National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS

1. *NAME OF THE MEDICINAL PRODUCT*

TRIVALAM H

2. *QUALITATIVE AND QUANTITATIVE COMPOSITION*

Each film-coated tablet containg 10 mg of Amlodipine (as amlodipine besilate), 160 mg of Valsartan and 25 mg of Hydrochlorothiazide

For the full list of excipients, see section 6.1.

3. *PHARMACEUTICAL FORM*

Film-coated tablet

Round, white tablet with a score line on one side of the tablet

4. *CLINICAL PARTICULARS*

4.1 Therapeutic indications

Treatment of essential hypertension as substitution therapy in adults whose blood pressure is adequately controlled on the combination of amlodipine, valsartan and hydrochlothiazide (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 TRIVALAM H is half a tablet, equivalent to 5 mg of amlodipine, 80 mg of valsartan and 12.5 mf of hydrochlorothiazide to one tablet per day, equivalent to 10 mg of amlodipine, 160 mg of valsartan and 25 mg of hydrochlorothiazide, to be taken preferably in the morning.

Before switching to TRIVALAM H patients should be controlled on stable doses of the monocomponents taken at the same time. The dose of TRIVALAM H should be based on the doses of the individual components of the combination at the time of switching.

The maximum recommended dose of the combination is 10 mg/320 mg/25 mg of amlodipine/valsartan/HCT.

Special population
Renal impairment
Due to the hydrochlorothiazide component, TRIVALAM H 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 section 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, TRIVALAM H is contraindicated in patients with severe hepatic

impairment (see section 4.3). In patients with mild to moderate hepatic impairment without chloestasis, the maximum recommended dose is 80 mg valsartan, half a tablet of TRIVALAM H

and therefore TRIVALAM H is not suitable in this group of patients (see section 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 impairement to TRIVALAM H, 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 the combination, particularily at the maximum dose, in patients with heart failure and coronary artery disease. Caution is advised in patients with heart failure and coronary disease, particularily at the maximum dose of 10 mg/320 mg/25 mg of amlodipine/valsartan/HCT.

Elderly (age 65 years or over)
Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularily at the maximum dose of 10 mg/320 mg/25 mg of amlodipine/valsartan/HCT, since available data in this patient population are limited. When switching eligible elderly hypertensive patients (see section 4.1) to TRIVALAM H, the lowest available dose of the amlodipine component should be used.

Paediatric population
There is no relevant use of TRIVALAM H in the paediatric population (patients below age 18 years) for the indication of essential hypertension.

Method of administration

Oral route

TRIVALAM H 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 derivates, or to any of the excipients listed in section 6.1.
- Second and third trimeters of pregnancy (see section 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 CARDIOVALAM® H with aliskiren-containing products in patients with diabetes mellitus or renal impairment (GFR < 60 mL/min/1.73 m²) (see section 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 aeortic 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 (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 TRIVALAM H. TRIVALAM H should be used only after correction of any pre-existing sodium and/or volume depletion.

If excessive hypotension occurs with TRIVALAM H, 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/hydrochlorothiazide
In the controlled trial of TRIVALAM H, the counteracting effect 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 internal to detect possible electrolyte imbalance, especially in patients with other risk factors such as impaired renal function, treatment with other medical 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 TRIVALAM H 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, TRIVALAM H should be discontinued until stable correction of the potassium balance.

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloroaemic 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 TRIVALAM H 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 TRIVALAM H is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended. TRIVALAM H is contraindicated in patients with renal impairment, anuria or undergoing dialysis (see section 4.3).

No dosage adjustment of TRIVALAM H is required for patients with mild to moderate renal impairment (GFR $\geq$ 30 mL/min/1.73 m^2).

Renal artery stenosis

TRIVALAM H 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 TRIVALAM H 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, TRIVALAM His not suitable in this group of patients (see section 4.2, 4.3 and 5.2).

Angioedema
Angiodema, 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. TRIVALAM H should be discontinued immediately in patients who develop angioedema and shouldnot be re-administered.

