

SUMMARY OF PRODUCT CHARACTERISTICS

Asomex D 2.5 (S (-) Amlodipine 2.5 mg & Hydrochlorothiazide 12.5 mg) Tablets

Asomex D 5 (S (-) Amlodipine 5 mg & Hydrochlorothiazide 12.5 mg) Tablets

1. Name of the medicinal product

Asomex D 2.5/5 tablets

2. Qualitative and quantitative composition

Each uncoated tablet contains:

S (-) Amlodipine Besilate equivalent to S (-) Amlodipine.....2.5 mg

Hydrochlorothiazide.....12.5 mg

Excipients.....q.s.

Each uncoated tablet contains:

S (-) Amlodipine Besilate equivalent to S (-) Amlodipine.....5 mg

Hydrochlorothiazide.....12.5 mg

Excipients.....q.s.

3. Pharmaceutical form

Oral Tablets.

4. Clinical particulars

4.1 Therapeutic indications

Hypertension

4.2 Posology and method of administration

One tablet to be taken once daily.

Use in special population

Patients with renal impairment:

No controlled clinical study of s (-) amlodipine has been performed in patients with renal impairment. Caution should be taken while administering Asomex D to patients with renal impairment.

Patients with hepatic impairment:

Clinical studies in patients with normal liver function have shown that there is no elevation in the hepatic enzymes with the use of s (-) amlodipine.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thus, caution should be taken while administering Asomex D to patients with hepatic impairment.

Children:

Safety and effectiveness of this product in children have not been established. Hence Asomex D should be used in children.

Elderly:

No initial dose adjustment is required in this group of patients. Nevertheless, Asomex D should be used with caution in elderly patients as such patients may have impaired renal function.

Method of administration

Oral

4.3 Contraindications

- Hypersensitivity to amlodipine, dihydropyridine derivatives or sulphonamide-derived substances or to any of the excipients listed in section 6.1.
- Severe hypotension.
- Shock (including cardiogenic shock).
- Obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- Hemodynamically unstable heart failure after acute myocardial infarction.
- Therapy resistant hypokalaemia or hypercalcaemia;
- Severe hepatic impairment; cholestasis and biliary obstructive disorders;
- Refractory hyponatraemia;
- Symptomatic hyperuricaemia/gout;
- Severe renal impairment (i.e. creatinine clearance <30 ml/min);
- 2nd and 3rd trimesters of pregnancy (see sections 4.4 and 4.6);
- Anuria;
- The concomitant use of hydrochlorothiazide with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m²) (see sections 4.5 and 5.1).

4.4 Special warnings and precautions for use

Warning and precautions with racemic amlodipine shall also be applicable for s(-) amlodipine and the same are described below:

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. 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.

Patients with hepatic impairment

Clinical studies in patients with normal liver function have shown that there is no elevation in the hepatic enzymes with the use of s (-) amlodipine.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Asomex D is contraindicated for patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

No controlled clinical study of s (-) amlodipine has been performed in patients with renal impairment. However, caution should be taken while administering Asomex D to patients with renal impairment.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatremia, hypochloremic alkalosis, hypomagnesemia or hypokalemia which may occur during intercurrent diarrhoea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatraemia may occur in oedematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required (see section 4.5). Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients.

Eye disorders

Choroidal effusion, acute myopia and secondary angle-closure glaucoma:

Sulfonamide or sulfonamide derivative drugs can cause an idiosyncratic reaction resulting in choroidal effusion with visual field defect, transient myopia and acute angle-closure glaucoma. Symptoms include acute onset of decreased visual acuity or ocular pain and typically occur within hours to weeks of drug initiation. Untreated acute angle-closure glaucoma can lead to permanent vision loss. The primary treatment is to discontinue drug intake as rapidly as possible. Prompt medical or surgical treatments may need to be considered if the intraocular pressure remains uncontrolled. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Acute Respiratory Toxicity

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

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 two epidemiological studies based on the Danish National Cancer Registry. Photosensitizing actions of hydrochlorothiazide could act as a possible mechanism for NMSC.

