactions with the following agents	Effect of the interaction with other medicinal products
Amlodipine	CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir)	Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors,azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.
	CYP3A4 inducers (anticonvulsant agents [e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum [St. John's wort])	Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).
	Simvastatin	Co-administration of multiple doses of 10 mg amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. It is recommended to limit the dose of simvastatin to 20 mg daily in patients on amlodipine.

	Dantrolene (infusion)	In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalaemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalaemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.
Valsartan and HCT	Non-steroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase-2 inhibitors (COX-2 inhibitors), acetylsalicylic acid (>3 g/day), and non-selective NSAIDs	NSAIDs can attenuate the antihypertensive effect of both angiotensin II antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of amlodipine/valsartan/HCT and NSAIDs may lead to 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.
Valsartan	Inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir)	The results of an in vitro study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and of the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampicin, ciclosporin) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.
HCT	Alcohol, barbiturates or narcotics	Concomitant administration of thiazide diuretics with substances that also have a blood pressure lowering effect (e.g. by reducing sympathetic central nervous system activity or direct vasodilatation) may potentiate orthostatic hypotension.
	Amantadine	Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by amantadine.
	Anticholinergic agents and other medicinal products affecting gastric motility	The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (e.g. atropine, biperiden), apparently due to a decrease in gastrointestinal motility and the stomach emptying rate. Conversely, it is anticipated that prokinetic substances such as cisapride may decrease the bioavailability of thiazide-type diuretics.
	Antidiabetic agents (e.g. insulin and oral antidiabetic agents)	Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary.
	Metformin	Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
	Beta blockers and diazoxide	Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hyperglycaemia. Thiazide diuretics, including hydrochlorothiazide, may enhance the hyperglycaemic effect of diazoxide.
	Ciclosporin	Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.
	Cytotoxic agents	Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic agents (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects
	Digitalis glycosides	Thiazide-induced hypokalaemia or hypomagnesaemia may occur as undesirable effects, favouring the onset of digitalis-induced cardiac

		arrhythmias.
	Iodine contrasting agents	In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of iodine products. Patients should be re-hydrated before the administration.
	Ion exchange resins	Absorption of thiazide diuretics, including hydrochlorothiazide, is decreased by cholestyramine or colestipol. This could result in sub-therapeutic effects of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide and resin such that hydrochlorothiazide is administered at least 4 hours before or 4-6 hours after the administration of resins would potentially minimise the interaction.
	Medicinal products affecting serum potassium level	The hypokalaemic effect of hydrochlorothiazide may be increased by concomitant administration of kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotrophic hormone (ACTH), amphotericin, carbenoxolone, penicillin G and salicylic acid derivatives or antiarrhythmics. If these medicinal products are to be prescribed with the amlodipine /valsartan /hydrochlorothiazide combination, monitoring of potassium plasma levels is advised.
	Medicinal products affecting serum sodium level	The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicinal products such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicinal products.
	Medicinal products that could induce torsades de pointes	Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce torsades de pointes, in particular Class Ia and Class III antiarrhythmics and some antipsychotics.
	Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)	Dose adjustment of uricosuric medicinal products may be necessary as hydrochlorothiazide may raise the level of serum uric acid. Increase of dose of probenecid or sulfinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.
	Methyldopa	There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.
	Non-depolarising skeletal muscle relaxants (e.g. tubocurarine)	Thiazides, including hydrochlorothiazide, potentiate the action of curare derivatives.
	Other anti-hypertensive medicinal products	Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, calcium channel blockers, ACE inhibitors, ARBs and Direct Renin Inhibitors [DRIs]).
	Pressor amines (e.g. noradrenaline, adrenaline)	Hydrochlorothiazide may reduce the response to pressor amines such as noradrenaline. The clinical significance of this effect is uncertain and not sufficient to preclude their use
	Vitamin D and calcium salts	Administration of thiazide diuretics, including hydrochlorothiazide, with vitamin D or with calcium salts may potentiate the rise in serum calcium. Concomitant use of thiazide type diuretics may lead to hypercalcaemia in patients pre-disposed for hypercalcaemia (e.g. hyperparathyroidism, malignancy or vitamin-D-mediated conditions) by increasing tubular calcium reabsorption.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren

Clinical trial data have shown that dual blockade of the RAAS through the combined use of ACE inhibitors, ARBs or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent (see sections 4.3, 4.4 and 5.1).