Heart failure and coronary disease/post-myocardial infraction
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 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 blokers, 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 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 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 section 4.3 and 4.6).

Primary hyperaldosteronism
Patients with primary hyperaldosteronism should not be treated with the angitensin II antagonist valsartan as their renin-angiotensin system is not activated. Therefore, TRIVALAM H is not recommended in this population.

Systemic lupuc 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, TRIVALAM H is contraindicated in symptomatic hyperuricaemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbated hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause intermittant and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. TRIVALAM H is contraindicated in patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia. TRIVALAM H 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 TRIVALAM H, it is recommended to stop the treatment. If a readministration of the diuretics is deemed necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

Acute angle-closure glaucoma
Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to a week of treatment initiation. Untreated acute-angle closure glaucoma can lead to permanent vision loss.

The primary treatment is to discontinue hydrochlorothiazide as rapidely as possible. Prompt medical or surgical treatment may need to be considered if the intraocullar pressure remains uncontrolled. Risk factors for developping acute angle-closure glaucome may include a history of sulphonamide 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 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 combination 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 section 4.5 and 5.1).

If dual blockade is considered as absolutely necessary, this should 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 neuropathy.

This medicine contains lactose. Its use is not advised in patients having lactose intolerance disorders.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies with other medicinal products were performed with the combination of 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 TRIVALAM H may increase the hypotensive effect of other antihypertensive agents.

Concomitant use not recommended

TRIVALAM H individual component	**Known interactions with the following agent**	**Effect of the interaction with other medicinal products**
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 including valsartan or thiazides. Since renal clearance of lithium is reduced by thiazides, the risk of lithium toxicity may presumably be increased further with TRIVALAM H. Therefore careful monitoring of serum lithium concentrations is recommended during concomitant administration. If a medicinal
Valsartan	*Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels*	product that affects potassium levels is considered necessary in combination with valsartan, frequent monitoring of potassium plasma levels is advised.
Amlodipine	*Grapefruit ot grepefruit 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

TRIVALAM H individual component	**Known interactions with the following agent**	**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], rifampicine, 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 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 medicines (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 angiotensine antagonists and hydrochlorothiazide when administered simultaneously. Furthermore, concomitant use of TRIVALAM H 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 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 othostatic 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), apparantly 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) - Metformin	Thiazides may alter glucose tolerance. Dose adjustment of the antidiabetic medicinal product may be necessary. 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 hyperglacaemic effect of diazoxide.
	Ciclosporin	Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications
	Cytotoxic agent	Thazides, 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 arrythmias.
	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 effect of thiazide diuretics. However, staggering the dosage of hydrochlorothiazide is administered at least 4 hours before and 4-6 hours after the administration of resins would potentially minimise the interaction.
	Medicinal products affecting serum potassium level	The hypokalaemic effect of hydrochorothiazide may be increased by concomitant adinistration of kaliuretic diuretics, corticosteroids, laxatives, adrenocrticotropic hormone (ACTH), amphotericin, carbonoloxone, penicillin G and salicylic acid derivatives or antiarrythmics. If these medicinal products are to be prescribed with the amlodipine/valsartan/HCT combination, monitoring of potassium plasma level 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	Due to the risk of hypokalaemia,

	could induce torsades de pointes	hydrochlorothiazide should be administered with caution when associated with medicinal products that could induce *torsades de pointes*, in particular Class Ia and Class III antiarrythmics and some antipsychotics.
	Medicinal products used in the treatment of gout (probenicid, sulfinpurazone 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 occuring 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-hypertensives	Thiazides potentiate the antihypertensive action of other antihypertensive drugs (e.g. guanethidine, methyldopa, beta-blockers, vasodilators, caclium channel blockers, ACE inhibitors, ARBs and Direct Rening 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 salt	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 vitamine D-mediated conditions) by increasing tubular calcium reabsorption.

