For the use of a Registered Medical Practitioner or a Hospital or a Laboratory Only

ESAM-LT

(Losartan Potassium and S-Amlodipine Besylate Tablets)

COMPOSITION

Each uncoated bilayered tablet contains:
Losartan Potassium I.P. 50 mg
S-Amlodipine Besylate I.P. equivalent to S-Amlodipine 2.5 mg
Colour: Lake of Sunset Yellow

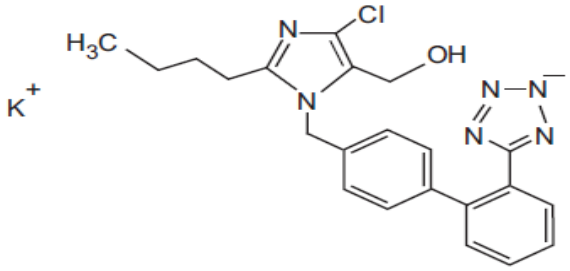
WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue product as soon as possible.
Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus

PROPERTIES

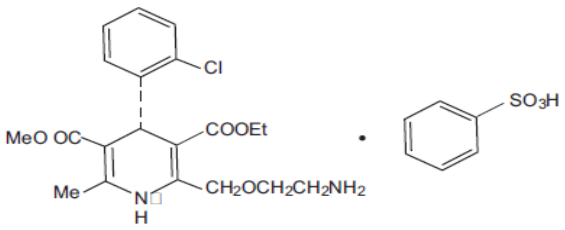
LOSARTAN

Losartan Potassium is the first of a new class of antihypertensives. It is an angiotensin II receptor (Type AT_1) antagonist. Losartan Potassium is a monopotassium salt of 4- butyl-4-chloro-1-{[2' (1H-tetrazol-5-yl)[1,1'-biphenyl]-4- yl]methyl}-1H-imidazole-5-methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ and the molecular weight is 461.0. The structure of Losartan Potassium is:



AMLODIPINE

S-Amlodipine Besylate is a white to pale yellow powder, freely soluble in methanol. Chemically it is (S)-3-ethyl-5-methyl-2-(2- aminoethoxymethyl)-4-(2-chlorophenyl) 1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5$. $C_6H_6O_3S$ with a molecular weight of 567.1, and its structural formula is:



PHARMACOLOGICAL PROPERTIES
PHARMACODYNAMICS
LOSARTAN

Pharmacotherapeutic group: Angiotensin II antagonists, plain ATC code: C09CA01 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.

S-AMLODIPINE

S-amlodipine is a long-acting calcium channel blocker that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. The contractile process of cardiac muscle and vascular smooth muscle are dependent upon movement of extra cellular calcium ions into these cells through specific ion channels. By inhibiting calcium ion influx it directly dialate vascular smooth muscle, resisting hypertension. The mechanism of remitting angina pectoris with S-amlodipine is not yet determined completely, but it is clear that this product can abate myocardial ischemia through the following functions:

1. Dilate the peripheral small artery, decreasing peripheral resistance, causing the reduction of energy consumption and oxygen requirement of cardiac muscle.

2. Dilate the coronary artery and the coronary small artery at normal and Ischaemic areas, increasing the oxygen supply of cardiac muscle in coronarospasm patients.

PHARMACOKINETICS

LOSARTAN

Losartan is readily absorbed from the gastrointestinal tract after oral doses, but undergoes substantial first pass metabolism resulting in a systemic bioavailability of about 33%. It is metabolized to an active carboxylic acid metabolite E-3174 (EXP-3174), which has greater pharmacological activity than losartan; some inactive metabolites are also formed. Metabolism is primarily by cytochrome P450 isoenzymes CYP2C9 and CYP3A4. Peak plasma concentrations of losartan and E-3174 occur about 1 hour and 3 to 4 hours, respectively, after an oral dose. Both losartan and E-3174 are more than 98% bound to plasma proteins. Losartan is excreted in the urine, and in the faeces via bile, as unchanged drug and metabolites. About 4% of an oral dose is excreted unchanged in urine and about 6% is excreted in urine as the active metabolite. The terminal elimination half-lives of losartan and E-3174 are about 1.5 to 2.5 hours and 3 to 9 hours, respectively.

