SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Asomex LT tablets

2. Qualitative and quantitative composition
Each uncoated tablet contains:
S (-) Amlodipine Besilate equivalent to S (-) Amlodipine…….2.5 mg
Losartan Potassium USP…….50 mg

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. No dosage adjustment is needed for losartan in patients with renal impairment unless they are volume-depleted.

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

Patients with hepatic impairment: There is no data available for the use of Asomex LT in patients with hepatic impairment.

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range for amlodipine. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment.

Similar effects are also expected with S (-) amlodipine. Asomex LT should be given with caution in patients with hepatic impairment.

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 LT 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 the active substance 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.
- 2nd and 3rd trimester of pregnancy
- Severe hepatic impairment
- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)

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.

In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.

There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, Asomex LT should be used with caution in these patient groups.

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.

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience with losartan in patients with severe hepatic impairment. Therefore, losartan must not be administered in patients with severe hepatic impairment.

Asomex LT 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.

Medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin-angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.

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

Hypersensitivity

Angioedema: Patients with a history of angiooedema (swelling of the face, lips, throat, and/or tongue) should be closely monitored.

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, including losartan. These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, losartan should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

Hypotension and Electrolyte/Fluid Imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used.

Electrolyte imbalances

Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. Plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.

The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes or other drugs that may increase serum potassium (e.g trimethoprim-containing products) with losartan is not recommended.

Renal transplantation

There is no experience in patients with recent kidney transplantation.

Primary hyperaldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

heart disease and cerebrovascular disease

As with any antihypertensive agents, excessive blood pressure decrease in patients with ischaemic cardiovascular and cerebrovascular disease could result in a myocardial infarction or stroke.

<u>Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy</u>

As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Pregnancy

Asomex LT should not be initiated during pregnancy. Unless continued losartan therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately, and, if appropriate, alternative therapy should be started

As observed for angiotensin converting enzyme inhibitors, losartan and the other angiotensin antagonists are apparently less effective in lowering blood pressure in black people than in non-blacks, possibly because of higher prevalence of low-renin states in the black hypertensive population.

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

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 due to risk of risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

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.

Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.

Losartan is predominantly metabolised by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin, trimethoprim-containing products), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors Co-administration of lithium and losartan should be undertaken with caution and serum lithium level monitoring is recommended.
When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.
Grapefruit juice contains components that inhibit CYP450 enzymes and may lower the concentration of the active metabolite of losartan which may reduce the therapeutic effect. Consumption of grapefruit juice should be avoided while taking losartan tablets.

4.6 Fertility, pregnancy and lactation

Pregnant women

Asomex LT is contraindicated during pregnancy. Exposure to Angiotensin II Receptor Inhibitors (AIIRA) therapy during the second and third trimesters is known to induce human foetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalaemia).

Nursing mothers

Asomex LT is not recommended during breastfeeding.

Fertility

Reversible biochemical changes in the head of spermatozoa have been reported in some patients treated by calcium channel blockers. Clinical data are insufficient regarding the potential effect of amlodipine on fertility.

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.

The other adverse reactions reported during treatment with amlodipine and losartan 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	Very rare	Leukocytopenia, thrombocytopeni a
	Not known	Anemia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
	Rare	hypersensitivity reactions, anaphylactic reactions, angioedema*, and vasculitis**
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, sleep disorders
	Very rare	Hypertonia, peripheral neuropathy
	Not known	Extrapyramidal disorder, migraine
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Common	vertigo
	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation), angina pectoris, cerebrovascular accident
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	(orthostatic) Hypotension (including dose-related orthostatic effects)
	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*
	Uncommon	Liver function abnormalities

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
	Not known	rhabdomyolysis
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
	Not known	Urinary tract infection, and flu-like symptoms
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, increase in blood urea, serum creatinine, and serum potassium
	Common	Hyperkalemia, hypoglycaemia
	Rare	increased alanine aminotransferase (ALT) [§]
	Not known	hyponatremia

*mostly consistent with cholestasis
**Including Henoch-Schönlein purpura
[§]Usually resolved upon discontinuationDuring post-marketing, the following adverse events were reported with s-amlodipine of Emcure:

Wrong technique in product usage process, upper gastrointestinal haemorrhage, toxicity to various agents, tooth infection, abdominal pain upper, tongue discomfort, depression, hypertension, dysphagia, insomnia, weight decreased, generalised anxiety disorder, cough, feeling abnormal, product administration error, tinnitus, peripheral swelling, thrombocytopenia, gingival hypertrophy, therapy partial responder, off label use, therapy non-responder, fall, sinusitis, upper limb fracture, therapeutic product effect incomplete, therapeutic product effect decreased, abdominal discomfort, nausea, pain, syncope, sars-cov-2 test positive, orthostatic hypotension, swelling, dizziness, somnolence, sleep disorder, urticaria, product use in unapproved indication, skin irritation, skin hyperpigmentation, pruritus, rash, skin abrasion, skin lesion, cerebrovascular accident, kaposi's sarcoma, psychological trauma, skin discolouration, thinking abnormal, sinus congestion, secretion discharge, skin burning sensation, skin disorder, skin exfoliation, accidental exposure to product, emotional distress, haemorrhagic diathesis, inappropriate schedule of product administration, incorrect dose administered, injection site haemorrhage, joint swelling, malaise, diarrhoea, dry skin, asthenia, fatigue, hypoaesthesia, renal impairment, blood pressure increased, drug hypersensitivity, laboratory test abnormal, dizziness postural, oedema peripheral, rash pruritic, pyrexia, product substitution issue, pain in extremity, presyncope, poor quality sleep, poor quality product administered, pollakiuria, palpitations, tremor, oedema, skin tightness, ototoxicity, oral discomfort, headache, non-hodgkin's lymphoma stage iv, drug ineffective, eructation, myocardial infarction, muscle spasms.