4.6 Fertility, pregnancy and lactation

Pregnancy

Amlodipine

The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses (see section 5.3). Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.

Valsartan

The use of Angiotensin II Receptor Antagonists (AIIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIIRAs is contraindicated during the second and third trimesters 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 Angiotensin II Receptor Antagonists (AIIIRAs), similar risks may exist for this class of drugs. Unless continued AIIIRA 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 AIIIRAs should be stopped immediately, and if appropriate, alternative therapy should be started.

Exposure to AIIIRAs therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia) (see section 5.3).

Should exposure to AIIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mothers have taken AIIIRAs should be closely observed for hypotension (see sections 4.3 and 4.4).

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

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

Amlodipine/valsartan/hydrochlorothiazide

There is no experience on the use of amlodipine/valsartan/HCT in pregnant women. Based on the existing data with the components, the use of amlodipine/valsartan/HCT is not recommended during first trimester and contra-indicated during the second and third trimester of pregnancy (see sections 4.3 and 4.4).

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. No information is available regarding the use of valsartan during breast-feeding. Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit milk production. The use of amlodipine/valsartan/HCT during breast-feeding is not recommended. If amlodipine/valsartan/HCT is used during breast-feeding, doses should be kept as low as possible. Alternative treatments with better established safety profiles during breast-feeding are preferable, especially while nursing a newborn or preterm infant.

Fertility

There are no clinical studies on fertility with amlodipine/valsartan/HCT.

Valsartan

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 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).

Amlodipine

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one rat study, adverse effects were found on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients taking amlodipine/valsartan/HCT and driving vehicles or using machines should take into account that dizziness or weariness may occasionally occur.

Amlodipine can have mild or moderate influence on the ability to drive and use machines. If patients taking amlodipine/valsartan/HCT suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

- 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)

The safety profile of amlodipine/valsartan/HCT presented below is based on clinical studies performed with amlodipine/valsartan/HCT and the known safety profile of the individual components amlodipine, valsartan and hydrochlorothiazide.

Summary of the safety profile

The safety of amlodipine/valsartan/HCT has been evaluated at its maximum dose of 10 mg/320 mg/25 mg in one controlled short-term (8 weeks) clinical study with 2,271 patients, 582 of whom received valsartan in combination with amlodipine and hydrochlorothiazide. Adverse reactions were generally mild and transient in nature and only infrequently required discontinuation of therapy. In this active controlled clinical trial, the most common reasons for discontinuation of therapy with amlodipine/valsartan/HCT were dizziness and hypotension (0.7%).

In the 8-week controlled clinical study, no significant new or unexpected adverse reactions were observed with triple therapy treatment compared to the known effects of the monotherapy or dual therapy components.

In the 8-week controlled clinical study, changes in laboratory parameters observed with the combination of amlodipine/valsartan/HCT were minor and consistent with the pharmacological mechanism of action of the monotherapy agents. The presence of valsartan in the triple combination attenuated the hypokalaemic effect of hydrochlorothiazide.

Tabulated list of adverse reactions

The following adverse reactions, listed by MedDRA System Organ Class and frequency, concern amlodipine/valsartan/HCT and amlodipine, valsartan and HCT individually.

MedDRA System Organ Class	Adverse reactions	Frequency			
		Amlodipine/valsartan/HCT	Amlodipine	Valsartan	HCT
Neoplasms benign, malignant and unspecified (incl	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	–	–	–	Not known

