PROFESSIONAL INFORMATION

CALSAR CO RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CALSAR CO 5 mg/160 mg/12,5 mg film coated tablets

CALSAR CO 5 mg/160 mg/25 mg film coated tablets

CALSAR CO 10 mg/160 mg/12,5 mg film coated tablets

CALSAR CO 10 mg/160 mg/25mg film coated tablets

CALSAR CO 10 mg/320 mg/25 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each CALSAR CO 5 mg/160 mg/12,5 mg film coated tablet contains amlodipine besylate (equivalent to 5 mg of amlodipine), 160 mg of valsartan and 12,5 mg hydrochlorothiazide. Contains sugar (sugar alcohol – mannitol 58,8 mg).

Each CALSAR CO 5 mg/160 mg/25 mg film coated tablet contains amlodipine besylate (equivalent to 5 mg of amlodipine), 160 mg of valsartan and 25 mg hydrochlorothiazide. Contains sugar (sugar alcohol – mannitol 58,8 mg).

Each CALSAR CO 10 mg/160 mg/12,5 mg film coated tablet contains amlodipine besylate (equivalent to 10 mg of amlodipine), 160 mg of valsartan and 12,5 mg hydrochlorothiazide. Contains sugar (sugar alcohol – mannitol 58,8 mg).

Each CALSAR CO 10 mg/160 mg/25 mg film coated tablet contains amlodipine besylate (equivalent to 10 mg of amlodipine), 160 mg of valsartan and 25 mg hydrochlorothiazide. Contains sugar (sugar alcohol – mannitol 58,8 mg).

Each CALSAR CO 10 mg/320 mg/25 mg film coated tablet contains amlodipine besylate (equivalent to 10 mg of amlodipine), 320 mg of valsartan and 25 mg hydrochlorothiazide. Contains sugar (sugar alcohol – mannitol 117,5 mg).

This medicine contains less than 1 mmol sodium (0,023 g) per film coated tablet and is essentially ‘sodium free’

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

CALSAR CO 5 mg/160 mg/12,5 mg: White or almost white, oval, biconvex, film coated tablets, engraved with mark K1 on one side of the tablet.

CALSAR CO 5 mg/160 mg/25 mg: Light yellow, oval, biconvex, film coated tablets, engraved with mark K3 on one side of the tablet.

CALSAR CO 10 mg/160 mg/12,5 mg: Pink, oval, biconvex, film coated tablets, engraved with mark K2 on one side of the tablet.

CALSAR CO 10 mg/160 mg 25 mg: Brown-yellow, oval, biconvex, film coated tablets, engraved with mark K4 on one side of the tablet.

CALSAR CO 10 mg/320 mg/25 mg: Brown-red, oval, biconvex, film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of essential hypertension in patients stabilised on the individual components given at the same doses.

CALSAR CO is not indicated for the initial therapy of hypertension (see section 4.2).

4.2 Posology and method of administration

Posology

The recommended dose is one tablet per day (of either of the 5 strengths listed under section 2).

If a tablet shows signs of cracking, the tablet should not be taken.

Patients stabilised with valsartan, amlodipine and hydrochlorothiazide (HCTZ) from separate tablets may be switched to CALSAR CO containing the same component doses.

The maximum antihypertensive effect of CALSAR CO is reached within two weeks after a change in dose. The maximum recommended dose of CALSAR CO is one 10/320/25 mg daily.

Special populations

Elderly

No adjustment of the initial dose is required for elderly patients (see section 5.2).

Renal impairment

No dosage adjustment is required for patients with mild to moderate renal impairment. Due to the hydrochlorothiazide component, CALSAR CO is not recommended in patients with severe renal impairment (creatinine clearance <30 mL/min) (see section 4.3 and 5.2).

Hepatic Impairment

Caution should be exercised when administering CALSAR CO to in patients with hepatic impairment or biliary obstructive disorders (see section 4.4). Due to the hydrochlorothiazide component, CALSAR CO is not recommended in patients with severe hepatic impairment (see section 4.3 and 5.2).

Paediatric population

CALSAR CO is not recommended for use in patients aged below 18 years due to a lack of data on safety and efficacy (see section 4.3).