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo (frequencies not known): back pain, urinary tract infection, and flu-like symptoms.

Renal and urinary disorders:
As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal function may be reversible upon discontinuation of therapy.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via national Pharmacovigilance Electronic Reporting Systems.

4.9 Overdose
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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

S (-) amlodipine - Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01. *Losartan* - Angiotensin II Receptor Antagonists, ATC code: C09CA01.

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.
Losartan is a synthetic oral angiotensin-II receptor (type AT_1) antagonist. Angiotensin II, a potent vasoconstrictor, is the primary active hormone of the renin/angiotensin system and an important

determinant of the pathophysiology of hypertension. Angiotensin II binds to the AT_1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland, kidneys and the heart) and elicits several important biological actions, including vasoconstriction and the release of aldosterone. Angiotensin II also stimulates smooth muscle cell proliferation.

Losartan selectively blocks the AT_1 receptor. *In vitro* and *in vivo* losartan and its pharmacologically active carboxylic acid metabolite E-3174 block all physiologically relevant actions of angiotensin II, regardless of the source or route of its synthesis.

Losartan does not have an agonist effect nor does it block other hormone receptors or ion channels important in cardiovascular regulation. Furthermore losartan does not inhibit ACE (kininase II), the enzyme that degrades bradykinin. Consequently, there is no potentiation of undesirable bradykinin-mediated effects.
During administration of losartan, removal of the angiotensin II negative feedback on renin secretion leads to increased plasma renin activity (PRA). Increase in the PRA leads to an increase in angiotensin II in plasma. Despite these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin II receptor blockade. After discontinuation of losartan, PRA and angiotensin II values fell within three days to the baseline values.
Both losartan and its principal active metabolite have a far greater affinity for the AT_1-receptor than for the AT_2-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

5.2 Pharmacokinetic properties

A randomized, open label, two treatment, two period, two sequence, two way crossover, single dose, bioequivalence study compared FDC of S-Amlodipine 5 mg and losartan potassium 50 mg with S-Amlodipine 5 mg tablets and losartan potassium 50 mg in 24 + 4 healthy adult human male subjects. The study was sponsored by Emcure Pharmaceuticals Limited. The study concluded that the test formulation of FDC of S-Amlodipine 5 mg and losartan potassium 50 mg was bioequivalent to S-Amlodipine 5 mg tablets and losartan potassium 50 mg, components of reference formulation (FDC of losartan and S-Amlodipine BE Study).
After administration of tablet containing losartan potassium 50 mg and S-Amlodipine 5 mg, following pharmacokinetic parameters were observed:

Pharmacokinetic Parameter	**Test**	**Reference**	**% Ratio with respect to the Reference Product**
Losartan			
C_{max} (ng/mL)	242.46	243.90	99.41
AUC_{0-72} (ng x hr/mL)	1145.666	1195.671	95.82
AUC_{0-inf} (ng x hr/mL)	1185.787	1203.748	96.27
T_{max} (hrs)	1.81	1.71	106.10
S(-) Amlodipine			
C_{max} (ng/mL)	8.32	8.41	98.99
AUC_{0-72} (ng x hr/mL)	288.228	284.860	101.18
AUC_{0-inf} (ng x hr/mL)	328.385	332.042	98.90
T_{max} (hrs)	7.75	8.00	98.88

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 aswell.

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 r e b ou nd 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).

Losartan
Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

6. Pharmaceutical particulars

6.1 List of excipients
S(-) amlodipine Besilate, Losartan potassium, Microcrystalline Cellulose, Croscarmellose Sodium, Purified water, Colloidal Silicon Dioxide, Purified talc, Lake of Quinoline yellow, Magnesium Stearate.

6.2 Incompatibilities
NA

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store in a dry & dark place. Below 30°C.

6.5 Nature and contents of container
10 tablets are packed in PVDC coated PVC film and Aluminium foil (0.02 mm) blister pack. 2 composite blister strips of 3x10 tablets each are placed in a printed carton.

6.6 Special precautions for disposal and other handling
Store in a cool, dry and dark place, below 30°C.
KEEP AWAY FROM THE REACH OF CHILDREN

7. Marketing authorization holder

Emcure Pharmaceuticals Ltd.

8. Marketing authorization number(s)

21256

9. Date of first authorization/renewal of the authorization

26.07.2026

10. Date of revision of the text

26.07.2026