For the use of a Registered Medical Practitioner or a Hospital or a Laboratory XXXXXXX-8883

TOZAM

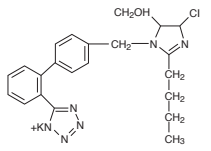
(Amlodipine besilate and losartan potassium tablets)

COMPOSITION

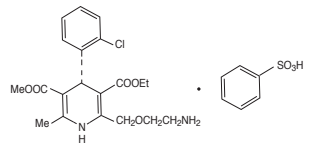
Each Film coated tablet contains:
Amlodipine besylate equivalent to
Amlodipine .BP. ……..……5 mg
Losartan potassium U.S.P. ……..……50 mg
Colours: Lake of Sunset Yellow and Titanium dioxide

PROPERTIES

Losartan potassium is the first of a new class of antihypertensive. It is an angiotensin II receptor (type AT1) antagonist. It is white to light yellow crystalline powder soluble in water, methanol and ethanol and insoluble in chloroform. Losartan is the potassium salt of 2-n-butyl-4-chloro-1-[2'-(tetrazol-5-yl)-1, 1'biphenyl–4-ylmethyl]–1H–imidazole– 5-methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ and the molecular weight is 461.01. The structure of Losartan Potassium is:



Amlodipine besylate is a white crystalline powder with a molecular weight of 567.1. It is lightly soluble in water and sparingly soluble in ethanol. Chemically it is described as (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and its structural formula is:



PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Losartan potassium

It is an angiotensin II receptor (type AT1) antagonist. Angiotensin II is a potentvasoconstrictor and an important component in the pathophysiology of hypertension. Losartan potassium blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland).

Amlodipine besylate

Amlodipine besylate is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-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 dilates vascular smooth muscle, resisting hypertension. The mechanism of relieve angina pectoris with 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 small coronary artery at normal and ischaemic areas, increasing the oxygen supply of cardiac muscle in patients with coronary spasm.

Pharmacokinetics

Losartan potassium

The pharmacokinetics of Losartan potassium and its active metabolite (E-3174) are linear with oral doses up to 200mg and do not change over the time. Neither Losartan potassium, nor its metabolite accumulates in plasma upon repeated once-a-day dosing. Following oral administration, Losartan potassium has a systemic bioavailability of around 33%. Losartan potassium undergoes substantial first Pass metabolism by cytochrome P450 enzymes. It is converted, in part, to an active carboxylic acid metabolite that is responsible for most of the angiotensin II receptor antagonism that follows Losartan potassium treatment. About 14% of an orally administered dose is converted to the active metabolite. After oral administration Losartan potassium is rapidly absorbed, reaching peak plasma concentrations within an hour. Losartan potassium and E-3174 have been reported to reach peak plasma concentration of 296 ng/ml and 249 ng/ml in 1.0 and 4.1 hours respectively after single oral dose of 50mg in healthy volunteers. The area under the plasma concentration time curve (AUC) for E-3174 is approximately 4 fold greater than for Losartan potassium (1915 vs.476 ng*h/ml). Absorption is slowed and Cmax reduced by food. Losartan potassium and E-3174 are highly protein bound (98.7% and 99.8 %) with volumes of distribution of 34L and 12L respectively. Approximately 35% of the drug is eliminated in the urine and approximately 60% is excreted in the feces. Losartan potassium and E-3174 have elimination half-lives of 2 and 6 - 9 hours respectively. The rate of renal clearance of Losartan potassium and E-3174 is 4.3 and 1.6L/h.

Amlodipine besylate

After oral administration of therapeutic doses of amlodipine besylate, absorption occurs gradually with peak plasma concentration occurring between 6 and 12 hours. Absolute bioavailability has been estimated to be between 64 and 90%. The bioavailability of amlodipine is not altered by the presence of food. Amlodipine has a large volume of distribution (Vd) of 21L/Kg and is highly plasma protein bound (95%). Amlodipine undergoes extensive, but slow hepatic metabolism. The dihydropyridine moiety is oxidized to the pyridine analogue during initial biotransformation, with minimal first-pass or presystemic metabolism. Metabolites have no significant activity. Less than 10% of an oral dose is excreted unchanged. Following oral administration 60% of oral dose is recovered in the urine mainly as metabolites and 20 to 25% in the faeces. The elimination half-life of Amlodipine is in the range of 30 to 50 hours in healthy subjects.

INDICATION

TOZAM is indicated in treatment of mild to moderate hypertension.

CONTRAINDICATIONS

TOZAM is contraindicated in patients allergic to angiotensin receptor blocker or dihydropyridine calcium channel antagonist. Patients with a history of angioedema or any other adverse effect related to previous treatment with an angiotensin receptor blocker or calcium channel antagonist.