Method of administration

For oral use.

CALSAR CO can be taken with or without food. It is recommended to take CALSAR CO with some water.

4.3 Contraindications

CALSAR CO is contraindicated in:

- hypersensitivity to amlodipine, valsartan, hydrochlorothiazide and other sulphonamides, dihydropyridine derivatives, or to any of the CALSAR CO excipients listed in section 6.1
- history of angioedema related to previous therapy with angiotensin receptor blockers (ARBs): These patients must never again be given these medicines
- concomitant use of fluroquinolones with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers is contraindicated in patients with moderate (creatinine clearance <60 mL/min) to severe renal function impairment (creatinine clearance less than 30 mL/min) and in the elderly
- concomitant use of CALSAR CO with aliskiren-containing medicines in patients with diabetes mellitus or renal impairment (glomerular filtration rate (GFR) < 60 mL/min/1,73 m^2) (see sections 4.5 and 5.1)
- lithium therapy: concomitant administration with CALSAR CO may lead to toxic blood concentrations of lithium (see section 4.5)
- concomitant therapy with potassium sparing diuretics such as spironolactone, triamterene, amiloride
- hereditary or idiopathic angioedema
- severe hepatic impairment (Child-Pugh C)
- CALSAR CO should not be given to patients with Addison's disease
- anuria, severe renal impairment (creatinine clearance less than 30 mL/min) and patients undergoing dialysis
- refractory hypokalaemia, hyponatraemia, hypercalcaemia and symptomatic hyperuricaemia
- obstruction of the outflow tract of the left ventricle (e.g. hypertrophic obstructive cardiomyopathy (HOCM) and high-grade aortic stenosis and mitral valve stenosis)
- bilateral renal artery stenosis, renal artery stenosis in patients with a single kidney
- pregnancy and lactation. CALSAR CO should be discontinued as soon as possible when pregnancy is suspected (see section 4.6)
- porphyria
- children under 18 years of age, as safety and efficacy have not been established

- patients with a history of previous and/or current basal cell carcinomas and/or squamous cell carcinomas of the skin and lip.

4.4 Special warnings and precautions for use

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

Pregnancy

Angiotensin II receptor antagonists (AIIRAs) should not be initiated during pregnancy. Patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. Should a woman become pregnant while receiving CALSAR CO, the treatment should be stopped promptly and switched to a different class of antihypertensive medicine (see sections 4.3 and 4.6)

Renal Impairment

Due to the hydrochlorothiazide component, CALSAR CO is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min, anuria or undergoing dialysis) (see section 4.3). Thiazide diuretics may precipitate uraemia in patients with chronic kidney disease. When CALSAR CO is used in patients with renal impairment periodic monitoring of serum electrolytes (including potassium), creatinine and uric acid serum levels is recommended.

Renal artery stenosis

CALSAR CO should not be used in bilateral renal artery stenosis and renal artery stenosis in patients with a single kidney since blood urea and serum creatinine may increase in such patients (see section 4.3).

Kidney transplantation

There is no experience with the use of CALSAR CO in patients with a recent kidney transplant.

Hepatic Impairment

Valsartan is mostly eliminated unchanged via the bile, whereas amlodipine is extensively metabolised by the liver. The half-life of amlodipine is prolonged and Area under the curve (AUC) values are higher in patients with impaired liver function, but dose recommendations have not been established. Particular caution should be exercised when administering CALSAR CO to patients with hepatic impairment or biliary obstructive disorders. CALSAR CO is contraindicated in patients with severe hepatic impairment, because of the hydrochlorothiazide component (see section 4.3).

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/HCTZ (10/320/25 mg) compared to 1,8 % of valsartan/HCTZ (320/25 mg) patients, 0,4 % of amlodipine/valsartan (10/320 mg) patients, and 0,2 % of HCTZ/amlodipine (25/10 mg) patients in a controlled trial in patients with moderate to severe uncomplicated hypertension.

In patients with an activated renin-angiotensin system, such as volume-and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur in patients receiving angiotensin receptor blockers. This condition should be corrected prior to administration of CALSAR CO, or the treatment should start under close medical supervision.

