1. NAME OF THE MEDICINAL PRODUCT

S Numlo 2.5 Tablets (S (-) Amlodipine Besilate Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
S (-) Amlodipine Besilate
Equivalent to S (-) Amlodipine….. 2.5 mg
Excipients….q.s.
Colour: Yellow Oxide of Iron

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Faint yellow coloured, uncoated heart shaped scored tablet.

4. Clinical particulars

4.1 Therapeutic indications

- Hypertension
- Angina pectoris

4.2 Posology and method of administration

The normal recommended dose of S (-) Amlodipine is 2.5 mg once daily in the treatment of hypertension and angina pectoris. If required, the dose may be increased up to 5 mg once daily

4.3 Contraindications

- Hypersensitivity to dihydropyridine derivatives, amlodipine 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).
- Haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special warnings and precautions for use

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

General: Since the vasodilation induced by S (-) Amlodipine besilate is gradual in

onset, acute hypotension has not been reported after oral administration of S (-) Amlodipine.

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:

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore 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.

Elderly patients

In the elderly increase of the dosage should take place with care. No controlled clinical study of S (-) Amlodipine has been performed in 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 (-) Am lod i pi ne. However, cautio n should be t ake n w hile administering S (-) Amlodipine to patients with hepatic impairment.

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.No controlled clinical study of S (-) Amlodipine has been performed in patients with renal impairment. Hence caution should be taken while administering S (-) Amlodipine to patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on 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.
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.

4.6 Pregnancy and Lactation

Pregnancy:
The safety of amlodipine in human pregnancy has not been established. In animal studies, reproductive toxicity was observed at high doses.
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus. 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.

Breast-feeding

Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. 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

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. In one rat study, adverse effects were found on male 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. Caution is recommended especially at the start of treatment.

4.8 Undesirable effects

On the basis of Clinical reports available, no adverse reactions have been

reported with the use of S (-) amlodipine

Summary of the safety profile

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 (≥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).

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
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
	Common	Dyspnoea

Respiratory, thoracic and mediastinal disorders	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

Exceptional cases of extrapyramidal syndrome have been reported.

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. Hence, caution should be taken in case of an overdosage with S (-) Amlodipine.

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.

There are no reported cases of overdosage with the use of S (-) Amlodipine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

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.

Clinical experience

SESA (Safety and efficacy of S-Amlodipine) study was designed to evaluate the efficacy and tolerability of effects of S-Amlodipine (JAMA-India, August 2003-Vol 2, No. 8, 87- 92). This study involved 1859 patients with hypertension from 359 different centers across India. This study states that S-Amlodipine has an excellent antihypertensive activity and is highly beneficial in all grades of hypertension with

concomitant cardiovascular diseases like angina pectoris. The SESA study also enrolled 552 patients who were earlier treated with conventional Amlodipine. Out of these, 314 patients presented with peripheral edema at the time of enrollment. When these patients were switched over to S-Amlodipine, in 310 (98.72%) patients, edema was found to be completely resolved. These patients remained without edema thereafter. The findings of this study therefore state that S-Amlodipine 2.5/5 mg was found to be effective and well tolerated in the treatment of hypertension and is an ideal switch over therapy for patients having peripheral edema with conventional Amlodipine.

A randomized double blind, double dummy multicentric parallel group comparative clinical trial of S Amlodipine 2.5mg versus Amlodipine 5mg in the treatment of mild to moderate hypertension was carried out (JAMA-India, Aug 2002, 86-92).

The objective of the study was to compare the efficacy and safety of 2.5mg S-Amlodipine with 5 mg of Amlodipine in the treatment of mild to moderate hypertension in 50 patients. The reduction in the average systolic & diastolic blood pressure, in the standing, supine and sitting postures in the S-Amlodipine group, as well as in the Amlodipine group after 6 weeks of treatment was highly significant (C.I. = 0.95). The reduction in total cholesterol as well as triglycerides was found to be statistically significant in the S- Amlodipine treatment group, whereas the other parameters did not show any statistically significant change. This observation carries significance in clinical practice, since Indian population is known to suffer from hypertriglyceridaemia as well as Hypercholesterolaemia. Thus S- Amlodipine on long term use may help to improve the lipid profile of the hypertensive patients, who are usually associated with Hyperlipidemia. None of the patients reported any adverse drug events during the study period. The results showed that since only half the racemate of Amlodipine was pharmacologically active, the dose of S Amlodipine could be reduced to half. Pure form of S Amlodipine shows similar efficacy as that of racemic Amlodipine in the treatment of hypertension. There were no adverse effects reported in both the treatment groups in 2 months study period. Significant differences in tolerability can be seen on long- term use.

