SUMMARY OF PRODUCT CHARACTERISTICS

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

1. Name of the medicinal product
Asomex D 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.
Colour: Lake of sunset Yellow**.**

3. Pharmaceutical form
Tablets

4. Clinical particulars
4.1 Therapeutic indications
Hypertension

4.2 Posology and method of administration
One tablet to be taken once daily.

Patients with renal impairment: No dosage adjustment is necessary for amlodipine for patients with renal impairment. Similar effects are expected with S(-)amlodipine. Periodic monitoring of renal function is advised.

There is no data available for the use of Asomex D in patients with renal impairment. Thus, caution may be necessary when giving Asomex D in these patients.

Patients with hepatic impairment: There is no data available for the use of Asomex D in patients with hepatic impairment. Asomex D should be used with caution in patients with impaired hepatic function.

Children: Safety and effectiveness of this product in children have not been established.

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

<u>Method of administration</u>
Oral

4.3 Contraindications

- Hypersensitivity to amlodipine 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);

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. 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

Amlodipine should be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Asomex D should be given with caution in patients with hepatic impairment.

Elderly patients

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

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

There is no data available for the use of Asomex D in patients with renal impairment. Thus, caution may be necessary when giving Asomex D in these patients.

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.

Hepatic impairment

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.

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.

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)

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.

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

Alcohol, barbiturates, narcotics or antidepressants

Potentiation 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 antiarrythmics (e.g. quinidine, hydroquinidine, disopyramide).

• Class III antiarrythmics (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

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

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 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.

Nursing mothers

Asomex D is not recommended during breastfeeding.

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 amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. When driving vehicles or operating machines 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.

4.8. Undesirable effects

On the basis of the clinical data available, no adverse events have been reported with the use of S (-) Amlodipine.

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

During post-marketing, the following adverse events were reported with s-amlodipine of Emcure:

Peripheral edema, palpitations, increased blood glucose, gastrointestinal hemorrhage, pollakiuria, headache, fall, somnolence, erectile dysfunction, tinnitus, tongue discomfort, depression, hypertension, dysphagia, insomnia, decreased weight, generalized anxiety disorder, cough, feeling abnormal, tooth infection, upper abdominal pain, dizziness, skull fracture, pyrexia, diarrhea.

The other adverse reactions reported during treatment with amlodipine and hydrochlorothiazide with the following frequencies included:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Uncommon	agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopaenia
Immune system disorders	Rare	anaphylactic reactions
Metabolism and nutrition disorders	Uncommon	anorexia, hyperglycaemia, hyperuricaemia, hypokalaemia, hyponatraemia
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), cephalalgia
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia, sleep disorders
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder
Eye disorders	Common	Visual disturbance (including diplopia)
	Uncommon	transient blurred vision, xanthopsia
	Not known	choroidal effusion, acute myopia, acute angle-closure glaucoma
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, necrotizing angiitis (vasculitis, cutaneous vasculitis)
	Common	Dyspnoea

Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, rhinitis, respiratory distress including pneumonitis and pulmonary oedema
	Very rare	acute respiratory distress syndrome (ARDS) (see section 4.4)
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth, sialoadenitis, spasms, stomach irritation
	Very rare	gastritis, gingival hyperplasia
Hepatobiliary disorders	Uncommon	icterus (intrahepatic cholestasis), pancreatitis
	Very rare	Hepatitis, jaundice, hepatic enzyme increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria, photosensitivity, toxic epidermal necrolysis
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema,
	Not known	Cutaneous lupus erythematosus
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma)
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency, glycosuria, interstitial nephritis, renal dysfunction, renal failure
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, fever, dizziness
Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

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).

4.9 Overdose

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.

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

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.

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.

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.

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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.

The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle.

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

5.2 Pharmacokinetic properties

Bioequivalence study has been conducted on higher strength of Asomex-D5 (S-Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg tablets).

A randomized, single dose, two treatment, two period, open label, crossover study in 24(+4) healthy human male subjects under fasting condition. After overnight fasting, subjects were randomly assigned to receive either one tablet of test product [Asomex-D5 (S-Amlodipine and Hydrochlorothiazide) tablets containing 5mg of S-Amlodipine and 12.5 mg Hydrochlorothiazide] or reference product [Asomex-5 S-Amlodipine Besylate) tablet containing 5mg S-Amlodipine and Microzide (Hydrochlorothiazide) capsule containing 12.5mg of Hydrochlorothiazide].

For S-Amlodipine the percentage ratios of least square means of the Test product versus reference product were found to be comparable for C_{max} (100.38 %), AUC0-t (101.48%), AUC0-inf (101.51%).

The 90% CI of log transformed data comparing Test for C_{max} was 96.40 %-104.65, for AUC0-t it was 96.23 -107.19% and AUC0-inf it was 96.32-107.155 %. All values are between acceptance criteria of 80 % -125 %.

For Hydrochlorothiazide the percentage ratios of least square means of the Test product versus reference product were found to be comparable for C_{max} (100.69 %), AUC0-t (96.89%), AUC0-inf (96.83%).

The 90% Cl of log transformed data comparing Test for C_{max} was 95.73 %-105.91 %, for AUC0-t it was 88.67 %-106.81% and AUC0-inf it was 88.67 %-106.65 %. All values are between acceptance criteria of 80 % -125 %.

Test product meets the Bioequivalence criteria when compared with reference product.

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 barbital-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 (R2 = 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).

6. Pharmaceutical particulars

6.1 List of excipients

1. Hydrochlorothiazide
2. Microcrystalline Cellulose
3. Pregelatinised Starch

4. Lake FD&C Yellow No. 6 (Sunset Yellow)
5. Colloidal Silicon Dioxide
6. Sodium Starch Glycolate
7. Talc
8. Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Proposed 36 months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Asomex-D tablets are packed in blister pack [Amber colured PVDC coated PVC film/Aluminium foil] of 10 tablets.

The proposed pack size for Asomex-D tablets is blister pack of 3 x 10 tablets in a carton along with pack insert.

6.6 Special precautions for disposal and other handling

Asomex-D tablets are packed in blister pack [Amber colured PVDC coated PVC film/Aluminium foil] of 10 tablets.

The proposed pack size for Asomex-D tablets is blister pack of 3 x 10 tablets in a carton along with pack insert.

7. Marketing authorization holder

Emcure Pharmaceuticals Limited, India.

8. Marketing authorization number(s)

Not Applicable

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text
02.08.2023