Dual blockade of the RAAS with ARBs, ACE inhibitors or aliskiren
Clincal data have shown that dual blockade of RAAS through the concomitant 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 section 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 (AIIRAs) is not recommended during the first trimester of pregnancy (see section 4.4). The use of AIIRAs is contraindicated during the second and third trimester of pregnancy (see section 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 (AIIRAs), similar risk may exist for this class of drugs. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with AIIRAs should be stopped immediately, and if appropriate, alternative therapy should be started.

Exposure to AIIRAs 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 AIIRAs have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Infants whose mother have taken AIIRAs 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 seond and thirs 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 the combination of amlodipine/valsartan/HCT in pregnant woman. Based on the existing data with the components, the use of TRIVALAM H is not recommended during first trimester and contraindicated during the second and third trimester of pregnancy (see section 4.3 and 4.4).

Breast-feeding
Amlodipine is excreted in human milk. The proportion of 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 and/or amlodipine 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 TRIVALAM H during breast-feeding is not recommended. If TRIVALAM H 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 infiant.

Fertility
There are no clinical studies on fertility with the combination of 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 (calculation assume an oral dose of 320 mg/day and a 60-kg patient).

Amlodipine

Reversible biochemical changes in the heaad 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

Patient taking TRIVALAM H 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 suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired.

4.8 Undesirable effects

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

Summary of the safety profile
The safety of the combination 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 the combination of 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 reaction, listed by MedDRA System Organ Class and frequency, concern the combination of amlodipine/valsartan/HCT and amlodipine and HCT individually.
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, not know (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse reactions**	**Frequency**			
		TRIVALAM H	**Amlodipine**	**Valsartan**	**HCT**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)	--	--	--	Not known
Blood and lymphatic system	Agranulocytosis, bone marrow failure	--	--	--	Very rare

disorders	Decrease in haemoglobin and in haematocrit	--	--	Not known	--
	Haemolytic anaemia	--	--	--	Very rare
	Leukopenia	--	Very rare	--	Very rare
	Neutropenia	--	--	Not known	--
	Thrombocytopenia, sometimes with purpura	--	Very rare	Not know	Rare
	Aplastic anaemia	--	--	--	Not known
Immune system disorder	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
	Hypomagneseamia	--	--	--	Common
	Hyponatraemia	Uncommon		--	Common
	Worsening of diabetic metabolic state	--	-- Uncommon	--	Rare
Psychiatric disorders	Depression	--	~~Uncommon~~	--	Rare
	Insomnia/sleep disturbances	Uncommon	Uncommon	--	Rare
	Mood swings	--	Rare	--	--
	Confusion	--		--	--
Nervous system disorders	Coordination adnormal	Uncommon	-- Common	--	--
	Dizziness	Common		--	Rare
	Dizziness postural, dizziness exertional	Uncommon	-- Uncommon	--	--
	Dysgueusia	Uncommon		--	--
	Extrapyramidal syndrome	--	~~Not known~~ Common	--	--
	Headache	Common	Very rare	--	Rare
	Hypertonia	--	--	--	----
	Lethargy	Uncommon	Uncommon	--	Rare
	Paresthaesia	Uncommon		--	
	Peripheral neuropathy, neuropathy	Uncommon	Very rare Common	--	--
	Somnolence	Uncommon	Uncommon		--
	Syncope	Uncommon	Uncommon	--	--
	Tremor	----	Uncommon	--	--
	Hypoesthesia			--	~~Not known~~
Eye disorders	Acute angle-closure glaucoma	--	--	--	--
	Visual disturbances	--	~~Uncommon~~	--	--

