SUMMARY OF PRODUCT CHARACTERISTICS

Asomex-LT

[S (-) Amlodipine and Losartan Potassium Tablets]
2.5 mg/ 50mg

Table of Contents

1. NAME OF THE MEDICINAL PRODUCT

Asomex-LT

[S (-) Amlodipine & Losartan Potassium Tablets 2.5/50 mg]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Asomex-LT

Each uncoated Tablet contains

S (-) Amlodipine Besilate

Equivalent to S (-) Amlodipine ……..… 2.5 mg

Losartan Potassium USP……..… 50 mg

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Uncoated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

S (-) Amlodipine & Losartan Potassium Tablets are indicated for the treatment of hypertension.

4.2 Posology and method of administration

S (-) Amlodipine & Losartan Potassium Tablets may be administered with or without food.

S (-) Amlodipine & Losartan Potassium Tablets may be administered with other antihypertensive agents if required. The concomitant use of angiotensin receptor blockers and ACE inhibitors has not been adequately studied.

Hypertension

The starting and maintenance dose of S (-) Amlodipine & Losartan Potassium Tablets is one tablet once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 2 tablets once daily.

Use in renal impairment: No data is available regarding use of S (-) Amlodipine & Losartan Potassium Tablets in patients with renal impairment. Therapy should be initiated with extreme caution if necessary.

Use in hepatic impairment: S (-) Amlodipine & Losartan Potassium Tablets should be used with great caution in patients with hepatic impairment and preferably at a lower dose.

Use in the elderly: No initial dose adjustment is required in this group of patients. However, S (-) Amlodipine & Losartan Potassium Tablets should be used with caution in elderly patients as such patients may have impaired renal function and an increase sensitivity of this group of patients to antihypertensive drugs cannot be ruled out.

Use in children and adolescents: The safety and efficacy of S (-) Amlodipine & Losartan Potassium Tablets has not been assessed in children.

4.3 Contraindications

S (-) Amlodipine & Losartan Potassium Tablets is contraindicated in patients with hypersensitivity to any components of this product. S (-) Amlodipine & Losartan Potassium Tablets are also contraindicated in pregnancy.

4.4 Special warnings and precautions for use

This FDC should be used with caution in patients of heart failure (NYHA II- IV), in patients with reduced cardiac reserve, in patients with haemodynamically significant obstructive valvular disease and cardiomyopathy.

Hypotension may be encountered in patients who are volume depleted while using this fixed dose combination. Hence, patients with reduced intravascular volume should be carefully observed and managed in case hypotension develops. Intravascular volume should be preferably restored before commencing the patient on this fixed dose combination.

Electrolyte disturbances, including excessive hyperkalemia, may be seen in patients, especially diabetics, receiving this fixed dose combination. S (-) Amlodipine & Losartan Potassium Tablets should be used with caution in such patients.

Use in patients with impaired hepatic function: The half life of amlodipine is prolonged in patients with reduced liver function. Hence, S (-) Amlodipine & Losartan Potassium Tablets should be used with caution in such patients.

Use in elderly patients: Dose titration should be done with caution in elderly patients.

Use in children: There is insufficient data to recommend use of S-amlodipine in children.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Hypersensitivity: S (-) Amlodipine & Losartan Potassium Tablets should not be used or should be used with caution in patients with history of hypersensitivity to amlodipine, any angiotensin receptor blockers or any component of this formulation.

Renal function impairment: As a consequence of inhibiting the renin-angiotensin-aldosterone 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 drugs 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. Hence, S (-) Amlodipine & Losartan Potassium Tablets should be used, if necessary, with extreme caution in such patients.

4.6 Pregnancy and lactation

Use during pregnancy
This combination is contraindicated in pregnancy owing to lack of supporting human data.

Use during lactation

It is not known whether losartan or S-amlodipine is excreted in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue breast-feeding or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines
There are no data regarding the effect of S (-) Amlodipine & Losartan Potassium Tablets on the ability to drive and use machines.

4.8 Undesirable effects

Side effects reported with S-amlodipine are few and include vertigo; tachycardia; cough; edema; headache; and mild difficulty in breathing. Side effects of losartan have usually been mild and transient in nature and have not required discontinuation of therapy. Dizziness, asthenia/fatigue, vertigo, hypotension, hyperkalemia, hypersensitivity reactions including angioedema of larynx, glottis; swelling of face, tongue, lips or pharynx; vasculitis including Henoch Schonlein purpura have been reported. Rarely anemia, thrombocytopenia, liver function abnormalities, hepatitis, diarrhea, myalgia, arthralgia, urticaria and rash may be seen with losartan.