Special Populations

In elderly hypertensive patients the plasma concentrations of losartan and its active metabolite do not differ essentially from those found in young hypertensive patients.
In female hypertensive patients the plasma levels of losartan were up to twice as high as in male hypertensive patients, while the plasma levels of the active metabolite did not differ between men and women. In patients with mild to moderate alcohol induced hepatic cirrhosis, the plasma levels of losartan and its active metabolite after oral administration were respectively 5 and 1.7 times higher than in young male volunteers.

Plasma concentrations of losartan are not altered in patients with a creatinine clearance above 10 ml/minute. Compared to patients with normal renal function, the AUC for losartan is about 2 times higher in haemodialysis patients.

The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.

Neither losartan nor the active metabolite can be removed by haemodialysis.

Pharmacokinetics in pediatric patients

The pharmacokinetics of losartan have been investigated in 50 hypertensive paediatric patients >1 month to <16 years of age following once daily oral administration of approximately 0.54 to 0.77 mg/ kg of losartan (mean doses).

The results showed that the active metabolite is formed from losartan in all age groups. The results showed roughly similar pharmacokinetic parameters of losartan following oral administration in infants and toddlers, preschool children, school age children and adolescents. The pharmacokinetic parameters for the metabolite differed to a greater extent between the age groups. When comparing preschool children with adolescents these differences became statistically significant. Exposure in infants/ toddlers was comparatively high.

S-AMLODIPINE

After oral administration of S-amlodipine besylate tablet, the blood-drug concentration reaches peak value within 6-12 hrs. The absolute bioavailability has been estimated to be in between 64-80% and the apparent distribution volume is approximately 21 L/kg. The blood-drug concentration comes up to homeostasis after successive administration with once a day for 7-8 days. Approximately 93% of the circulating drug is bound to plasma proteins. S-amlodipine besylate is extensively converted to inactive metabolites via hepatic metabolism. Samlodipine is excreted out along with urine, with 10% of the parent, and 60% of the metabolites. The terminal elimination half-life for S-amlodipine is 35-50 hrs. The average final elimination half-life period of S-amlodipine is 49.6 hrs while for R-amlodipine it is 34.9 hrs.

INDICATIONS

ESAM-LT is indicated in treatment of mild to moderate hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose of ESAM-LT is one tablet once daily taken with or without food.

CONTRAINDICATIONS

ESAM-LT is contraindicated in patients allergic to angiotensin receptor blocker or dihydropyridine calcium channel blocker. Patients with a history of angioedema or any other adverse effect related to previous treatment with an angiotensin receptor blocker or calcium channel blocker. Do not co-administer aliskiren with Losartan in patients with diabetes.

WARNINGS

Fetal Toxicity

Pregnancy Category D

Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces renal function and increases fetal and neonatal morbidity and death. Resulting oligohydramnios can be associated with fetal lung hypoplasia and skeletal deformations. Potential neonatal adverse effects include skull hypoplasia, anuria, hypotension, renal failure, and death. When pregnancy is detected, discontinue Losartan as soon as possible. These adverse outcomes are usually associated with the use of these drugs in the second and third trimester of pregnancy. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. Appropriate management of maternal hypertension during pregnancy is important to optimize outcomes for both mother and fetus.

In the unusual case that there is no appropriate alternative to therapy with drugs affecting the reninangiotensin system for a particular patient, apprise the mother of the potential risk to the fetus. Perform serial ultrasound examinations to assess the intra-amniotic environment.

If oligohydramnios is observed, discontinue Losartan, unless it is considered life-saving for the mother. Fetal testing may be appropriate, based on the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Closely observe infants with histories of *in utero* exposure to Losartan for hypotension, oliguria, and hyperkalemia. Losartan potassium has been shown to produce adverse effects in rat fetuses and neonates, including decreased body weight, delayed physical and behavioral development, mortality and renal toxicity. With the exception of neonatal weight gain (which was affected at doses as low as 10 mg/kg/day), doses associated with these effects exceeded 25 mg/kg/day (approximately three times the maximum recommended human dose of 100 mg on a mg/m2 basis). These findings are attributed to drug exposure in late gestation and during lactation. Significant levels of losartan and its active metabolite were shown to be present in rat fetal plasma during late gestation and in rat milk.