	Visual impairment	Uncommon	Uncommon	--	Rare
Ear and labyrinth disorders	Tinnitus	--	Uncommon	--	--
	Vertigo	Uncommon	--	Uncommon	--
Cardiac dirsoders	Palpitations	--	Common	--	--
	Tachycardia	Uncommon	--	--	--
	Arrythmias (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	--	--	--
Gastrointestinal disorders	Abdominal discomfort, abdominal pain upper	Uncomon	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	--	Common Very rare
	Nausea	Uncommon	Common	--	Common
	Pancreatitis	--	Very rare	--	
	Vomiting	Uncommon	Uncommon	--	
Hepatobiliary disorders	Liver function test abnormal, including blood bilirubin increase	--	Very rare**	Not known	--
	Hepatitis	--	Very rare	--	--
	Intrahepatic chloestasis, jaundice	--	Very rare	--	--
Skin and	Alopecia	--	Uncommon	--	

subcutaneous tissue disorders	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
	Exanthema	--	Uncommon	--	--
	Hyperhidrosis	Uncommon	Uncommon	--	--
	Photosensitivity reaction*	--	Very rare	--	Rare
	Pruritus	Uncommon	Uncommon	Not known	--
	Purpura	------	Uncommon	--	Rare
	Rash	--	Uncommon	Not known	Common
	Skin discolouration		Uncommon	--	--
	Urticaria and other forms of rash		Very rare	--	Common
	Vasculitis necrotising and toxic epidemal necrolysis	-- --	--	--	Very rare
	Exfoliative dermatitis	--	Very rare	--	--
	Stevens-Johson syndrome	-- --	Very rare	--	--
	Quincke oedema	Uncommon	Very rare	--	--
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon	Uncommon	--	--
	Back pain	Uncommon	Uncommon	--	--
	Joint swelling	Uncommon	--	--	--
	Muscle spasm	Uncommon	Uncommon	--	Uncommon
	Muscular weakness	Uncommon	--	--	--------
	Myalgia	--	Uncommon	Not known	--
	Pain in extremity	~~Uncommon~~	--Common	----	
	Ankle swelling		--	~~Not known~~	--
Renal and urinary disorders	Blood creatinine increased	--	~~Uncommon~~	--	--
	Micturition disorder	-- Common	Uncommon	--	-- Not known
	Nocturia	--	Uncommon	--	Not known
	Pollakiuria	Uncommon	----	--	~~Rare~~
	Renal dysfunction	--	--	--	Common
	Acute renal failure			~~Not known~~	--
	Renal failure and impairment	Uncommon	Uncommon ~~Uncommon~~	--	--
Reproductive system and breast disorders	Impotence				--
	Gynecomastia	Uncommon	--		Not known
General disorders and administration site conditions	Abasia, gait disturbance	Uncommon ~~Uncommon~~	Uncommon ~~Uncommon~~	--	--
	Asthenia				--
	Discomfort, malaise	Common	Common	-- Uncommon	
	Fatigue				

	Non cardiac chest pain	Uncommon	Uncommon	--	--
	Oedema	Common	Common	--	--
	Pain	----	Uncommon	--	--
	Pyrexia		--	--	Not known
Investigations	Lipids increased	-- Uncommon	--	--	Very common
	Blood urea nitrogen increased	Uncommon --	--	--	--
	Blood uric acid increased	Uncommon	--	--	--
	Glycosuria		--	--	Rare
	Blood potassium decreased	Uncommon --	--	--	--
	Blood potassium increased	Uncommon	--	Not known	--
	Weight increase	--	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 hydrochlorothiazide and NMSC has been observed (see also section 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 the national reporting system.

4.9 Overdose

Symptoms
There is no experience of overdose with the combination of amlodipine/valsartan/HCT. The major symptom of overdose with valsartan is possible 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 the combination overdose calls for active cardiovascular support, including frequent monitoring of cardiac and respiratory function, elevation of extremeties, and attention to circulating fluid volume and urine output. A vasocontrictior may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. Intravenous calclium gluconate may be beneficial in reversing the effects of calcium channel blockade.

Amlodipine
If ingestion is recent, induction of vomitting 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 haemodyalisis.

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. Hypokalemia may result in muscle spasms and or accentuate arrythmia associated with the concimitant use of digitalis glycosides or certain anti-arrythmic 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 of the renin-angiotensin system, Angiotensin II antagonists, other combinations ATC code: C09DX01.