Patients taking hydrochlorothiazide should be informed of the risk of NMSC and advised to regularly check their skin for any new lesions and promptly report any suspicious skin lesions. Possible preventive measures such as limited exposure to sunlight and UV rays and, in case of exposure, adequate protection should be advised to the patients in order to minimize the risk of skin cancer. Suspicious skin lesions should be promptly examined potentially including histological examinations of biopsies. The use of hydrochlorothiazide may also need to be reconsidered in patients who have experienced previous NMSC (see also section 4.8).

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematosus has been reported with the use of thiazides.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

S-amlodipine did not show any incidence of drug interaction when used along with aspirin, nitrates, beta-blockers, ACE inhibitors, H2 blockers, and Proton Pump Inhibitors.

However, the interactions with amlodipine shall also be applicable for s (-) amlodipine.

CYP3A4 inhibitors

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 resulting in an increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

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).

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.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, 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.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable

trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Hydrochlorothiazide

When given concurrently, the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, narcotics or antidepressants

Potential of orthostatic hypotension may occur.

Antidiabetic drugs (oral agents and insulin)

The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.

Other antihypertensive drugs

Additive effect.

Cholestyramine and colestipol resins

Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Corticosteroids, ACTH

Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (e.g. adrenaline)

Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine)

Possible increased responsiveness to the muscle relaxant.

Lithium

Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.

Medicinal products used in the treatment of gout (probenecid, sulfinpyrazone and allopurinol)

Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of probenecid or sulfinpyrazone may be

necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)

Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates

In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporine

Concomitant treatment with cyclosporine may increase the risk of hyperuricaemia and gout-type complications.

Digitalis glycosides

Thiazide-induced hypokalaemia or hypomagnesaemia may favour the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmics) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmics), hypokalaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmics (e.g. quinidine, hydroquinidine, disopyramide).
- Class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory Test Interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function (see section 4.4).

Carbamazepine

Risk of symptomatic hyponatremia. Clinical and biological monitoring is required.

Iodine Contrast Media

In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.

Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice)

Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalaemia.

4.6 Fertility, pregnancy and lactation

Pregnant women

There is no data available on the use of s (-) amlodipine in pregnant women, hence the drug should be administered only when the potential benefits outweighs the risk to the patient.

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 second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopaenia.

Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.

Asomex D should not be administered in pregnant women.

Nursing mothers

There is no data available on the use of s (-) amlodipine in nursing mothers, hence the drug should be administered only when the potential benefits outweighs the risk to the patient

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production.

Asomex D is not recommended during breastfeeding.

Fertility

There is no data available on the clinical use of s (-) amlodipine in fertility.

4.7. Effects on ability to drive and use machines

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking s-amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

No studies on the reactions on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

Asomex D can have minor or moderate influence on the ability to drive and use machines. Caution is recommended especially at the start of treatment.

4.8. Undesirable effects

Amlodipine

Side-effects reported with racemic amlodipine shall also be seen with s (-) amlodipine and the same are mentioned below.

The most commonly reported adverse reactions during treatment with amlodipine are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

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

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, mood changes (including anxiety), insomnia
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia

	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzyme increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain

Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased

*Mostly consistent with cholestasis

Hydrochlorothiazide

The adverse reactions below are classified where appropriate by system organ class and frequency according to the following convention:

very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

System organ class	Adverse reaction	Frequency
Blood and lymphatic system disorders	agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopaenia	uncommon
Immune system disorders	anaphylactic reaction	rare
Metabolism and nutrition disorders	anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia	uncommon
Psychiatric disorders	insomnia	uncommon
Nervous system disorders	cephalalgia	common
Eye disorders	transient blurred vision, xanthopsia	uncommon
	choroidal effusion, acute myopia, acute angle-closure glaucoma	not known
Vascular disorders	necrotising angiitis (vasculitis, cutaneous vasculitis)	uncommon
Respiratory, thoracic and mediastinal disorders	respiratory disorders including pneumonitis and pulmonary oedema	uncommon
	acute respiratory distress syndrome (ARDS) (see section 4.4)	very rare
Gastrointestinal disorders	sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation	uncommon
Hepato-biliary disorders	icterus (intrahepatic cholestasis), pancreatitis	uncommon
Skin and subcutaneous	photosensitivity, urticaria, toxic epidermal	uncommon