PRECAUTIONS

Impaired Liver Function: Losartan potassium and Amlodipine besylate combination should be given with caution in patients with impaired hepatic function since the half-life of amlodipine is prolonged in patients with impaired liver function. Impaired Renal patients: As a consequence of inhibiting the renin-angiotensinaldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin receptor blocker may be associated with oliguria and/ or progressive azotemia and (rarely) with acute renal failure and/ or death.

WARNINGS

Hypotension: Losartan potassium can cause symptomatic hypotension. Symptomatic hypotension is most likely to occur in patients who have been volume and/ or saltdepleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/ or salt depletion should be corrected before initiating therapy with Losartan potassium and Amlodipine besylate combination. Hepatic Failure: Rarely, angiotensin receptor inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving this combination who develop jaundice or marked elevations of hepatic enzymes should discontinue the therapy and receive appropriate medical follow-up.

USE IN PREGNANCY, NURSING MOTHERS AND CHILDREN

Pregnancy: There is no clinical experience with TOZAM in pregnancy or lactation. So, TOZAM should not be administered during pregnancy or lactation or to women of childbearing potential unless effective contraception is ensured.
Nursing Mothers: Women receiving TOZAM should not breast-feed.
Use in children: Since there is no clinical experience of TOZAM, use of this product is not currently recommended for children and adolescents of less than 18 years of age.

SIDE EFFECTS

Losartan potassium

In general, treatment with Losartan potassium was well tolerated. Following adverse events occurring in at least 1% of patients treated with Losartan potassium and that were more frequent in Losartan potassium than placebo.
Digestive: Diarrhea, dyspepsia.
Musculoskeletal: Muscle cramp, myalgia, back pain, leg pain.
Nervous System/Psychiatric: Dizziness, insomnia.
Respiratory: Nasal congestion, cough, upper respiratory tract infection, sinus disorder, sinusitis.
The following adverse events were also reported at a rate 1% or greater in patients treated with Losartan, but were as, or more frequent, in the placebo group: asthenia/fatigue, oedema/ swelling, abdominal pain, chest pain, nausea, headache, pharyngitis.

Amlodipine besylate

The most commonly observed side effects are edema, flushing, palpitation, fatigue, headache, somnolence, abdominal pain and dizziness.
The following events occurred in <1% but >0.1% of patients in controlled clinical trials:
Cardiovascular: Arrhythmia (including ventricular tachycardia and atrial fibrillation),bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis.
Central and Peripheral Nervous System: Hypoesthesia, neuropathy peripheral, paresthesia, tremor, and vertigo.
Gastrointestinal: Anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia.
General: Allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease.
Musculoskeletal System: Arthralgia, arthrosis, muscle cramps, myalgia.
Psychiatric: Sexual dysfunction (male and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization.
Respiratory System: Dyspnea, epistaxis.
Skin and Appendages: Angioedema, erythema multiforme, pruritus, rash, rash erythematous, rash maculopapular.
Special Senses: Abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus.
Urinary System: Micturition frequency, micturition disorder, nocturia.
Autonomic Nervous System: Dry mouth, sweating increased.
Metabolic and Nutritional: Hyperglycemia, thirst.
Hemopoietic: Leukopenia, purpura, thrombocytopenia.

DRUG INTERACTIONS

Losartan Potassium

Losartan potassium administered for 12 days, did not affect the pharmacokinetics or pharmacodynamics of a single dose of warfarin. Losartan potassium did not affect the harmacokinetics of oral and intravenous digoxin. Co administration of Losartan potassium and cimetidine led to an increase of about 18% in AUC of Losartan potassium but did not affect the pharmacokinetics of E-3174. Co administration of Losartan potassium and phenobarbital led to reduction of about 20% in the AUC of Losartan potassium and E-3174. There is no pharmacokinetic interaction between Losartan potassium and Hydrochlorothiazide. Inhibitors of Cytochrome P3A4 are unlikely to have significant drug interactions while potent inducers of Cytochrome P34A might cause a significant interaction. As with other drugs that block angiotensin II or its effects, concomitant use of potassiumsparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium.

Amlodipine besylate

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

DOSAGE AND ADMINISTRATION

One tablet once a day or as directed by the physician. It may be administered with or with out food.

DIRECTION FOR USE

SWALLOW WHOLE TABLET DO NOT CRUSH OR CHEW.

OVER DOSAGE

Losartan potassium

Symptom: The most likely manifestation of over-dosage would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.
Treatment: If symptomatic hypotension occurs, supportive treatment should be instituted. Neither Losartan Potassium nor E-3174 can be removed by haemodialysis.

Amlodipine besylate:

Symptoms: Available data suggests that the gross over dosage could result in excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia.
Treatment: Since absorption of Amlodipine besylate 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 amlodipine is highly protein bound, dialysis is unlikely to be of benefit.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store below 30°C, Protect from Light and Moisture

PRESENTATION

TOZAM is available in strip of 10 Tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
Baddi 173 205, Dist. Solan (H.P.) INDIA.