Mechanism of action
TRIVALAM H 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 medicine and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these substances has an additive antihypertensive effect.

Amlodipine/Valsartin/Hydrochlorothiazide

Clinical efficacy and safety
TRIVALAM H was 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/hydrochlorothiaide 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 reduction in systolic/diastolic blood pressure were 39.7/24.7 mmHg with amlodipine/valsartan/hydrochlorothiazide, 32.0/19.7 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 reduction 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/hydrochlorothiaide. The full blood pressure lowering effect was achieved 2 weeks after 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 components of TRIVALAM H inhibit 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 reduction 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 effect 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) r 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 enrolment) 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 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 ration (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 vascular 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 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 AT_1, 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 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 the inhibition of the Na^+ Cl^- symporter perhaps by competing for the Cl^- site, thereby affecting electrolyte reabsorption mechanism: 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.

Non-melanoma skin cancer
Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide 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 hydrochlorothiazide use (≥50000 mg cumulative) was associated with an adjusted odd ratio (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 hydrochlorothiazide: 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 (~25000 mg) and OR 7.7 (5.7-10.5) for the highest cumulative dose (~100000 mg) (see also section 4.4).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with the combination of amlodipine/valsartan/hydrochlorothiazide in all subsets of 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) 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 history of cardiovascular diseases or cerebrovascular diseases, or with type 2 diabetes accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes and diabetic nephropathy.

The 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 pharmacodynamics 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.

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.

5.2 Pharmacokinetic properties

Linearity
Amlodipine, valsartan and hydrochlorothiazide exhibit linear pharmacokinetics.

Amlodipine/valsartan/hydrochlorothiazide
Following oral administration of the combination of amlodipine/valsartan/HCT 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 the combination 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 bioavailibility is unaffected by food ingestion.

Distribution
Volume of distribution is approximately 211/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 llitres, 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 metabolites 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 ($t_{1/2}$ < 1 h and $t_{1/2}$ about 9 h). Valsartan is primarily eliminated in faeces (about 83 % of doses) 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.

Hydrchlorothiazide

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 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 population

Paediatric patients (age below 18 years)
No pharmacokinetic data are available in the paediatric population.

Elderly (age 65 years and 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 systematic 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 to youg 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 section 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 obseved. In patients with severe renal impairment an 8-fold increase in AUC has been observed. TRIVALAM H is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3).

Hepatic impairment
Very limited 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 valsartan component, TRIVALAM H is contraindicated in patients with hepatic impairment (see section 4.2 and 4.3).

5.3 Preclinical safety data

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

Preclinical safety studies 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/hydrochlorothiaide 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 tested individually for genotoxicity and carcinotoxicity 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 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 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.

* Bases 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 dose (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, heamoglobin, 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, paricularly in marmosets. For therapeutic doses of valsartan inhumans, the hypertrophy of the renal juxtaglomerular cells does not seem to have any relevance.

6. *PHARMACEUTICAL PARTICULARS*

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, celloidal anhydrous silica, croscarmellose sodium, hypromellose, Opadry II (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

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/PVDC blisters. A blister contains 10 film-coated tablets.
Presentation: 30 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. *CATEGORY OF DISTRIBUTION*

☐ Over-the counter medicine ☒ Prescription only medicine

8. *MARKETING AUTHORISATION HOLDER*

Exphar s.a.
Zoning Industriel de Nivelles Sud, Zone II
Avenue Thomas Edison 105
1402 Thines
BELGIQUE
Phone+32 (0)67 68 84 00
Fax +32 (0)67 68 84 19

9. *MANUFACTURER*

Gracure Pharmaceuticals Ltd.,
E-1105, Industrial Area, Phase-III,
Bhiwadi, Dist. Alwar (Raj.), INDE
Phone+91.11.259.207.48
Fax +91.11.259.207.47

10. *DATE OF REVISION OF THE TEXT*

June 2024