tissue disorders	necrolysis	
	cutaneous lupus erythematosus	not known
Musculoskeletal and connective tissue disorders	muscle cramps	uncommon
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)	not known
Renal and urinary disorders	glycosuria, interstitial nephritis, renal dysfunction, renal failure	uncommon
General disorders and administration site conditions	fever, dizziness	uncommon

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 and 5.1).

During post-marketing, the following adverse events were reported with s-amlodipine of Emcure: Diarrhoea, oedema, edematous feet or pedal edema, stomach pain, swelling of ankles, feet, legs and limbs, bilateral legs ankle region with feet pitting edema, dizziness, hypertension, fever, frequent urination, fall, ear buzzing, hands trembled, headache, hoarseness, feeling abnormal, depression, swallowing difficulty, sleeping difficulty, weight loss, blood pressure increased, generalised anxiety disorder, gastro intestinal bleeding, increased urinary frequency, cough, racing thoughts, fractures on the brain, overdose, body paraesthesia, boiling sensation of the body, facial swelling, warm hands, accelerated heart rate, tooth infection, burning tongue, depression, dysphagia, erectile dysfunction, skull fracture, sleepy, and spike in blood sugar level.

4.9 Overdose

There are no reported cases of overdosage with the use of s (-) amlodipine.

However, the symptoms observed with racemic amlodipine are also stated here, as they could occur in patients treated with s (-) amlodipine.

Amlodipine

In humans experience with intentional overdose is limited.

Symptoms:

Available data 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.

Treatment:

Clinically significant hypotension due to amlodipine overdosage 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.

Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalaemia, hypochloraemia, hyponatraemia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalaemia may accentuate cardiac arrhythmias.

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

5. Pharmacological properties**5.1 Pharmacodynamic properties****Amlodipine****Mechanism of action**

S(-)amlodipine, the chirally pure form of amlodipine is a calcium channel antagonist belonging to the dihydropyridine class. The S(-)isomer of amlodipine is found to possess greater pharmacological effects than R(+)amlodipine. S(-)amlodipine is 1000 times more potent than the R(+)isomer in binding to the dihydropyridine receptor. In humans, the dominant effects of amlodipine are consequent to vasodilation. S(-)amlodipine lowers peripheral vascular resistance without causing a reflex tachycardia. It is effective as a once daily dosage in the control of hypertension.

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx 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. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions:

- 1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.

- 2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

Non-melanoma skin cancer:

Based on available data from epidemiological studies, cumulative dose-dependent association between hydrochlorothiazide and NMSC has been observed.

5.2 Pharmacokinetic properties

Amlodipine

Administration of s (-) amlodipine 2.5 mg as a single dose in the fasting state produced maximum plasma concentration (C_{max}) of 8.30 ± 1.071 ng/ml in 2.73 ± 0.88 hrs. (T_{max}). Amlodipine is extensively (about 90%) converted to inactive metabolites via hepatic metabolism with 10% of the

parent compound and 60% of the metabolites excreted in the urine. Ex vivo studies have shown that approximately 93% of the circulating drug is bound to plasma proteins in hypertensive patients. The mean AUC_{0-t} value (t = 48 hrs.) of Tablet s (-) amlodipine (2.5mg) is 95.33 ± 14.45 ng.hr/ml. The AUC_{0-∞} value is recorded to be 140.91 ± 28.06 ng.hr/ml. The plasma elimination half-life of s (-) amlodipine has been found to be in the range of 14.62- 68.88 hrs.

The pharmacokinetics of racemic amlodipine is discussed below:

Absorption, distribution, plasma protein binding:

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.

The bioavailability of amlodipine is not affected by food intake.

Biotransformation/elimination

The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.