cysts and polyps)					
Blood and lymphatic system disorders	Agranulocytosis, bone marrow failure	–	–	–	Very rare
	Haemoglobin and haematocrit decreased	–	–	Not known	–
	Haemolytic anaemia	–	–	–	Very rare
	Leukopenia	–	Very rare	–	Very rare
	Neutropenia	–	–	Not known	–
	Thrombocytopenia, sometimes with purpura	–	Very rare	Not known	Rare
	Aplastic anaemia	–	–	–	Not known
Immune system disorders	Hypersensitivity	–	Very rare	Not known	Very rare
Metabolism and nutrition disorders	Anorexia	Uncommon	–	–	–
	Hypercalcaemia	Uncommon	–	–	Rare
	Hyperglycaemia	–	Very rare	–	Rare
	Hyperlipidaemia	Uncommon	–	–	–
	Hyperuricaemia	Uncommon	–	–	Common
	Hypochloraemic alkalosis	–	–	–	Very rare
	Hypokalaemia	Common	–	–	Very common
	Hypomagnesaemia				Common
	Hyponatraemia	Uncommon			Common
	Worsening of diabetic metabolic state	–	–	–	Rare
Psychiatric disorders	Depression	–	Uncommon	–	Rare
	Insomnia/sleep disorders	Uncommon	Uncommon	–	Rare
	Mood swings	–	Uncommon	–	
	Confusion	–	Rare	–	–
Nervous system disorders	Coordination abnormal	Uncommon	–	–	–
	Dizziness	Common	Common	–	Rare
	Dizziness postural, dizziness exertional	Uncommon	–	–	–
	Dysgeusia	Uncommon	Uncommon	–	–
	Extrapyramidal syndrome	–	Not known	–	–
	Headache	Common	Common	–	Rare
	Hypertonia	–	Very rare	–	–
	Lethargy	Uncommon	–	–	–
	Paraesthesia	Uncommon	Uncommon	–	Rare
	Peripheral neuropathy, neuropathy	Uncommon	Very rare	–	–
	Somnolence	Uncommon	Common	–	–
	Syncope	Uncommon	Uncommon	–	–
	Tremor	–	Uncommon	–	–
	Hypoesthesia	–	Uncommon	–	–
Eye disorders	Acute angle-closure glaucoma	–	–	–	Not known
	Visual disturbance	–	Uncommon	–	–
	Visual impairment	Uncommon	Uncommon	–	Rare
	Choroidal effusion	–	–	–	Not known
Ear and labyrinth	Tinnitus	–	Uncommon	–	–

disorders					
	Vertigo	Uncommon	–	Uncommon	–
Cardiac disorders	Palpitations	–	Common	–	–
	Tachycardia	Uncommon	–	–	–
	Arrhythmias (including bradycardia, ventricular tachycardia, and atrial fibrillation)	–	Very rare	–	Rare
	Myocardial infarction	–	Very rare	–	–
Vascular disorders	Flushing	–	Common	–	–
	Hypotension	Common	Uncommon	–	–
	Orthostatic hypotension	Uncommon	–	–	Common
	Phlebitis, thrombophlebitis	Uncommon	–	–	–
	Vasculitis	–	Very rare	Not known	–
Respiratory, thoracic and mediastinal disorders	Cough	Uncommon	Very rare	Uncommon	–
	Dyspnoea	Uncommon	Uncommon	–	–
	Respiratory distress, pulmonary oedema, pneumonitis	–	–	–	Very rare
	Rhinitis	–	Uncommon		
	Throat irritation	Uncommon	–	–	–
	Acute respiratory distress syndrome (ARDS) (see section 4.4)	–	–	–	Very rare
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncommon	Common	Uncommon	Rare
	Breath odour	Uncommon	–	–	–
	Change of bowel habit	–	Uncommon	–	–
	Constipation	–	–	–	Rare
	Decreased appetite	–	–	–	Common
	Diarrhoea	Uncommon	Uncommon	–	Rare
	Dry mouth	Uncommon	Uncommon	–	–
	Dyspepsia	Common	Uncommon	–	–
	Gastritis	–	Very rare	–	–
	Gingival hyperplasia	–	Very rare	–	–
	Nausea	Uncommon	Common	–	Common
	Pancreatitis	–	Very rare	–	Very rare
	Vomiting	Uncommon	Uncommon	–	Common
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	–	Very rare**	Not known	–
	Hepatitis	–	Very rare	–	–
	Intrahepatic cholestasis, jaundice	–	Very rare	–	Rare
Skin and subcutaneous tissue disorders	Alopecia	–	Uncommon	–	
	Angioedema	–	Very rare	Not known	–
	Dermatitis bullous	–	–	Not known	–
	Cutaneous lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus	–	–	–	Very rare
	Erythema multiforme	–	Very rare	–	Not known