Hypotension — Volume-Depleted Patients
In patients who are intravascularly volume-depleted (e.g., those treated with diuretics), symptomatic hypotension may occur after initiation of therapy with Losartan. These conditions should be corrected prior to administration of Losartan, or a lower starting dose should be used.

PRECAUTIONS

General
Hypersensitivity: Angioedema

Impaired Hepatic Function: Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of losartan in cirrhotic patients, a lower dose should be considered for patients with impaired liver function

Impaired Renal Function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals treated with Losartan; in some patients, these changes in renal function were reversible upon discontinuation of therapy.

In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Losartan.
In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. Similar effects have been reported with Losartan; in some patients, these effects were reversible upon discontinuation of therapy.

Electrolyte Imbalance: Electrolyte imbalances are common in patients with renal impairment, with or without diabetes, and should be addressed. In a clinical study conducted in type 2 diabetic patients with proteinuria, the incidence of hyperkalemia was higher in the group treated

with Losartan as compared to the placebo group; however, few patients discontinued therapy due to hyperkalemia.

Information for Patients: Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to Losartan during pregnancy. Discuss treatment options with women planning to become pregnant.

Patients should be asked to report pregnancies to their physicians as soon as possible.

Potassium Supplements: A patient receiving Losartan should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician

Carcinogenesis, Mutagenesis, Impairment of Fertility
Losartan potassium was not carcinogenic when administered at maximally tolerated dosages to rats and mice for 105 and 92 weeks, respectively. Female rats given the highest dose (270 mg/kg/day) had a slightly higher incidence of pancreatic acinar adenoma. The maximally tolerated dosages (270 mg/kg/day in rats, 200 mg/kg/day in mice) provided systemic exposures for losartan and its pharmacologically active metabolite that were approximately 160- and 90-times (rats) and 30- and 15-times (mice) the exposure of a 50 kg human given 100 mg per day.

Losartan potassium was negative in the microbial mutagenesis and V-79 mammalian cell mutagenesis assays and in the *in vitro* alkaline elution and *in vitro* and *in vivo* chromosomal aberration assays. In addition, the active metabolite showed no evidence of genotoxicity in the microbial mutagenesis, *in vitro* alkaline elution, and *in vitro* chromosomal aberration assays.

Fertility and reproductive performance were not affected in studies with male rats given oral doses of losartan potassium up to approximately 150 mg/kg/day. The administration of toxic dosage levels in females (300/200 mg/kg/day) was associated with a significant ($p<0.05$) decrease in the number of corpora lutea/female, implants/female, and live fetuses/female at C-section. At 100 mg/kg/day only a decrease in the number of corpora lutea/female was observed. The relationship of these findings to drug treatment is uncertain since there was no effect at these dosage levels on implants/pregnant female, percent post-implantation loss, or live animals/litter at parturition. In nonpregnant rats dosed at 135 mg/kg/day for 7 days, systemic exposure (AUCs) for losartan and its active metabolite were approximately 66 and 26 times the exposure achieved in man at the maximum recommended human daily dosage (100 mg).

Nursing Mothers
It is not known whether losartan is excreted in human milk, but significant levels of losartan and its active metabolite were shown to be present in rat milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Neonates with a history of *in utero* exposure to Losartan
If oliguria or hypotension occurs, direct attention toward support of blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing

hypotension and/or substituting for disordered renal function. Antihypertensive effects of Losartan have been established in hypertensive pediatric patients aged 6 to 16 years. There are no data on the effect of Losartan on blood pressure in pediatric patients under the age of 6 or in pediatric patients with glomerular filtration rate <30 mL/min/1.73 m^2