Hydrochlorothiazide

Distribution

Hydrochlorothiazide crosses the placental but not the blood-brain barrier and is excreted in breast milk.

Elimination

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours

5.3 Preclinical safety data

S-amlodipine

S-amlodipine is the active isomer of racemic amlodipine. Pre-clinical studies done with racemic amlodipine will therefore be equally applicable to the S-isomer as well.

Platelets are known to contribute to the initiation and progression of coronary artery narrowing by atherosclerotic plaques. Platelets also initiate periodic occlusive coronary arterial thrombosis that leads to unstable angina and myocardial infarction. Aspirin is the most widely used platelet inhibitor. However, if blood levels of epinephrine are elevated, some of the platelet inhibition produced by aspirin is diminished. Amlodipine, a second generation dihydropyridine calcium channel blocker, was studied in a widely used dog model of experimental coronary artery thrombosis. Amlodipine 1 mg/kg alone or amlodipine 0.4 mg/kg

with 5 mg/kg of aspirin I.V. completely abolished the experimental coronary thrombosis and prevented the exacerbation of coronary thrombosis by epinephrine 0.2 microg/kg/min. This protective effect did not appear until 60 minutes after the amlodipine was given, suggesting a delayed onset of action. Long-acting dihydropyridine calcium channel blockers are used in patients with hypertension, angina, and coronary artery disease. They also may offer the patient some protection against fatal or nonfatal myocardial infarction via their platelet-inhibiting effects (Int J Cardiol. 1997 Dec 31;62 Suppl 2: S111-7).

The cardioprotective effect of amlodipine, a long-acting dihydropyridine derivative, was studied in 2 experimental models of ischemia and reperfusion. Isolated and blood-perfused feline hearts were made globally ischemic for 60 minutes and then reperfused for 60 minutes. Alterations of left ventricular developed pressure and compliance were monitored in both amlodipine-treated hearts and saline-treated control animals. Changes in perfusion pressure indicated that amlodipine significantly reduced myocardial oxygen consumption and coronary vascular resistance. Furthermore, a progressive increase in resting left ventricular diastolic pressure indicated that amlodipine, administered before the onset of global ischemia, attenuated the development of ischemic contracture. Return of contractile function 60 minutes after reperfusion and maintenance of tissue concentrations of electrolytes were significantly better in the amlodipine-treated group than in the control animals. In intact canine hearts, regional myocardial ischemia was induced for 90 minutes, followed by 6 hours of reperfusion. Although the hemodynamic variables and the size of the region of risk did not differ significantly between treated animals and control animals, the infarct size was significantly smaller in the amlodipine-treated group than in the control animals, and a gradual reduction in coronary blood flow was observed in the control group that was prevented in the amlodipine group. A comparison of these findings with those observed with oxygen radical scavengers also is discussed (Am J Cardiol. 1990 Nov 20;66(18):10H-16H.).

In a study, hemodynamic actions of amlodipine were assessed and compared with those of nitrendipine using anesthetized dogs and were also investigated in conscious dogs with and without beta-adrenergic blockade. After bolus intravenous administration, amlodipine (25 to 1600 micrograms/kg) or nitrendipine (1 to 128 micrograms/kg) was administered to anesthetised dogs at 30-minute intervals, caused dose-related reductions in systemic and coronary vascular resistances with corresponding increases in cardiac output and coronary flow. Nitrendipine, unlike amlodipine, caused marked acute hypotension. The onset of action of amlodipine was markedly slower than that of nitrendipine, and effects were maintained for 30 minutes--recovery from nitrendipine was largely complete at 30 minutes. In conscious dogs, amlodipine (250, 500, 1000 micrograms/kg IV) caused dose-related reductions in systemic vascular resistance that approached maximum within 5 minutes and persisted for over 4 hours. There were no marked adverse effects on cardiac contraction or conduction. (Cardiovasc Drugs Ther. 1989 Aug;3(4):545-55).