Health Products Regulatory Authority

	Exanthema	–	Uncommon	–	–
	Hyperhidrosis	Uncommon	Uncommon	–	–
	Photosensitivity reaction*		Very rare	–	Rare
	Pruritus	Uncommon	Uncommon	Not known	–
	Purpura	–	Uncommon	–	Rare
	Rash	–	Uncommon	Not known	Common
	Skin discoloration	–	Uncommon	–	–
	Urticaria and other forms of rash	–	Very rare	–	Common
	Vasculitis necrotising and toxic epidermal necrolysis	–	Not known	–	Very rare
	Exfoliative dermatitis	–	Very rare	–	–
	Stevens-Johnson syndrome	–	Very rare	–	–
	Quincke oedema	–	Very rare	–	–
Musculoskeletal and connective tissue disorders	Arthralgia	–	Uncommon	–	–
	Back pain	Uncommon	Uncommon	–	–
	Joint swelling	Uncommon	–	–	–
	Muscle spasm	Uncommon	Uncommon	–	Not known
	Muscular weakness	Uncommon	–	–	–
	Myalgia	Uncommon	Uncommon	Not known	–
	Pain in extremity	Uncommon	–	–	–
	Ankle swelling	–	Common	–	–
Renal and urinary disorders	Blood creatinine increased	Uncommon	–	Not known	–
	Micturition disorder		Uncommon		
	Nocturia	–	Uncommon	–	–
	Pollakiuria	Common	Uncommon		
	Renal dysfunction	–	–	–	Not known
	Acute renal failure	Uncommon	–	–	Not known
	Renal failure and impairment	–	–	Not known	Rare
Reproductive system and breast disorders	Impotence	Uncommon	Uncommon	–	Common
	Gynaecomastia		Uncommon	–	–
General disorders and administration site conditions	Abasia, gait disturbance	Uncommon	–	–	–
	Asthenia	Uncommon	Uncommon	–	Not known
	Discomfort, malaise	Uncommon	Uncommon	–	–
	Fatigue	Common	Common	Uncommon	–
	Non cardiac chest pain	Uncommon	Uncommon	–	–
	Oedema	Common	Common	–	–
	Pain	–	Uncommon	–	–
	Pyrexia	–	–	–	Not known
Investigations	Lipids increased		–		Very common
	Blood urea nitrogen increased	Uncommon	–	–	
	Blood uric acid increased	Uncommon	–	–	
	Glycosuria				Rare
	Blood potassium decreased	Uncommon	–	–	–
	Blood potassium increased	–	–	Not known	–
	Weight increase	Uncommon	Uncommon	–	–
	Weight decrease	–	Uncommon	–	–

* See section 4.4 Photosensitivity

** Mostly consistent with cholestasis

Description of selected adverse reactions

Non-melanoma skin cancer: Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed (see also sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance,

Website: www.hpra.ie.

4.9 Overdose

Symptoms

There is no experience of overdose with amlodipine/valsartan/HCT. The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness. Overdose with amlodipine may result in excessive peripheral vasodilation and, possibly, reflex tachycardia. Marked and potentially prolonged systemic hypotension, including shock with fatal outcome, have been reported with amlodipine.

Treatment

Amlodipine/Valsartan/Hydrochlorothiazide

Clinically significant hypotension due to amlodipine/valsartan/HCT overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine

If ingestion is recent, induction of vomiting or gastric lavage may be considered. Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine has been shown to significantly decrease amlodipine absorption.

Amlodipine is unlikely to be removed by haemodialysis.

Valsartan

Valsartan is unlikely to be removed by haemodialysis.

Hydrochlorothiazide

Overdose with hydrochlorothiazide is associated with electrolyte depletion (hypokalaemia, hypochloraemia) and hypovolaemia resulting from excessive diuresis. The most common signs and symptoms of overdose are nausea and somnolence. Hypokalaemia may result in muscle spasms and or accentuate arrhythmia associated with the concomitant use of digitalis glycosides or certain anti-arrhythmic medicinal products.

The degree to which hydrochlorothiazide is removed by haemodialysis has not been established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system; angiotensin II antagonists, other combinations, ATC code: C09DX01.

Mechanism of action

Amlodipine/Valsartan/Hydrochlorothiazide Krka combines three antihypertensive compounds with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class and valsartan to the angiotensin II antagonist class of medicines and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.

Amlodipine/Valsartan/Hydrochlorothiazide

Clinical efficacy and safety

Amlodipine/valsartan/hydrochlorothiazide studied in a double-blind, active controlled study in hypertensive patients. A total of 2,271 patients with moderate to severe hypertension (mean baseline systolic/diastolic blood pressure was 170/107 mmHg) received treatments of amlodipine/valsartan/hydrochlorothiazide 10 mg/320 mg/25 mg, valsartan/hydrochlorothiazide 320 mg/25 mg, amlodipine/valsartan 10 mg/320 mg, or hydrochlorothiazide/amlodipine 25 mg/10 mg. At study initiation patients were assigned lower doses of their treatment combination and were titrated to their full treatment dose by week 2.