A similar study was conducted to compare the efficacy and tolerability of S-Amlodipine 2.5 mg with Amlodipine 5 mg in the treatment of mild of moderate hypertension (JAPI March 2004; 52, 197-202). Two hundred patients of both sexes, with clinically confirmed stage 1 and stage 2 hypertension were enrolled for the study. The reduction in the average systolic and diastolic blood pressure was found to be statistically significant. Although both the treatment groups showed significant reduction in the average systolic and diastolic blood pressure, the reduction was not found to be statistically significant between the two treatment groups. The reduction in total cholesterol as well as triglycerides was found to be higher in the S-Amlodipine treatment group. None of the patients in either drug group reported any adverse drug effects.

Hence it may be concluded that 2.5 mg daily dose of S-Amlodipine has a better effect on the lipid profile of the patients, where as its blood pressure lowering activity is similar to that of 5 mg daily dose of racemic Amlodipine. From the present study it can be concluded that, S-Amlodipine 2.5 mg is equivalent in efficacy to Amlodipine 5 mg in the treatment of mild to moderate hypertension.

Another randomized double blind, double dummy multicentric parallel group comparative clinical trial of S Amlodipine 2.5mg versus Amlodipine 5mg in the treatment of mild to moderate hypertension was carried out. The objective of the study was to compare the efficacy and safety of 2.5mg S- Amlodipine with 5 mg of Amlodipine in the treatment of mild to moderate hypertension. There was a significant reduction in systolic and diastolic BP of hypertensive patients in both of the treatment groups. The reduction in triglycerides was found to be statistically significant in both the treatment groups. None of the patients reported the adverse events (Indian Journal of Clinical Practice, April 2003, 49-54).

An open non-comparative PMS study to assess the efficacy and tolerability of S- Amlodipine 2.5 / 5 mg in the treatment of hypertension was carried out in 1042 patients with hypertension from 121 centers across India. All patients were given either 2.5/5 mg of S-Amlodipine (Asomex) depending upon the baseline BP values. Patients with history of MI, cerebrovascular accident, asthma, anemia, edema with earlier treatment and obesity were also included in the study. Results were analyzed by student's 't' test. Reduction in the average SBP and DBP in S-Amlodipine 2.5 and 5 mg group after 4 weeks of treatment was found to be statistically significant. The average SBP and DBP reduced from 161/99 mm Hg to 132/84 mm Hg in the 2.5 mg group (n=848); and from 180/107mm Hg to 138/86mm Hg in the 5 mg group (n=194) after 4 weeks. Of the 247 patients, 243 (98.38%) reported resolution of edema after switching over from conventional Amlodipine to Asomex. Only 21 patients reported mild side effects, such as vertigo, tachycardia, cough, headache, fever, difficulty in breathing and edema (1.15%). S-Amlodipine 2.5 and 5 mg are effective and well tolerated in the treatment of hypertension and is an ideal switch over therapy for patients having peripheral edema with conventional Amlodipine.

The database on Amlodipine, a calcium antagonist of the 1,4-dihydropyridine class, was obtained from clinical trials in the United States, Canada, and Europe. The clinical dossier describing the efficacy and safety of once-daily Amlodipine in the treatment of hypertension is extensive, well organized, and logically designed. It shows that Amlodipine is an effective antihypertensive drug, providing smooth 24 hr blood pressure control without orthostatic hypotension, and that it is well tolerated as monotherapy and in combination with other antihypertensive drugs. A total of 18 clinical studies were reviewed; 1,091 patients received Amlodipine whereas 805 received either placebo or another drug for comparison. The common entry criteria include a supine and standing diastolic blood pressure in the range 95-114 mg Hg. Blood pressure measurements were made 24 hr after the last dose of Amlodipine in all studies. Amlodipine is clearly superior to placebo and induces a clinically significant reduction in blood pressure (mean reductions 23/13 mm Hg supine, 24/12 upright in one representative study) with similar heart rates in the supine and standing positions. Blood pressure control shows a smooth profile over 24 hr with once-daily dosing, and there is no tolerance with long-term administration of the drug. The useful clinical dose is in the range of 5-10 mg, which is well tolerated in comparison with clinical doses of atenolol, hydrochlorothiazide, or verapamil. Amlodipine can be used as monotherapy in a large proportion of patients but may also be combined with a beta-blocker, diuretic, or angiotensin converting enzyme inhibitor. Based on these observations, Amlodipine may prove to be an attractive addition to our antihypertensive armamentarium (J Cardiovasc Pharmacol 12(7): p. S27-S33 (1988)).

