

CALSAR CO

SCHEDULING STATUS [53]

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/25 mg 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 6.9 mg (equivalent to amlodipine 5 mg), valsartan 160 mg and hydrochlorothiazide 12.5 mg. Contains sugar (sugar alcohol – mannitol 58.8 mg).

Each CALSAR CO 5 mg/160 mg/25 mg film coated tablet contains amlodipine besylate 6.9 mg (equivalent to amlodipine 5 mg), valsartan 160 mg and hydrochlorothiazide 25 mg. Contains sugar (sugar alcohol – mannitol 58.8 mg).

Each CALSAR CO 10 mg/160 mg/12.5 mg film coated tablet contains amlodipine besylate 13.9 mg (equivalent to amlodipine 10 mg), valsartan 160 mg and hydrochlorothiazide 12.5 mg. Contains sugar (sugar alcohol – mannitol 58.8 mg).

Each CALSAR CO 10 mg/160 mg/25 mg film coated tablet contains amlodipine besylate 13.9 mg (equivalent to amlodipine 10 mg), valsartan 160 mg and hydrochlorothiazide 25 mg. Contains sugar (sugar alcohol – mannitol 117.5 mg).

Each CALSAR CO 10 mg/320 mg/25 mg film coated tablet contains amlodipine besylate 13.9 mg (equivalent to amlodipine 10 mg), valsartan 320 mg and hydrochlorothiazide 25 mg. 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, biconvex, film coated tablets.

4.1. 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. Dosage and method of administration

Possology

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 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

• 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 these medicines

• hypersensitivity to angiotensin II receptor blockers (ARBs). These patients must never again be given these medicines

• concomitant use of fluoroquinolones 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 alkali-metal cations in patients with diabetes mellitus or renal impairment (Glomerular Filtration Rate (GFR) <60 mL/min/1.73 m²) (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 angioedema, especially 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 (ARBs) are not to be initiated during pregnancy. Patients planning pregnancy should be counselled 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 area 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

Valartan 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 when administered with impaired liver function, but dose recommendations have not been established.

Caution should be exercised when administering CALSAR CO to 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, 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/valsartan (25/160 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 higher 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.

Valartan:

Concomitant use with potassium supplements, potassium-sparing diuretics, salt substitutes containing potassium, or other medicines that may increase potassium levels (heparin, etc.) are 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 renal 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 pre-exal (cardiogenic) impairment of renal function.

If hypokalaemia develops during hydrochlorothiazide therapy, CALSAR CO should be discontinued until stable correction of the potassium balance.

Thiazide diuretics can precipitate renal onset hyponatraemia and hyponatraemic alkalosis or exacerbate pre-existing hyponatraemia. Thiazide diuretics should be administered without the urinary excretion of magnesium, which may result in hyponatraemia.

Hyponatraemia, accompanied by neurological symptoms (nausea, progressive disorientation, apathy) has been observed in patients receiving 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 sodium.

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 hyperuricaemia. Hydrochlorothiazide may raise the serum uric acid level due to reduced clearance of uric acid and may cause or exacerbate hyperuricaemia as well as precipitate gout in susceptible patients.

Thiazides reduce urinary calcium excretion and may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. 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 hydrochlorothiazide therapy.

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 tongue, causing airway obstruction and/or swelling of the face, lips, pharynx and/or larynx, 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 on CALSAR CO should be undertaken with caution and assessment of renal function.

In a long-term, placebo-controlled study of amlodipine in patients with NYHA (New York Heart Association Classification) II 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 4.4). A photosensitivity reaction could occur 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 UV light.

Acute angle-closure glaucoma

Hydrochlorothiazide, a sulphonamide, has been associated with an idiosyncratic renal 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 to be discontinued hydrochlorothiazide as rapidly as possible. Prompt medical or surgical treatment may not be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle closure glaucoma may include a history of suphonomamide 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 aldosterone antagonists is associated with hyperkalaemia and decreases renal function (including acute renal failure). Dual blockade of RAAS through the combined use of CALSAR CO and aldosterone antagonists is contraindicated (see section 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 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).

Exipients 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.

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 aldosterone antagonists:

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 aldosterone antagonists is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia and decreases renal function.

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).

Valartan

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:

ATP3A4 inhibitors (e.g. telaprevir, boceprevir, ritonavir): Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors potently inhibits,azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem may give rise to significant increase in amlodipine exposure. The clinical translation of these pharmacokinetic variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers (anticonvulsant agents (e.g. carbamazepine, phenobarbital, phenytoin, fosphenytoin, primidone), rifampicin, Hypericium 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 7.7 % increase in exposure to simvastatin. The concomitant use of amlodipine 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 and acute renal failure after intravenous administration of dantrolene. Due to the 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.

Valartan:

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 OATP1 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.

Valartan 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 inducing sympathetic central nervous system activity or direct vasodilation) may potentiate orthostatic hypotension.

Anaesthetics: Thiazides, including hydrochlorothiazide, may increase the risk of adverse reactions caused by anaesthesia or direct vasodilation.

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 cholinergic substances such as scopolamine 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 diuretics: Concomitant use of thiazide diuretics, including hydrochlorothiazide, with beta blockers may increase the risk of hypoglycaemia. 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, diagnosing 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.