At week 8, the mean reductions in systolic/diastolic blood pressure were 39.7/24.7 mmHg with amlodipine/valsartan/hydrochlorothiazide, 32.0/19.7 mmHg with valsartan/hydrochlorothiazide, 33.5/21.5 mmHg with amlodipine/valsartan, and 31.5/19.5 mmHg with amlodipine/hydrochlorothiazide. The triple combination therapy was statistically superior to each of the three dual combination treatments in reduction of diastolic and systolic blood pressures. The reductions in systolic/diastolic blood pressure with amlodipine/valsartan/hydrochlorothiazide were 7.6/5.0 mmHg greater than with valsartan/hydrochlorothiazide, 6.2/3.3 mmHg greater than with amlodipine/valsartan, and 8.2/5.3 mmHg greater than with amlodipine/hydrochlorothiazide. The full blood pressure lowering effect was achieved 2 weeks after being on their maximal dose of amlodipine/valsartan/hydrochlorothiazide. Statistically greater proportions of patients achieved blood pressure control (<140/90 mmHg) with amlodipine/valsartan/hydrochlorothiazide (71%) compared to each of the three dual combination therapies (45-54%) ($p < 0.0001$).

In a subgroup of 283 patients focusing on ambulatory blood pressure monitoring, clinically and statistically superior reductions in 24-hour systolic and diastolic blood pressures were observed with the triple combination compared to valsartan/hydrochlorothiazide, valsartan/amlodipine, and hydrochlorothiazide/amlodipine.

Amlodipine

Mechanism of action

The amlodipine component of amlodipine/valsartan/hydrochlorothiazide inhibits the transmembrane entry of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle, causing reductions in peripheral vascular resistance and in blood pressure.

Pharmacodynamic effects

Experimental data suggest that amlodipine binds to both dihydropyridine and non-dihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels.

Following administration of therapeutic doses to patients with hypertension, amlodipine produces vasodilation, resulting in a reduction of supine and standing blood pressures. These decreases in blood pressure are not accompanied by a significant change in heart rate or plasma catecholamine levels with chronic dosing.

Plasma concentrations correlate with effect in both young and elderly patients.

In hypertensive patients with normal renal function, therapeutic doses of amlodipine resulted in a decrease in renal vascular resistance and increases in glomerular filtration rate and effective renal plasma flow, without change in filtration fraction or proteinuria.

As with other calcium channel blockers, haemodynamic measurements of cardiac function at rest and during exercise (or pacing) in patients with normal ventricular function treated with amlodipine have generally demonstrated a small increase in cardiac index without significant influence on dP/dt or on left ventricular end diastolic pressure or volume. In haemodynamic

studies, amlodipine has not been associated with a negative inotropic effect when administered in the therapeutic dose range to intact animals and humans, even when co-administered with beta blockers to humans.

Amlodipine does not change sinoatrial nodal function or atrioventricular conduction in intact animals or humans. In clinical studies in which amlodipine was administered in combination with beta blockers to patients with either hypertension or angina, no adverse effects on electrocardiographic parameters were observed.

Amlodipine has been studied in patients with chronic stable angina, vasospastic angina and angiographically documented coronary artery disease.

Clinical efficacy and safety

Use in patients with hypertension

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) was performed to compare newer therapies: amlodipine 2.5-10 mg/day (calcium channel blocker) or lisinopril 10-40 mg/day (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic, chlorthalidone 12.5-25 mg/day in mild to moderate hypertension.

A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional coronary heart disease risk factor, including: previous myocardial infarction or stroke (>6 months prior to enrollment) or documentation of other atherosclerotic cardiovascular disease (overall 51.5%), type 2 diabetes (36.1%), high density lipoprotein - cholesterol <35 mg/dl or <0.906 mmol/l (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).

The primary endpoint was a composite of fatal coronary heart disease or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: risk ratio (RR) 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% versus 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy RR 0.96 95% CI [0.89-1.02] p=0.20.

Valsartan

Mechanism of action

Valsartan is an orally active, potent and specific angiotensin II receptor antagonist. It acts selectively on the receptor subtype AT1, which is responsible for the known actions of angiotensin II.