If excessive hypotension occurs with CALSAR CO, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of 0,9 % sodium chloride solution. Treatment can be continued once blood pressure has been stabilised.

Serum electrolyte changes

Amlodipine/valsartan/hydrochlorothiazide:

A controlled trial indicates, 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 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 medicines or history of prior electrolyte imbalances.

Valsartan:

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) contraindicated (see section 4.3). Monitoring of potassium should be undertaken as appropriate.

Hydrochlorothiazide:

Concomitant use with potassium supplements, potassium sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) could lead to hyperkalaemia and should be used with caution. Hypokalaemia has been reported under treatment with thiazide diuretics including hydrochlorothiazide. Frequent monitoring of potassium is recommended (see section 4.3).

Treatment with CALSAR CO should only start after correction of hypokalaemia and any co-existing 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, CALSAR CO should be discontinued until stable correction of the potassium balance.

Thiazide diuretics can precipitate new onset hyponatraemia and hypochloraemic alkalosis or exacerbate pre-existing hyponatraemia. Thiazides, including hydrochlorothiazide increase the urinary excretion of magnesium, which may result in hypomagnesaemia. 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 CALSAR CO therapy, the treatment should be discontinued until normalisation of natremia.

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

Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy

Special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy (see section 4.3).

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 medicines may be required.

Due to the hydrochlorothiazide component, CALSAR CO is contraindicated in symptomatic hyperuricemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricemia 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. CALSAR CO is contraindicated in

patients with hypercalcaemia and should only be used after correction of any pre-existing hypercalcaemia (see section 4.3). CALSAR CO 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.

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 medicines including ACE inhibitors. CALSAR CO 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 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 CALSAR CO, 10/320/25 mg, since available data in these patient populations is limited.

Concomitant use of fluoroquinolones and ACE inhibitors /angiotensin receptor blockers

Concomitant use of fluoroquinolones and ACE inhibitors/Angiotensin receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment and monitored during treatment with fluoroquinolones or ACE inhibitors/angiotensin receptor blockers, whether used separately and/or concomitantly.

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, CALSAR CO is not recommended in this population.

Photosensitivity

Cases of photosensitivity reactions have been reported with thiazide diuretics (see section 4.8). If photosensitivity reaction occurs during treatment with CALSAR CO, it is recommended to stop the treatment. If a re-administration of the diuretic 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 rapidly as possible. Prompt medical or surgical treatment may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma 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

Caution, including more frequent monitoring of blood pressure, is recommended in elderly patients, particularly at the maximum dose of CALSAR CO, 10 /320 /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 decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of CALSAR CO and aliskiren is therefore contraindicated (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 exposure has been observed in pharmaco-epidemiological studies. The risk for NMSC appears to increase with long-term use. Photosensitising actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide, alone or in combination, should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions, as well as changes to existing ones, and promptly report any suspicious skin lesions.

Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies.

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 minimise the risk of skin cancer.

The use of hydrochlorothiazide is contraindicated in patients who have experienced previous NMSC (see also section 4.8).

Paediatric population

Safety and efficacy of CALSAR CO in patients aged below 18 years has not been established (see section 4.3).

Excipients with known effect

Sodium

CALSAR CO contains less than 1 mmol sodium (0,023 g) per film coated tablet, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies with other medicines have been performed with CALSAR CO.

Thus, only information on interactions with other medicines that are known for the individual active substances is provided in this section.

However, it is important to take into account that CALSAR CO may increase the hypotensive effect of other antihypertensive medicines.

Concomitant use not recommended

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

Clinical trial data has shown that dual blockade of the renin-angiotensin-aldosterone-system (RAAS) through the combined use of ACE inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreased renal function (see sections 4.3 and 4.4).

Fluoroquinolones: Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (see section 4.3).

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 CALSAR CO. Therefore, the concomitant use of CALSAR CO with lithium is contraindicated (see section 4.3).