A 20-week, open-label, uncontrolled clinical investigation of the long-acting calcium antagonist Amlodipine was conducted in 33 male or female patients with essential hypertension and left ventricular hypertrophy (LVH). A once-daily dose (5-10 mg/day) of Amlodipine provided a consistent antihypertensive effect, reducing the sitting diastolic (- 13.8% change) and systolic (- 13.0% change) blood pressures by clinically meaningful and statistically significant ($p = 0.0001$, $n = 33$) amounts. Amlodipine had no effect on heart rate. A significant regression in LVH was seen (left ventricular mass index reduced from 169.0 [SD 30.7] g/m (2) to 140.6 [SD 19.6] g/m (2), $p < 0.01$, $n = 12$). There was also a significant reduction in total peripheral resistance and

improvement in left ventricular diastolic filling (E/A ratio increased from 0.86 pre-treatment to 1.03 post-treatment, p = 0.038, n = 12). These results are consistent with other studies in showing that a relatively short treatment regimen with Amlodipine is associated with a significant reduction in left ventricular mass index (Cardiology 96(1): p.10-18 (2001)).

The use of cyclosporin A (CsA) has improved the success of renal transplantation, but is associated with hypertension and significant renal toxicity. Previous reports suggest that calcium channel blockers may be useful in opposing the adverse effects of CsA. A study evaluated the effects of Amlodipine (5 mg, once daily for 8 weeks) on renal function in 2 7 normotensive renal transplant recipients with stable renal function, in a double-blind, placebo-controlled, multicentre, cross over study. Amlodipine significantly reduced serum creatinine concentration relative to placebo (mean+/-SD: 168+/-65 vs 177+/- 66 micromol/l; P=0.002) and there was a strong trend towards an increase in effective renal plasma flow on Amlodipine relative to placebo (238+/-92 vs 217+/-87 ml/min; P=0.055). Glomerular filtration rate and lithium clearance were unaffected. Trough CsA blood concentration was unaffected. Amlodipine was well tolerated, with a low incidence of adverse events, and did not affect blood pressure or heart rate. In conclusion, Amlodipine reduced serum creatinine in normotensive renal transplant recipients after only 8 weeks treatment, and was well tolerated in concomitant administration with CsA (Nephrol Dial Transplant. 1999 Feb;14(2):384-8).

The calcium channel blocker nifedipine is widely used in children with systemic hypertension: however, because of the short duration of action, three to four daily doses of the standard preparation are required. Amlodipine once-daily, a calcium channel blocker structurally related to nifedipine with an excellent bioavailability and a long elimination half-time, has been shown to reduce blood pressure in adults. The effects of Amlodipine once-daily (5 to 10 mg) were assessed in 28 paediatric patients with hypertension. Amlodipine was withdrawn in five patients who experienced oedema and flushing. In the remaining 23 patient's blood pressure was significantly reduced 3 weeks after Amlodipine (on average by 7/5 mm Hg) and further decreased at 12 weeks (by 21/12 mm Hg). Heart rate and body weight were unchanged. In eight patients concomitantly treated with cyclosporine, the blood level of this agent was stable throughout the study, thus not requiring any dose adjustment. CONCLUSION: The study illustrates the antihypertensive properties of Amlodipine once-daily in paediatric hypertension. Amlodipine appears particularly indicated in patients concomitantly treated with cyclosporine (Eur J Pediatr. 1998 Aug;157(8):618-21).

In the Prospective Randomized Amlodipine Survival Evaluation Study, 1,153 patients with severe heart failure were randomized to receive Amlodipine (up to 10 mg/day) or placebo. A trend toward a decreased mortality was noted in the Amlodipine group, with a more pronounced survival benefit in the subgroup of patients with non-ischemic cardiomyopathy (Goodman and Gilman's The Pharmacological Basis of Therapeutics).

5.2 Pharmacokinetic properties

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 AUC0-t value (t= 48 hrs.) of T ab l e t S (-) Amlodipine (2.5mg) is 95.33 ± 14.45 ng.hr/ml. The AUC_{0-t} 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.

5.3 Preclinical safety data

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 b y 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

Microcrystalline Cellulose
Croscarmellose Sodium
Colloidal Silicon Dioxide
Magnesium Stearate
Colour Iron Oxide Yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 30°C.

6.5 Nature and contents of container

10 tablets are packed in a blister pack. 3 such blisters are packed in carton along with pack insert.

6.6 Special precautions for disposal

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

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Emcure Nigeria Limited
Plot No. P1 & P2, IT-BT Park, Phase II,
M.I.D.C., Hinjawadi, Pune- 411026, Maharashtra, INDIA.

8. DRUG PRODUCT MANUFACTURER

Emcure Pharmaceuticals Limited
Lane No. 3, Phase-II, SIDCO Industrial Complex
Bari-Brahmana, Jammu (J&K)- 181133, INDIA

9. NAFDAC REGISTRATION NUMBER(S)

A4-4175

10. DATE OF REVISION OF THE TEXT

13.12.2024