AMLODIPINE, LOSARTAN POTASSIUM AND HYDROCHLORIDE TABLETS

AMLOZAAR-H

13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Amlodipine, Losartan Potassium and Hydrochlorothiazide

13.1 Strength:

Losartan Potassium 50mg
Amlodipine 5mg
Hydrochlorothiazide 12.5mg

13.2 Pharmaceutical form

Tablets for oral administration

14. Quality and Quantitative Composition

Each film-coated tablet contains:
Losartan Potassium USP 50.0mg
Amlodipine Besilate BP equivalent to Amlodipine 5mg Hydrochlorothiazide BP 12.5mg

15. Pharmaceutical Form

Tablets

16. Clinical Particulars

16.1 Therapeutic indications

It is indicated for the treatment of essential hypertension. It may be used alone or in combination with other antihypertensive agents, including diuretics.

16.2 Posology and method of administration

The usual recommended dose is once daily.
No dose adjustment of amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

16.3 Method of administration

For oral use
Once a day

16.4 Contraindications

Amlodipine

Amlodipine besylate tablets are contraindicated in patients with known sensitivity to amlodipine.

Losartan

It is contraindicated in patients who are hypersensitive to any component of this product.
Do not co-administer aliskiren with Losartan in patients with diabetes.

Hydrochlorothiazide

Anuria
Hypersensitivity to this product or to other sulfonamide-derived drugs

16.5 Special warning and precautions

Amlodipine

Hypotension

Symptomatic hypotension is possible, particularly in patients with severe aortic stenosis. Because of the gradual onset of action, acute hypotension is unlikely.

Increased Angina or Myocardial Infarction

Worsening angina and acute myocardial infarction can develop after starting or increasing the dose of Amlodipine, particularly in patients with severe obstructive coronary artery disease.

Patients with Hepatic Failure

Because Amlodipine is extensively metabolized by the liver and the plasma elimination half-life (t 1/2) is 56 hours in patients with impaired hepatic function, titrate slowly when administering Amlodipine to patients with severe hepatic impairment.

Losartan

Hypersensitivity

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

Hypotension and Electrolyte/Fluid Imbalance

Symptomatic hypotension, especially after the first dose and after increasing of the dose, may occur in patients who are volume- and/or sodium-depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea or vomiting. These conditions should be corrected prior to administration of losartan, or a lower starting dose should be used. This also applies to children 6 to 18 years of age.

Electrolyte imbalances

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 nephropathy, the incidence of hyperkalemia was higher in the group treated with losartan as

compared to the placebo group. Therefore, the plasma concentrations of potassium as well as creatinine clearance values should be closely monitored, especially patients with heart failure and a creatinine clearance between 30-50 ml/min should be closely monitored.
The concomitant use of potassium-sparing diuretics, potassium supplements and potassium-containing salt substitutes with losartan is not recommended.

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

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

Use in Paediatric patients with renal impairment
Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2 as no data are available.
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended

Renal transplantation
There is no experience in patients with recent kidney transplantation.
Primary hyperaldosteronism
Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of losartan is not recommended.

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

Heart failure
In patients with heart failure, with or without renal impairment, there is - as with other medicinal products acting on the renin-angiotensin system - a risk of severe arterial hypotension, and (often acute) renal impairment.
There is no sufficient therapeutic experience with losartan in patients with heart failure and concomitant severe renal impairment, in patients with severe heart failure (NYHA class IV) as well as in patients with heart failure and symptomatic life-threatening cardiac arrhythmias. Therefore, losartan should be used with caution in these patient groups. The combination of losartan with a beta-blocker should be used with caution.
Aortic and mitral valve stenosis, obstructive hypertrophic cardiomyopathy
As with other vasodilators, special caution is indicated in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.

Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

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

Hydrochlorothiazide
Hypotension and electrolyte/fluid imbalance
As with all antihypertensive therapy, symptomatic hypotension may occur in some patients. Patients should be observed for clinical signs of fluid or electrolyte imbalance, e.g. volume depletion, hyponatreamia, hypochloremic alkalosis, hypomagnesaemia or hypokalemia which

may occur during intercurrent diarrhea or vomiting. Periodic determination of serum electrolytes should be performed at appropriate intervals in such patients. Dilutional hyponatreamia may occur in edematous patients in hot weather.

Metabolic and endocrine effects

Thiazide therapy may impair glucose tolerance. Dosage adjustment of antidiabetic agents, including insulin, may be required. Latent diabetes mellitus may become manifest during thiazide therapy.

Thiazides may decrease urinary calcium excretion and may cause intermittent and slight elevation of serum calcium. Marked hyperkalemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Thiazide therapy may precipitate hyperuricemia and/or gout in certain patients. Because losartan decreases uric acid, losartan in combination with hydrochlorothiazide attenuates the diuretic-induced hyperuricaemia.

Hepatic impairment

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

It is contraindicated for patients with severe hepatic impairment.

Other

In patients receiving thiazides, hypersensitivity reactions may occur with or without a history of allergy or bronchial asthma. Exacerbation or activation of systemic lupus erythematous has been reported with the use of thiazides.

16.6 Paediatric population

Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2 as no data are available.

16.7 Interaction with other medicinal products and other forms of interactions

Amlodipine

Impact of Other Drugs on Amlodipine

CYP3A Inhibitors

Co-administration with CYP3A inhibitors (moderate and strong) results in increased systemic exposure to amlodipine and may require dose reduction. Monitor for symptoms of hypotension and edema when amlodipine is co-administered with CYP3A inhibitors to determine the need for dose adjustment.