Valsartan

Potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium and other substances that may increase potassium levels: If a medicine that affects potassium levels (e.g. heparin) 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

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, phenobarbitone, phenytoin, fosphenytoin, primidone], rifampicin, Hypericum perforatum): 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 therapy, particularly with strong CYP3A4 inducers (e.g. rifampicin, St. John's Wort (*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

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.

Valsartan and Hydrochlorothiazide

Nonsteroidal anti-inflammatory medicines (NSAIDs), including selective cyclooxygenase-2 (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 CALSAR CO and NSAIDs may lead to an increased risk of worsening of renal function and an increase in serum potassium. Therefore, monitoring of renal function at the beginning of the treatment is recommended, as well as adequate hydration of the patient.

Hydrochlorothiazide

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 medicines: The bioavailability of thiazide-type diuretics may be increased by anticholinergic medicines (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 medicines: It may prove necessary to readjust the dosage of insulin and of oral antidiabetic medicines.

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 may enhance the hyperglycaemic effect of diazoxide.

Carbamazepine: Patients receiving hydrochlorothiazide concomitantly with carbamazepine may develop hyponatraemia. Such patients should therefore be advised about the possibility of hyponatraemic reactions, and should be monitored accordingly.

Ciclosporin: Concomitant treatment with ciclosporin may increase the risk of hyperuricaemia and gout-type complications.

Cytotoxic medicines: Thiazides, including hydrochlorothiazide, may reduce the renal excretion of cytotoxic medicines (e.g. cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.

Digitalis glycosides: Thiazide-induced hypokalaemia or hypomagnesaemia may occur as unwanted effects, favouring the onset of digoxin-induced cardiac dysrhythmias.

Iodine contrasting medicines: 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.

Medicines affecting potassium: The hypokalaemic effect of diuretics may be increased by kaliuretic diuretics, corticosteroids, laxatives, adrenocorticotropic hormone (ACTH), amphotericin, carbenoxolone, penicillin G, salicylic acid derivatives or anti-dysrhythmics. If these medicines are to be prescribed with CALSAR CO, monitoring of potassium plasma levels is advised.

Medicines affecting serum sodium level: The hyponatraemic effect of diuretics may be intensified by concomitant administration of medicines such as antidepressants, antipsychotics, antiepileptics, etc. Caution is indicated in long-term administration of these medicines.

Medicines that could induce torsade de pointes: Due to the risk of hypokalaemia, hydrochlorothiazide should be administered with caution when associated with medicines that could induce *torsade de pointes*, in particular Class Ia and Class III anti-dysrhythmics and some antipsychotics.

Medicines used in the treatment of gout: (probenecid, sulphinpyrazone and allopurinol). Dose adjustment of uricosuric medicines may be necessary as hydrochlorothiazide may raise the level of serum uric acid. An increase of the dose of probenecid or sulphinpyrazone may be necessary. Co-administration of thiazide diuretics, including hydrochlorothiazide, may increase the incidence of hypersensitivity reactions to allopurinol.

Methyldopa: There have been reports in the literature of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Non-depolarising muscle relaxants: Thiazides, including hydrochlorothiazide, potentiate the action of non-depolarising muscle relaxants.

Other anti-hypertensive medicines: Thiazides potentiate the antihypertensive action of other antihypertensive medicines (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.

Monotherapy

In monotherapy, amlodipine has been safely administered with thiazide diuretics, beta blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, atorvastatin, sildenafil, aluminium hydroxide gel, magnesium hydroxide and simeticone, cimetidine, non-steroidal anti-inflammatory medicines, antibiotics, and oral hypoglycaemic medicines.

In monotherapy with valsartan, no medicine interactions of clinical significance have been found with the following medicines: cimetidine, warfarin, furosemide, digoxin, atenolol, indomethacin, hydrochlorothiazide, amlodipine, glibenclamide.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing age should use effective contraception.

Pregnancy

CALSAR CO is contraindicated in pregnancy as teratogenicity has been shown in experimental animals (see section 4.3). Medicines affecting the renin-angiotensin system, such as CALSAR CO, can cause embryonal toxicity, foetal and neonatal morbidity and mortality when administered to pregnant women. When pregnancy is detected, CALSAR CO should be discontinued as soon as possible. Pregnant women should be informed of the potential hazards to the foetus and must not take CALSAR CO during pregnancy (see section 4.3). Patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with CALSAR CO should be stopped immediately and if appropriate, alternative therapy should be started.