Amlodipine, a second generation dihydropyridine calcium channel blocker, was studied in a widely used dog model of experimental coronary artery thrombosis. Amlodipine 1 mg/kg alone or amlodipine 0.4 mg/kg with 5 mg/kg of aspirin I.V. completely abolished the experimental coronary thrombosis and prevented the exacerbation of coronary thrombosis by epinephrine 0.2 microg/kg/min. This protective effect did not appear until 60 minutes after the amlodipine was given, suggesting a delayed onset of action. No toxic effects were observed with amlodipine at a dose of 1 mg/kg (Int J Cardiol. 1997 Dec 31;62 Suppl 2: S111-7).

The effects of amlodipine on ischemia-induced myocardial conduction delay was studied in anesthetized pigs paced at a constant heart rate. After intravenous injection of amlodipine (0.3 mg/kg, n = 6), subsequent periods of ischemia greatly reduced (p less than 0.01) all indexes of subepicardial conduction delay. In the subendocardium, amlodipine decreased only time to onset (-25 +/- 4%, p less than 0.01) within the ischemic zone. Significant delays in all indexes were present during repeated ischemic periods in the placebo-treated control group (n = 5). Amlodipine also increased regional myocardial blood flow within the nonischemic myocardium by 25 +/- 10% and decreased mean aortic pressure by 7 +/- 2% without altering flow in the ischemic region. Left atrial pressure remained unchanged. Indexes of ischemia-induced conduction delay were more rapidly restored after reperfusion in amlodipine-pretreated than in control animals. In conclusion, amlodipine produced a beneficial blood flow-independent effect on ischemia-induced injury potentials at 0.3 mg/kg dose with no adverse effects observed (Am J Cardiol. 1989 Nov 7;64(17):78I-83I).

The effects of amlodipine on subendocardial segment shortening (%SS), regional myocardial blood flow, myocardial high-energy phosphate levels and tissue water content were compared to those of a saline-treated group of barbitol-anesthetized dogs subjected to a 45-minute coronary artery occlusion followed by 60 minutes of reperfusion. Saline or amlodipine (200 micrograms/kg, IV) were administered 15 minutes prior to coronary occlusion. There were no significant differences between groups in ischemic bed size or hemodynamics, although dP/dt was higher following amlodipine. Subepicardial collateral blood flow was higher in the amlodipine group during coronary occlusion. Following occlusion, %SS in the ischemic region was markedly decreased in both series and passive systolic lengthening resulted. In spite of similar decreases in %SS during occlusion, the amlodipine- treated dogs showed a marked improvement in myocardial segment function (%SS) of the ischemic-reperfused region throughout 60 minutes of reperfusion as compared to saline-treated animals. In addition, amlodipine prevented the rebound increase in phosphocreatine and attenuated the loss of adenine nucleotides and the increase in tissue water in the ischemic-reperfused area at 60 minutes of reperfusion. These results suggest that amlodipine has a favorable effect on the functional and metabolic recovery of the ischemic-reperfused myocardium (Cardiovasc Drugs Ther. 1989 Aug;3(4):535-43).

The efficacy of amlodipine (AML) was tested in hypertensive cats in a placebo-controlled, randomized, blinded clinical trial. Five cats were randomized to receive 0.625 mg AML once daily and 4 cats to receive placebo (PLA) once daily. The average systolic blood pressure (SBP) recorded by the Doppler method on day 0 was 212 +/- 21 mm Hg in the AML group and 216 +/- 32 mm Hg in the PLA group. On day 7, the cats receiving AML had a significantly lower average daily SBP (160 +/- 30 mm Hg) but SBP in the PLA group was unchanged (207 +/- 31 mm Hg). On day 7, all cats receiving PLA and one cat receiving AML were crossed over to the other group because of inadequate response. Blood pressure did not decrease adequately in 3 cats by day 14 (7 days of PLA and 7 days AML) and the treatment code was broken. Each of these cats was subsequently administered 1.25 mg AML daily. Cats requiring 1.25 mg AML once daily (6.1 kg +/- 0.7 kg) weighed significantly more than cats that responded to 0.625 mg AML once daily (4.1 +/- 0.7 kg). The average daily SBP recorded in the 6 cats that completed the study was significantly lower after 16 weeks of treatment (152 +/- 14 mm Hg) compared to day 0 (221 +/- 24 mm Hg). SBPs measured 24 hours after AML administration were similar to the average daily SBP, suggesting that AML effectively controlled SBP for a 24-hour period. AML was shown to be an effective once-daily antihypertensive agent when administered to cats at a dosage of 0.18 +/- 0.03 mg/kg (J Vet Intern Med. 1998 May-Jun;12(3):157-62).