Clinical efficacy and safety

Administration of valsartan to patients with hypertension results in a drop in 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 drop in blood pressure is achieved within 4-6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2-4 weeks.

Hydrochlorothiazide

Mechanism of action

The site of action of thiazide diuretics is primarily in the renal distal convoluted tubule. It has been shown that there is a high-affinity receptor in the renal cortex as the primary binding site for the thiazide diuretic action and inhibition of NaCl transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the Na⁺Cl⁻ symporter perhaps by competing for the Cl⁻ site, thereby affecting electrolyte reabsorption mechanisms: directly increasing sodium and chloride excretion to an approximately equal extent, and indirectly, by this diuretic action, reducing plasma volume, with consequent increases in plasma renin activity, aldosterone secretion and urinary potassium loss, and a decrease in serum potassium.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with amlodipine/valsartan/hydrochlorothiazide in all subsets of the paediatric population in essential hypertension (see section 4.2 for information on paediatric use).

Other: dual blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial] and VA NEPHRON-D [The Veterans Affairs Nephropathy in Diabetes]) have examined the use of the combination of an ACE inhibitor with an ARB.

ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.

These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE inhibitors and ARBs.

ACE inhibitors and ARBs should therefore not be used concomitantly in patients with diabetic nephropathy (see section 4.4).

ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE inhibitor or an ARB in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Non-melanoma skin cancer

Based on available data from epidemiological studies, cumulative dose-dependent association between HCTZ and NMSC has been observed. One study included a population comprised of 71,533 cases of BCC and of 8,629 cases of SCC matched to 1,430,833 and 172,462 population controls, respectively. High HCTZ use ($\geq 50,000$ mg cumulative) was associated with an adjusted OR of 1.29 (95% CI: 1.23-1.35) for BCC and 3.98 (95% CI: 3.68-4.31) for SCC. A clear cumulative dose response relationship was observed for both BCC and SCC. Another study showed a possible association between lip cancer (SCC) and exposure to HCTZ: 633 cases of lip-cancer were matched with 63,067 population controls, using a risk-set sampling strategy. A cumulative dose-response relationship was demonstrated with an adjusted OR 2.1 (95% CI: 1.7-2.6) increasing to OR 3.9 (3.0-4.9) for high use ($\sim 25,000$ mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose ($\sim 100,000$ mg) (see also section 4.4).

5.2 Pharmacokinetic properties

Linearity

Amlodipine, valsartan and hydrochlorothiazide exhibit linear pharmacokinetics.

Amlodipine/valsartan/hydrochlorothiazide

Following oral administration of amlodipine/valsartan/hydrochlorothiazide in normal healthy adults, peak plasma concentrations of amlodipine, valsartan and hydrochlorothiazide are reached in 6-8 hours, 3 hours, and 2 hours, respectively. The rate and extent of absorption of amlodipine, valsartan and hydrochlorothiazide from amlodipine/valsartan/hydrochlorothiazide are the same as when administered as individual dosage forms.

Amlodipine

Absorption

After oral administration of therapeutic doses of amlodipine alone, peak plasma concentrations of amlodipine are reached in 6-12 hours. Absolute bioavailability has been calculated as between 64% and 80%. Amlodipine bioavailability is unaffected by food ingestion.

Distribution

Volume of distribution is approximately 21 l/kg. In vitro studies with amlodipine have shown that approximately 97.5% of circulating drug is bound to plasma proteins.

Biotransformation

Amlodipine is extensively (approximately 90%) metabolised in the liver to inactive metabolites.

Elimination

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

Valsartan

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 transformed 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.

Elimination

Valsartan shows multiexponential decay kinetics ($t_{1/2\alpha} < 1$ h and $t_{1/2\beta}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83% of dose) and 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.

Hydrochlorothiazide

Absorption

The absorption of hydrochlorothiazide, after an oral dose, is rapid (T_{max} about 2 hours). The increase in mean AUC is linear and dose proportional in the therapeutic range.

The effect of food on hydrochlorothiazide absorption, if any, has little clinical significance. Absolute bioavailability of hydrochlorothiazide is 70% after oral administration.

Distribution

The apparent volume of distribution is 4-8 l/kg. Circulating hydrochlorothiazide is bound to serum proteins (40-70%), mainly serum albumin. Hydrochlorothiazide also accumulates in erythrocytes at approximately 3 times the level in plasma.