Foetal exposure to ACE inhibitors during the first trimester of pregnancy has been reported to be associated with an increased risk of malformations of the cardiovascular (atrial and/or ventricular septal defect, pulmonic stenosis, patent ductus arteriosus) and central nervous system (microcephaly spina bifida) and of kidney malformations.

CALSAR CO passes through the placenta and can be presumed to cause disturbance in foetal blood pressure regulatory mechanisms.

Oligohydramnios as well as hypotension, oliguria and anuria in newborn infants, have been reported after administration of CALSAR CO during the second and third trimester. Cases of defective skull ossification have been observed. Prematurity and low birth mass can occur (see section 4.3).

Breastfeeding

It is not known whether valsartan and/or amlodipine are excreted in human milk. Valsartan was excreted in the milk of lactating rats. Hydrochlorothiazide is excreted into breast milk. CALSAR CO is

contraindicated in women who are breastfeeding (see section 4.3).

Fertility

There is no data on fertility with CALSAR CO.

4.7 Effects on ability to drive and use machines

CALSAR CO can lead to dizziness or weariness, patients should be advised not to drive, operate machinery or perform hazardous tasks until they know how CALSAR CO affects them.

4.8 Undesirable effects

a) Summary of the safety profile

Adverse reactions were generally mild and transient in nature and only infrequently required discontinuation of therapy. The most common reasons for discontinuation of therapy were dizziness and hypotension.

b) Tabulated summary of adverse reactions

Side effects for CALSAR CO

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	*Frequency unknown*	Thrombocytopenia
Immune system disorders	*Frequency unknown*	Angioedema

Metabolism and nutrition disorders	*Frequent* *Less frequent* *Frequency unknown*	Hypokalaemia Anorexia, hypercalcaemia, hyperlipidaemia, hyperuricaemia, hyponatraemia Blood potassium increased
Psychiatric disorders	*Less frequent*	Insomnia/sleep disorders
Nervous system disorders	*Frequent* *Less frequent*	Dizziness, headache Abnormal coordination dysgeusia, lethargy, paraesthesia, peripheral neuropathy, somnolence, syncope, dizziness postural, dizziness exertional
Eye disorders	*Less frequent*	Visual impairment
Ear and labyrinth disorders	*Less frequent*	Vertigo
Cardiac disorders	*Less frequent*	Tachycardia
Vascular disorders	*Frequent* *Less frequent* *Frequency unknown*	Hypotension Orthostatic hypotension, phlebitis, thrombophlebitis Vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Cough, dyspnoea, throat irritation

Gastrointestinal disorders	*Frequent* *Less frequent*	Dyspepsia Abdominal discomfort and pain, breath odour, diarrhoea, dry mouth, nausea, vomiting
Hepato-biliary disorders	*Frequency unknown*	Elevation of liver function values including serum bilirubin
Skin and subcutaneous tissue disorders	*Less frequent*	Hyperhidrosis, pruritus
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Back pain, joint swelling, muscle spasm, muscular weakness, myalgia, pain in extremity
Renal and urinary disorders	*Frequent* *Less frequent*	Pollakiuria Blood creatinine increased, renal impairment acute renal failure
Reproductive system and breast disorders	*Less frequent*	Impotence
General disorders and administrative site conditions	*Frequent* *Less frequent*	Fatigue, oedema Asthenia, discomfort, malaise, non-cardiac chest pain, abasia, gait disturbance
Investigations	*Less frequent*	Blood urea nitrogen increased, blood uric acid increased, blood potassium decreased, weight increase