Geriatric Use
Of the total number of patients receiving Losartan in controlled clinical studies for hypertension, 391 patients (19%) were 65 years and over, while 37 patients (2%) were 75 years and over. In a controlled clinical study for renal protection in type 2 diabetic patients with proteinuria, 248 patients (33%) were 65 years and over. In a controlled clinical study for the reduction in the combined risk of cardiovascular death, stroke and myocardial infarction in hypertensive patients with left ventricular hypertrophy, 2857 patients (62%) were 65 years and over, while 808 patients (18%) were 75 years and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Race
In the LIFE study, Black patients with hypertension and left ventricular hypertrophy had a lower risk of stroke on atenolol than on Losartan. Given the difficulty in interpreting subset differences in large trials, it cannot be known whether the observed difference is the result of chance. However, the LIFE study does not provide evidence that the benefits of Losartan on reducing the risk of cardiovascular events in hypertensive patients with left ventricular hypertrophy apply to Black patients.

DRUG INTERACTIONS
LOSARTAN
No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine and phenobarbital. Rifampin, an inducer of drug metabolism, decreased the concentrations of losartan and its active metabolite. In humans, two inhibitors of P450 3A4 have been studied.

Ketoconazole did not affect the conversion of losartan to the active metabolite after intravenous administration of losartan, and erythromycin had no clinically significant effect after oral administration.

Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration and increased losartan concentration. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined. Subjects who do not metabolize losartan to active metabolite have been shown to have a specific, rare defect in cytochrome P450 2C9. These data suggest that the conversion of losartan to its active metabolite is mediated primarily by P450 2C9 and not P450 3A4.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Lithium: As with other drugs which affect the excretion of sodium, lithium excretion may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be co-administered with angiotensin II receptor antagonists.

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors): In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with angiotensin II receptor antagonists (including losartan) may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving losartan and NSAID therapy.

The antihypertensive effect of angiotensin II receptor antagonists, including losartan, may be attenuated by NSAIDs, including selective COX-2 inhibitors.

Dual Blockade of the Renin-Angiotensin System (RAS): Dual blockade of the RAS with angiotensin receptor blockers, ACE inhibitors, or aliskiren is associated with increased risks of hypotension, syncope, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy.

Closely monitor blood pressure, renal function, and electrolytes in patients on Losartan and other agents that affect the RAS.

Do not co-administer aliskiren with Losartan in patients with diabetes. Avoid use of aliskiren with Losartan in patients with renal impairment (GFR <60 ml/min).

S-AMLODIPINE

S-amlodipine has been safely administered with thiazide diuretics, beta adrenoceptor blocking drugs, angiotensin converting enzyme inhibitors, long acting nitrates, sublingual glyceryl trinitrate, nonsteroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic agents.

Co administration of S-amlodipine with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. Co administration of cimetidine did not alter the pharmacokinetics of S-amlodipine.

In healthy volunteers, co administration of S-amlodipine did not significantly alter the effect of warfarin on prothrombin time. The introduction of S-amlodipine is not likely to result in the need for modification of an established warfarin regimen.

ADVERSE REACTIONS

LOSARTAN

Hypertension

Losartan has been evaluated for safety in more than 3300 adult patients treated for essential hypertension and 4058 patients/subjects overall. Over 1200 patients were treated for over 6 months and more than 800 for over one year. In general, treatment with Losartan was well-tolerated. The overall incidence of adverse experiences reported with Losartan was similar to placebo. In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences was required in 2.3 percent of patients treated with Losartan and 3.7 percent of patients given placebo.

The following table of adverse events is based on four 6- to 12-week, placebo-controlled trials involving over 1000 patients on various doses (10-150 mg) of losartan and over 300 patients given placebo. All doses of losartan are grouped because none of the adverse events appeared to have a dose-related frequency. The adverse experiences reported in ≥1% of patients treated with Losartan and more commonly than placebo are shown in the table below.

	Losartan (n=1075) Incidence %	Placebo (n=334) Incidence %
Musculoskeletal		
Cramp, muscle	1	0
Pain, back	2	1
Pain, leg	1	0
Nervous System/Psychiatric		
Dizziness	3	2
Respiratory		
Congestion, nasal	2	1
Infection, upper respiratory	8	7
Sinusitis	1	0

The following adverse events were also reported at a rate of 1% or greater in patients treated with losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, edema/swelling, abdominal pain, chest pain, nausea, headache, pharyngitis, diarrhea, dyspepsia, myalgia, insomnia, cough, sinus disorder.