Biotransformation

Hydrochlorothiazide is eliminated predominantly as unchanged compound.

Elimination

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 to 15 hours in the terminal elimination phase. There is no change in the kinetics of hydrochlorothiazide on repeated dosing, and accumulation is minimal when dosed once daily. More than 95% of the absorbed dose is being excreted as unchanged compound in the urine. The renal clearance is composed of passive filtration and active secretion into the renal tubule.

Special populations

Paediatric patients (age below 18 years)

No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years or over)

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in the area under the curve (AUC) and elimination half-life. Mean systemic AUC of valsartan is higher by 70% in the elderly than in the young, therefore caution is required when increasing the dosage.

Systemic exposure to valsartan is slightly elevated in the elderly as compared to the young, but this has not been shown to have any clinical significance.

Limited data suggest that the systemic clearance of hydrochlorothiazide is reduced in both healthy and hypertensive elderly subjects compared to young healthy volunteers.

Since the three components are equally well tolerated in younger and elderly patients, normal dose regimens are recommended (see section 4.2).

Renal impairment

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. 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.

Patients with mild to moderate renal impairment may therefore receive the usual initial dose (see sections 4.2 and 4.4).

In the presence of renal impairment, mean peak plasma levels and AUC values of hydrochlorothiazide are increased and the urinary excretion rate is reduced. In patients with mild to moderate renal impairment, a 3-fold increase in hydrochlorothiazide AUC has been observed. In patients with severe renal impairment an 8-fold increase in AUC has been observed.

Amlodipine/valsartan/hydrochlorothiazide is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3).

Hepatic impairment

Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic impairment have decreased clearance of amlodipine with resulting increase of approximately 40–60% in AUC. On average, in patients with mild to moderate chronic liver disease, exposure (measured by AUC values) to valsartan is twice that

found in healthy volunteers (matched by age, sex and weight). Due to the valsartan component, amlodipine/valsartan/hydrochlorothiazide is contraindicated in patients with hepatic impairment (see sections 4.2 and 4.3).

5.3 Preclinical safety data

Amlodipine/Valsartan/Hydrochlorothiazide

In a variety of preclinical safety studies conducted in several animal species with amlodipine, valsartan, hydrochlorothiazide, valsartan/hydrochlorothiazide, amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide, there was no evidence of systemic or target organ toxicity that would adversely affect the development of amlodipine/valsartan/hydrochlorothiazide for clinical use in humans.

Preclinical safety studies of up to 13 weeks in duration were conducted with amlodipine/valsartan/hydrochlorothiazide in rats. The combination resulted in expected reduction of red blood cell mass (erythrocytes, haemoglobin, haematocrit, and reticulocytes), increase in serum urea, increase in serum creatinine, increase in serum potassium, juxtaglomerular (JG) hyperplasia in the kidney and focal erosions in the glandular stomach in rats. All these changes were reversible after a 4-week recovery period and were considered to be exaggerated pharmacological effects.

The amlodipine/valsartan/hydrochlorothiazide combination was not tested for genotoxicity or carcinogenicity as there was no evidence of any interaction between these substances, which have been on the market for a long time. However, amlodipine, valsartan and hydrochlorothiazide have been tested individually for genotoxicity and carcinogenicity with negative results.

Amlodipine

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

* Based on patient weight of 50 kg

Valsartan

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

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 blood urea nitrogen, 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 comparable doses, the changes were similar though more severe, particularly in the kidney where the changes developed to a nephropathy including raised blood urea nitrogen 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
Povidone K25
Croscarmellose sodium
Sodium laurilsulfate
Mannitol
Silica, colloidal anhydrous
Magnesium stearate (E470b)

Film coating

Poly(vinyl alcohol)
Macrogol 3350
Titanium dioxide (E171)
Talc
Iron oxide, yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (OPA/Alu/PVC//Alu foil): 7, 10, 14, 28, 30, 56, 60, 84, 90, 98, 100, 7 x 1, 10 x 1, 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 84 x 1, 90 x 1, 98 x 1 and 100 x 1 film-coated tablets, in a box.

Blister (OPA/Alu/PVC//Alu foil), calendar packs: 7, 14, 28, 56, 84, 98, 7 x 1, 14 x 1, 28 x 1, 56 x 1, 84 x 1 and 98 x 1 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th October 2020

10 DATE OF REVISION OF THE TEXT

March 2022