Side effects for Amlodipine

System Organ Class	Frequency	Side effects
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopenia sometimes with purpura, leucocytopenia
Immune system disorders	*Less frequent*	Hypersensitivity, allergic reactions, angioedema
Metabolism and nutrition disorders	*Less frequent*	Hyperglycaemia
Psychiatric disorders	*Less frequent*	Insomnia, mood changes, anxiety, depression, confusion
Nervous system disorders	*Frequent* *Less frequent* *Frequency unknown*	Headache, somnolence, dizziness Tremor, hypoesthesia, dysgeusia, paraesthesia, syncope, hypertonia, peripheral neuropathy, neuropathy Extrapyramidal syndrome
Eye disorders	*Less frequent*	Visual impairment, diplopia, visual disturbance
Ear and labyrinth disorders	*Less frequent*	Tinnitus
Cardiac disorders	*Frequent* *Less frequent*	Palpitations Dysrhythmia, bradycardia, atrial fibrillation, ventricular tachycardia, myocardial infarction

Vascular disorders	*Frequent* *Less frequent*	Flushing Hypotension, vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, rhinitis, cough
Gastrointestinal disorders	*Frequent* *Less frequent*	Vomiting, abdominal pain, nausea Dyspepsia, dry mouth, constipation, diarrhoea, vomiting Pancreatitis, gastritis, gingival hyperplasia, change of bowel habit
Hepato-biliary disorders	*Less frequent*	Liver function test abnormal including blood bilirubin increase, hepatitis, jaundice, intrahepatic cholestasis
Skin and subcutaneous tissue disorders	*Less frequent* *Frequency unknown*	Alopecia, hyperhidrosis, pruritus, rash, purpura, skin discoloration, photosensitivity, exfoliative dermatitis, urticaria, erythema multiforme, Stevens-Johnson syndrome, exanthema, Quincke oedema Vasculitis necrotising and toxic epidermal necrolysis

Musculoskeletal, connective tissue and bone disorders	*Frequent* *Less frequent*	Ankle swelling Back pain, muscle spasms, myalgia, arthralgia
Renal and urinary disorders	*Less frequent*	Micturition disorder, nocturia, pollakiuria
Reproductive system and breast disorders	*Less frequent*	Gynecomastia, erectile dysfunction, impotence
General disorders and administration site conditions	*Frequent* *Less frequent*	Oedema, fatigue Asthenia, pain, malaise, non-cardiac chest pain
Investigations	*Less frequent* *Less frequent*	Weight decreased, weight increased Hepatic enzyme increased (*mostly consistent with cholestasis*)

Side effects for Valsartan

System Organ Class	**Frequency**	**Side effects**
Infections and Infestations	*Frequency unknown*	Viral infections, upper respiratory tract infection, sinusitis, pharyngitis, rhinitis
Blood and lymphatic system disorders	*Frequency unknown*	Decrease in haemoglobin, decrease in haematocrit, neutropenia, thrombocytopenia sometimes with purpura

Immune system disorders	*Frequency unknown*	Hypersensitivity including serum sickness, angioedema
Psychiatric disorders	*Frequency unknown*	Insomnia, decreased libido
Ear and labyrinth disorders	Less frequent	Vertigo
Vascular disorders	Frequency unknown	Vasculitis
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Cough
Gastrointestinal disorders	*Less frequent*	Abdominal pain, discomfort
Hepato-biliary disorders	*Frequency unknown*	Liver function test abnormal, including blood bilirubin increase
Skin and subcutaneous tissue disorders	*Frequency unknown*	Rash, pruritus, angioedema, dermatitis bullous
Musculoskeletal, connective tissue and bone disorders	*Frequency unknown*	Myalgia
Renal and urinary disorders	*Frequency unknown*	Elevation of serum creatinine, increased blood urea, renal failure and impairment

General disorders and administrative site conditions	*Less frequent*	Fatigue
Investigations	*Frequency unknown*	Blood potassium increased