Adverse events occurred at about the same rates in men and women, older and younger patients, and Black and non-Black patients. A patient with known hypersensitivity to aspirin and penicillin, when treated with Losartan, was withdrawn from study due to swelling of the lips and eyelids and facial rash, reported as angioedema, which returned to normal 5 days after therapy was discontinued. Superficial peeling of palms and hemolysis were reported in one subject.

In addition to the adverse events above, potentially important events that occurred in at least two patients/subjects exposed to losartan or other adverse events that occurred in <1% of patients in clinical studies are listed below. It cannot be determined whether these events were causally related to losartan:

Body as a Whole: facial edema, fever, orthostatic effects, syncope; *Cardiovascular:* angina pectoris, second degree AV block, CVA, hypotension, myocardial infarction, arrhythmias including atrial fibrillation, palpitation, sinus bradycardia, tachycardia, ventricular tachycardia, ventricular fibrillation; *Digestive:* anorexia, constipation, dental pain, dry mouth, flatulence, gastritis, vomiting; *Hematologic:* anemia; *Metabolic:* gout; *Musculoskeletal:* arm pain, hip pain, joint swelling, knee pain, musculoskeletal pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness; *Nervous System/Psychiatric:* anxiety, anxiety disorder, ataxia, confusion, depression, dream abnormality, hypesthesia, decreased libido, memory impairment, migraine, nervousness, paresthesia, peripheral neuropathy, panic disorder, sleep disorder, somnolence, tremor, vertigo; *Respiratory:* dyspnea, bronchitis, pharyngeal discomfort, epistaxis, rhinitis, respiratory congestion; *Skin:* alopecia, dermatitis, dry skin, ecchymosis, erythema, flushing, photosensitivity, pruritus, rash, sweating, urticaria; *Special Senses:* blurred vision, burning/stinging in the eye, conjunctivitis, taste perversion, tinnitus, decrease in visual acuity; *Urogenital:* impotence, nocturia, urinary frequency, urinary tract infection. Persistent dry cough (with an incidence of a few percent) has been associated with ACE-inhibitor use and in practice can be a cause of discontinuation of ACE-inhibitor therapy. Two prospective, parallel group, double-blind, randomized, controlled trials were conducted to assess the effects of losartan on the incidence of cough in hypertensive patients who had experienced cough while receiving ACE-inhibitor therapy. Patients who had typical ACE-inhibitor cough when challenged with lisinopril, whose cough disappeared on placebo, were randomized to losartan 50 mg, lisinopril 20 mg, or either placebo (one study, n=97) or 25 mg hydrochlorothiazide (n=135). The double-blind treatment period lasted up to 8 weeks. The incidence of cough is shown below.

Study 1*	HCTZ	Losartan	Lisinopril
Cough	25%	17%	69%

Study 2†	Placebo	Losartan	Lisinopril
Cough	35%	29%	62%

* Demographics = (89% caucasian, 64% female)
† Demographics = (90% caucasian, 51% female)

These studies demonstrate that the incidence of cough associated with losartan therapy, in a population that all had cough associated with ACE-inhibitor therapy, is similar to that associated with hydrochlorothiazide or placebo therapy.

Cases of cough, including positive re-challenges, have been reported with the use of losartan in postmarketing experience.
Pediatric Patients: No relevant differences between the adverse experience profile for pediatric patients and that previously reported for adult patients were identified.

Hypertensive Patients with Left Ventricular Hypertrophy
In the LIFE study, adverse events with Losartan were similar to those reported previously for patients with hypertension.

Nephropathy in Type 2 Diabetic Patients

In the RENAAL study involving 1513 patients treated with Losartan or placebo, the overall incidences of reported adverse experiences were similar for the two groups. Losartan was generally well tolerated as evidenced by a similar incidence of discontinuations due to side effects compared to placebo (19% for Losartan, 24% for placebo). The adverse experiences, regardless of drug relationship, reported with an incidence of ≥4% of patients treated with Losartan and occurring more commonly than placebo, on a background of conventional antihypertensive therapy, are shown in the table below.