The antihypertensive effects of oral administration of amlodipine (AML), were investigated in hypertensive animals. In renal hypertensive dogs (RHD), the effect of AML (0.1, 0.3, 1.0 mg/kg) was maximum at 4-6 hr and long-lasting, producing similar reductions of both systolic and diastolic BP (ED₃₀: 0.3-0.4 mg/kg respectively). In RHD (0.2 mg/kg/day for 20 days) chronically receiving AML, there was an enhancement of the antihypertensive effect of AML within a few days after starting chronic dosing, and thereafter a significant reduction of BP at 24 hr after dosing and constant effects of AML during subsequent treatment. BP after cessation of the chronic dosing gradually recovered to the level before the start of the experiments. No significant changes in HR were observed throughout the experiments. These results indicate that AML produces the antihypertensive effect with a similar potency to nifedipine but with a profile of slow onset and long duration, and there was no development of tolerance to the antihypertensive effects and changes of HR during long-term treatment (Nippon Yakurigaku Zasshi. 1991 Feb;97(2):115-26).

In another study 10 cats with partial nephrectomy were administered 0.25 mg of amlodipine/kg, PO, q 24 h (group A). Ten cats with partial nephrectomy served as a control group (group C). Systolic BP (SBP), diastolic BP (DBP), and mean BP (MBP), physical activity, and pulse rate were measured continuously for 36 days by use of radiotelemetric devices. Compared with values for clinically normal cats, SBP, DBP, and MBP were significantly increased in cats of group C. Cats in group A had significant reduction in SBP, DBP, and MBP, compared with values for cats in group C. Albuminuria but not urine protein-to-creatinine ratio was significantly correlated ($R^2 = 0.317$) with SBP in hypertensive cats. Prevalence of ocular lesions attributable

to systemic hypertension in group C (7 cats) was greater than that observed in group A (2). In conclusion, amlodipine had an antihypertensive effect in cats with coexistent systemic hypertension and renal insufficiency (Am J Vet Res. 2002 Jun;63(6):833-9).

Hydrochlorothiazide

Although equivocal evidence for a genotoxic or carcinogenic effect was found in some experimental models, the extensive human experience with hydrochlorothiazide has failed to show an association between its use and an increase in neoplasms.

6. Pharmaceutical particulars

6.1 List of excipients

Asomex D 2.5

Pregelatinised starch

Lake FD&C yellow No 6 (Sunset yellow)

Microcrystalline Cellulose (PH 102)

Colloidal Silicon Dioxide

Sodium Starch Glycolate

Talc

Magnesium Stearate

Asomex D 5

Pregelatinised starch

Lake of Quinoline yellow

Microcrystalline Cellulose (PH 102)

Colloidal Silicon Dioxide

Sodium Starch Glycolate

Talc

Magnesium Stearate

6.2 Incompatibilities

None of the in-active ingredients of the formulation have been known to exhibit incompatibility with the active ingredients.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a dry and dark place, below 30°C.

6.5 Nature and contents of container

10 tablets are packed in a Alu-PVC Blister pack (Amber color PVC film & printed Aluminium foil). 3 such blisters are packed in a printed carton along with leaflet.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

Emcure Pharmaceuticals Limited

8. Marketing authorization number(s)

Asomex D 2.5 – CTD409

Asomex D 5 – CTD1944

9. Date of first authorization/renewal of the authorization

Asomex D 2.5 – 04.10.2012

Asomex D 5 – 04.09.2014

10. Date of revision of the text

27.11.2025