Side effects for Hydrochlorothiazide

System Organ Class	Frequency	Side effects
Neoplasms benign, malignant and unspecified	*Frequency unknown*	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Blood and lymphatic system disorders	*Less frequent*	Thrombocytopenia, purpura, leucopenia, agranulocytosis, bone marrow failure, haemolytic anaemia, aplastic anaemia
Immune system disorders	*Less frequent*	Hypersensitivity reactions - respiratory distress including pneumonitis and pulmonary oedema
Metabolism and nutrition disorders	*Frequent* *Less frequent*	Hypokalaemia, increased blood lipids, hyponatremia, hypomagnesaemia, hyperuricaemia Hypercalcaemia, hyperglycaemia, glycosuria and worsening of

		diabetic metabolic state, hypochloraemic alkalosis
Psychiatric disorders	*Less frequent*	Insomnia, sleep disorders, depression
Nervous system disorders	*Less frequent*	Headache, dizziness, sleep disorders, paraesthesia
Eye disorders	*Less frequent*	Visual impairment, acute angle-closure glaucoma
Cardiac disorders	*Less frequent*	Dysrhythmia (including bradycardia, ventricular tachycardia, and atrial fibrillation)
Vascular disorders	*Frequent*	Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Respiratory distress, pulmonary oedema, pneumonitis
Gastrointestinal disorders	*Frequent* *Less frequent*	Decreased appetite, mild nausea, vomiting Abdominal discomfort, constipation, diarrhoea, pancreatitis
Hepato-biliary disorders	*Less frequent*	Intrahepatic cholestasis, jaundice
Skin and subcutaneous tissue disorders	*Frequent* *Less frequent*	Urticaria, and other forms of rash Photosensitivity reaction, necrotizing vasculitis, toxic epidermal necrolysis, cutaneous

		lupus erythematosus-like reactions, reactivation of cutaneous lupus erythematosus, erythema multiforme, purpura
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Muscle spasms
Renal and urinary disorders	*Less frequent*	Acute renal failure, renal dysfunction
Reproductive system and breast disorders	*Frequent*	Impotence
General disorders and administrative site conditions	*Less frequent*	Pyrexia, asthenia
Investigations	*Frequent* *Less frequent*	Increased lipids Glycosuria

c) 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 sections 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

There is no experience of overdose with CALSAR CO.

Overdose with amlodipine may result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and potentially prolonged systemic hypotension up to, and including, shock with fatal outcome have been reported.

The major symptom of overdose with valsartan is possibly pronounced hypotension with dizziness.

Available data for amlodipine suggest that gross overdosage could result in excessive peripheral vasodilatation and possibly reflex tachycardia. Marked and probably prolonged systemic hypotension up to and including shock with fatal outcome have been reported.

Non-cardiogenic pulmonary oedema has rarely been reported as a consequence of amlodipine overdose that may manifest with a delayed onset (24 - 48 hours post-ingestion) and require ventilatory support. Early resuscitative measures (including fluid overload) to maintain perfusion and cardiac output may be precipitating factors.

Management of overdose

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.

Clinically significant hypotension due to CALSAR CO 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.

Both valsartan and amlodipine are unlikely to be removed by haemodialysis whereas clearance of

HCTZ will be achieved by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Agents acting on the renin-angiotensin system, angiotensin II receptor blockers, other combinations

ATC code: C09DX01.

Pharmacological classification: 7.1.3 vascular medicines – other hypotensives

Mechanism of action

Amlodipine/valsartan/hydrochlorothiazide combines three antihypertensive active ingredients with complementary mechanisms to control blood pressure in patients with essential hypertension: amlodipine belongs to the calcium antagonist class, valsartan to the angiotensin II (Ang II) antagonist class and hydrochlorothiazide belongs to the thiazide diuretics class of medicines. The combination of these ingredients has an additive antihypertensive effect, reducing blood pressure to a greater degree than either component alone.

Amlodipine

The amlodipine component of the tablet 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 a reduction in peripheral vascular resistance and reduction in blood pressure. 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 vasodilatation 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 an increase in glomerular filtration rate and effective renal plasma flow without change in filtration fraction or proteinuria.

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 change in pressure per unit time (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.

Valsartan

Valsartan is an orally active, and specific angiotensin II receptor antagonist. It acts selectively on the angiotensin type 1 (AT_1) receptor subtype, which is responsible for the known actions of angiotensin II. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor, which appears to counterbalance the effect of the AT_1 receptor. Valsartan does not exhibit any partial agonist activity at the AT_1 receptor and has much (about 20 000-fold) greater affinity for the AT_1 receptor than for the AT_2 receptor.