	Losartan and Conventional Antihypertensive Therapy Incidence % (n=751)	Placebo and Conventional Antihypertensive Therapy Incidence % (n=762)
Body as a Whole		
Asthenia/Fatigue	14	10
Chest Pain	12	8
Fever	4	3
Infection	5	4
Influenza-like disease	10	9
Trauma	4	3
Cardiovascular		
Hypotension	7	3
Orthostatic hypotension	4	1
Digestive		
Diarrhea	15	10
Dyspepsia	4	3
Gastritis	5	4
Endocrine		
Diabetic neuropathy	4	3
Diabetic vascular disease	10	9
Eyes, Ears, Nose and Throat	7	5
Cataract	6	5
Sinusitis		
Hemic		
Anemia	14	11
Metabolic and Nutrition		
Hyperkalemia	7	3
Hypoglycemia	14	10
Weight gain	4	3
Musculoskeletal		
Back pain	12	10
Leg pain	5	4
Knee pain	5	4
Muscular weakness	7	4
Nervous System		
Hypesthesia	5	4
Respiratory		
Bronchitis	10	9
Cough	11	10
Skin		
Cellulitis	7	6
Urogenital		
Urinary tract infection	16	13

Postmarketing Experience
The following additional adverse reactions have been reported in postmarketing experience:
Digestive: Hepatitis (reported rarely).

General Disorders and Administration Site Conditions: Malaise.

Hemic: Thrombocytopenia (reported rarely).

Hypersensitivity: Angioedema, including swelling of the larynx and glottis, causing airway obstruction and/or swelling of the face, lips, pharynx, and/or tongue has been reported rarely in patients treated with losartan; some of these patients previously experienced angioedema with other drugs including ACE inhibitors. Vasculitis, including Henoch-Schönlein purpura, has been reported. Anaphylactic reactions have been reported.

Metabolic and Nutrition: Hyperkalemia, hyponatremia have been reported with losartan.

Musculoskeletal: Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Nervous system disorders: Dysgeusia

Respiratory: Dry cough (see above)

Skin: Erythroderma.

Laboratory Test Findings
In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Losartan.

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with Losartan alone.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 grams percent and 0.09 volume percent, respectively) occurred frequently in patients treated with Losartan alone, but were rarely of clinical importance. No patients were discontinued due to anemia.

Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with Losartan alone, one patient (<0.1%) was discontinued due to these laboratory adverse experiences.

S-AMLODIPINE
The most commonly observed side effects are headache, edema, fatigue, flushing and dizziness. Less common side effects include nausea, abdominal pain, somnolence and palpitations.

Rare side effects include muscle cramps, frequency of micturition or nocturia, coughing, breathlessness, epitasis, impotence, nervousness and conjunctivitis. No clinically significant pattern of laboratory test abnormalities related to S-amlodipine has been observed.

OVERDOSAGE

Losartan

Significant lethality was observed in mice and rats after oral administration of 1000 mg/kg and 2000 mg/kg, respectively, about 44 and 170 times the maximum recommended human dose on a mg/m^2 basis.

Limited data are available in regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither losartan nor its active metabolite can be removed by hemodialysis.

S-Amlodipine

Symptoms: Available data suggests that the gross over dosage could result in excessive peripheral vasodilation with subsequent marked and probably prolonged hypotension.

Treatment: Since absorption of S-Amlodipine is slow, gastric lavage should be performed. Active cardiovascular support including monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output should be given. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. A vasoconstrictor agent may be helpful in restoring vascular tone and blood pressure provided that there is no contraindication to its use. Since S-amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

EXPIRY

Do not use after the date of expiry.

STORAGE

Store at a temperature not exceeding 30^oC, protected from light and moisture.
Keep all medicines out of reach of children

PRESENTATION

ESAM-LT is available in strips of 10 tablets.

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

ESLT/OCT 2014/VER 03