4.9 Overdose

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

The most likely manifestation of overdosage would be peripheral vasodilatation with marked hypotension and tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. In case of massive overdose, active supportive therapy including elevation of lower extremities and IV fluid infusions should be initiated along with adequate cardiac and respiratory monitoring including frequent blood pressure measurements. Gastric lavage may be attempted. As this product is highly plasma protein bound, hemodialysis is not likely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

S (-) amlodipine is the chirally pure form of amlodipine, a calcium channel blocker of the dihydropyridine group. Only the S-isomer of amlodipine has the vasodilatory property attributable to its calcium channel blocking activity. The R (+) isomer has no calcium channel blocking activity and is inactive. In humans, the dominant effects of amlodipine are a result of its vasodilatory action. S (-) amlodipine lowers peripheral vascular resistance without causing a reflex tachycardia. It is effective as a once daily dosage in the control of hypertension. In patients with angina pectoris, S (-) amlodipine is thought to exert its effect by reducing the myocardial oxygen demand. This is due to the direct vasodilatory action of S-amlodipine on the coronary artery and arterioles.

Losartan is an oral, specific angiotensin-II receptor (type AT1) antagonist. Angiotensin II binds to the AT1 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 proliferation. Both 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 synthesis.

During losartan administration, removal of angiotensin-II negative feedback on renin secretion leads to increased plasma renin activity. Increases in plasma renin activity lead to increases in angiotensin II in plasma. Even with these increases, antihypertensive activity and suppression of plasma aldosterone concentration are maintained, indicating effective angiotensin-II receptor blockade.

Losartan binds selectively to the AT1 receptor and does not bind to or 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, effects not directly related to blocking the AT1 receptor, such as the potentiation of bradykinin-mediated effects, the generation of edema, are not associated with losartan.

Losartan has been shown to block responses to angiotensin I and angiotensin II without affecting responses to bradykinin, a finding which is consistent with the specific mechanism of action of losartan. In contrast, ACE inhibitors have been shown to block responses to angiotensin I and enhance responses to bradykinin without altering the response to angiotensin II, thus providing a pharmacodynamic distinction between losartan and ACE inhibitors. Losartan has no effect on autonomic reflexes and no sustained effect on plasma noradrenaline.

Losartan potassium does not cause clinically important changes in fasting triglycerides, total cholesterol or HDL cholesterol in patients with hypertension.

5.2 Pharmacokinetic properties

Absorption

S-amlodipine and losartan are well absorbed on oral administration. Losartan undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. The plasma concentration of losartan is not affected by food.

Distribution

93% of amlodipine is bound to plasma proteins. Both losartan and its active metabolite are 99% bound to plasma proteins, primarily albumin. Losartan crosses the blood-brain barrier poorly, if at all.

Biotransformation

Amlodipine is extensively metabolized to inactive metabolites via hepatic metabolism (approximately 90%). About 14% of an intravenously or orally-administered dose of losartan is converted to its active metabolite. In addition to the active metabolite, inactive metabolites are formed, including two major metabolites formed by hydroxylation of the butyl side chain and a minor metabolite, an N-2 tetrazole glucuronide.

Elimination

Around 10% of the parent compound and 60% of metabolites are excreted in urine. The half life of S-amlodipine is 27.90 ± 7.89 hours. When losartan is administered orally, about 4% of the

dose is excreted unchanged in the urine, and about 6% of the dose is excreted in the urine as active metabolite. The half life of Losartan is 2.91 ± 1.153 hours. During once-daily dosing with 100 mg, neither losartan nor its active metabolite accumulates significantly in plasma. Both biliary and urinary excretions contribute to the elimination of losartan and its metabolites.

5.3 Preclinical safety data

Preclinical data with amlodipine failed to reveal any special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction in rats at high doses delayed parturition, difficult labour and impaired fetal and pup survival were seen .S-amlodipine is the active isomer of racemic amlodipine. Hence studies done with racemic amlodipine will be equally applicable to the S-isomer as well.

The toxic potential of losartan potassium was evaluated in a series of repeated dose oral toxicity studies of up to three months in monkeys and up to one year in rats and dogs. There were no findings that would preclude administration at the therapeutic dosage level.

Losartan potassium was not shown to be carcinogenic in animal studies. There was no evidence of direct genotoxicity in studies conducted with losartan potassium or its primary pharmacologically active metabolite (E-3174). Losartan was not shown to adversely affect fertility and reproductive performance in animal studies.

Losartan potassium has been shown to produce adverse effects in fetuses and neonates in animal studies. The effects include decreased bodyweight, mortality and/or renal toxicity. In addition, significant levels of losartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Microcrystalline Cellulose
2. Croscarmellose Sodium
3. Purified Water
3. Colloidal Silicon Dioxide
4. Purified Talc
5. Lake of Quinoline Yellow
6. Magnesium Stearate

6.2 Incompatibilities

None of the In-active ingredients of the formulation have been known to exhibit incompatibility with the Active Ingredients.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

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

6.5 Nature and contents of container

10 tablets are packed in PVDC coated PVC film and Aluminium foil (0.02 mm) blister pack. 2 such composite blister strips of 3 X10 tablets each are placed in a printed carton.

6.6 Special precautions for disposal and other handling

Store in a dry and dark place below 30 °C.
KEEP AWAY FROM THE REACH OF CHILDREN

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not Applicable.

10. DATE OF REVISION OF THE TEXT

Not Applicable.

11. LEGAL CATEGORY

For Prescription use only