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

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs within 2 hours, and the peak reduction of blood pressure is achieved within 4 - 6 hours. The antihypertensive effect persists over 24 hours after administration. During repeated administration, the maximum reduction in blood pressure with any dose is generally attained within 2 - 4 weeks and is sustained during long-term therapy. Abrupt withdrawal of valsartan has not been associated with rebound hypertension or other adverse clinical events.

Hydrochlorothiazide

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 sodium chloride transport in the distal convoluted tubule. The mode of action of thiazides is through inhibition of the sodium-chloride (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.

5.2 Pharmacokinetic properties

Linearity/non-linearity

Amlodipine, valsartan and HCTZ exhibit linear pharmacokinetics.

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 compound is bound to plasma proteins.

Biotransformation

Amlodipine is extensively (approximately 90 %) metabolized in the liver to inactive metabolites with 10 % of the parent compound and 60 % of the metabolites excreted in the urine.

Elimination

Amlodipine elimination from plasma is biphasic with a terminal elimination half-life of approximately 30 - 50 hours. Steady-state plasma levels are reached after continuous administration for 7 - 8 days. Ten percent 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 %. Valsartan shows multi exponential decay kinetics ($t_{1/2}$ α <1 h and $t_{1/2}$ β about 9 h). Food decreases the exposure (as measured by AUC) to valsartan by about 40 % and peak plasma concentration (C_{max}) by about 50 %, although from about 8 hours post dosing plasma valsartan concentrations are similar for the fed and fasted group. This reduction in AUC, however, is not 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 is primarily eliminated in faeces (about 83 % of dose) and urine (about 13 % of dose) mainly as unchanged compound. 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 h). The increase in mean AUC is linear and dose proportional in the therapeutic range.
Concomitant administration with food has been reported to both increase and decrease the systemic availability of hydrochlorothiazide compared with the fasted state. The magnitude of these effects is small and has little clinical importance. Absolute bioavailability of hydrochlorothiazide is 60 - 80 % after oral administration.

Distribution

The distribution and elimination kinetics have generally been described as a bi-exponential decay function, with a terminal half-life of 6 - 15 h. 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

HCTZ is eliminated as unchanged compound.

Elimination

Hydrochlorothiazide is eliminated from plasma with a half-life averaging 6 - 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 being excreted as unchanged compound in the urine.

Amlodipine/valsartan/hydrochlorothiazide

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

Pharmacokinetics in special patient groups

Elderly

Time to peak plasma amlodipine concentrations is similar in young and elderly patients. In elderly patients, amlodipine clearance tends to decline, causing increases in AUC and elimination half-life. 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 is not significantly influenced by renal impairment. There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. 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. The combination medicine is contraindicated in patients with severe renal impairment, anuria or undergoing dialysis (see section 4.3)**.**

Hepatic impairment

Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase in AUC 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, this combination is contraindicated in patients with hepatic impairment (see sections 4.2 and 4.3).

Paediatric population

No pharmacokinetic data are available in the paediatric population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone

Sodium lauryl sulphate

Coating

Ferric oxide yellow (E172) (only CALSAR CO 5/160/25 mg and CALSAR CO 10/160/25 mg)

Ferric oxide red (E172) (only CALSAR CO 10/160/12,5 mg and CALSAR CO 10/320/25 mg)

Macrogol

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep blisters in carton until required for use.

6.5 Nature and contents of container

CALSAR CO is packed in blisters (OPA/Alu/PVC – Alu): 7, 10, 14, 28, 30, 56, 60, 84, 90, 98, 100 film coated tablets, in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, 7945

Cape Town, South Africa

8. REGISTRATION NUMBERS

CALSAR CO 5/160/12,5 mg: A57/7.1.3/0101

CALSAR CO 5/160/25 mg: A57/7.1.3/0102

CALSAR CO 10/160/12,5 mg: A57/7.1.3/0103

CALSAR CO 10/160/25 mg: A57/7.1.3/0104

CALSAR CO 10/320/25 mg: A57/7.1.3/0105

9. DATE OF FIRST AUTHORISATION

18 March 2025