CYP3A Inducers
No information is available on the quantitative effects of CYP3A inducers on amlodipine. Blood pressure should be closely monitored when amlodipine is co-administered with CYP3A inducers.
Sildenafil
Monitor for hypotension when sildenafil is co-administered with amlodipine.

Impact of Amlodipine on Other Drugs
Simvastatin
Co-administration of simvastatin with amlodipine increases the systemic exposure of simvastatin. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

Immunosuppressant
Amlodipine may increase the systemic exposure of cyclosporine or tacrolimus when co-administered. Frequent monitoring of trough blood levels of cyclosporine and tacrolimus is recommended and adjust the dose when appropriate

Losartan
Other antihypertensive agents may increase the hypotensive action of losartan. Concomitant use with other substances which may induce hypotension as an adverse reaction (like tricyclic antidepressants, antipsychotics, baclofen and amifostine) may increase the risk of hypotension.
Losartan is predominantly metabolized by cytochrome P450 (CYP) 2C9 to the active carboxy-acid metabolite. In a clinical trial it was found that fluconazole (inhibitor of CYP2C9) decreases the exposure to the active metabolite by approximately 50%. It was found that concomitant treatment of losartan with rifampicin (inducer of metabolism enzymes) gave a 40% reduction in plasma concentration of the active metabolite. The clinical relevance of this effect is unknown. No difference in exposure was found with concomitant treatment with fluvastatin (weak inhibitor of CYP2C9).
As with other medicinal products that block angiotensin II or its effects, concomitant use of other medicinal products which retain potassium (e.g. potassium-sparing diuretics: amiloride, triamterene, spironolactone) or may increase potassium levels (e.g. heparin), potassium supplements or salt substitutes containing potassium may lead to increases in serum potassium. Co-medication is not advisable.
Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Co-administration of lithium and losartan should be undertaken with caution. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.
When angiotensin II antagonists are administered simultaneously with NSAIDs (i.e. selective COX-2 inhibitors, acetylsalicylic acid at anti-inflammatory doses and non-selective NSAIDs), attenuation of the antihypertensive effect may occur. Concomitant use of angiotensin II

antagonists or diuretics and NSAIDs may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.
Clinical trial data have shown that dual blockade of the renin-angiotensin-aldosterone system (RAAS) through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is associated with a higher frequency of adverse events such as hypotension, hyperkalemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent

Hydrochlorothiazide
When given concurrently, the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, narcotics or antidepressants
Potentiation of orthostatic hypotension may occur.
Antidiabetic drugs (oral agents and insulin)
The treatment with a thiazide may influence the glucose tolerance. Dosage adjustment of the antidiabetic drug may be required. Metformin should be used with caution because of the risk of lactic acidosis induced by possible functional renal failure linked to hydrochlorothiazide.
Other antihypertensive drugs
Additive effect.
Cholestyramine and colestipol resins
Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.
Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.
Pressor amines (e.g. adrenaline)
Possible decreased response to pressor amines but not sufficient to preclude their use.
Skeletal muscle relaxants, nondepolarizing (e.g. tubocurarine)
Possible increased responsiveness to the muscle relaxant.
Lithium
Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity; concomitant use is not recommended.
Medicinal products used in the treatment of gout (Probenecid, sulfinpyrazone and allopurinol)
Dosage adjustment of uricosuric medicinal products may be necessary since hydrochlorothiazide may raise the level of serum uric acid. Increase in dosage of Probenecid or sulfinpyrazone may be necessary. Coadministration of a thiazide may increase the incidence of hypersensitivity reactions to allopurinol.

Anticholinergic agents (e.g. atropine, biperiden)

Increase of the bioavailability to thiazide-type diuretics by decreasing gastrointestinal motility and stomach emptying rate.

Cytotoxic agents (e.g. cyclophosphamide, methotrexate)

Thiazides may reduce the renal excretion of cytotoxic medicinal products and potentiate their myelosuppressive effects.

Salicylates

In case of high dosages of salicylates hydrochlorothiazide may enhance the toxic effect of the salicylates on the central nervous system.

Methyldopa

There have been isolated reports of haemolytic anaemia occurring with concomitant use of hydrochlorothiazide and methyldopa.

Cyclosporin

Concomitant treatment with cyclosporin may increase the risk of hyperuricemia and gout-type complications.

Digitalis glycosides

Thiazide-induced hypokalemia or hypomagnesaemia may favor the onset of digitalis-induced cardiac arrhythmias.

Medicinal products affected by serum potassium disturbances

Periodic monitoring of serum potassium and ECG is recommended when losartan/hydrochlorothiazide is administered with medicinal products affected by serum potassium disturbances (e.g. digitalis glycosides and antiarrhythmic) and with the following torsades de pointes (ventricular tachycardia)-inducing medicinal products (including some antiarrhythmic), hypocalcaemia being a predisposing factor to torsades de pointes (ventricular tachycardia):

- Class Ia antiarrhythmic (e.g. quinidine, hydro quinidine, disopyramide).
- Class III antiarrhythmic (e.g. amiodarone, sotalol, dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, Amisulpride, tiapride, pimozide, haloperidol, Droperidol).
- Others (e.g. bepridil, cisapride, diphemanil, erythromycin IV, halofantrin, mizolastin, pentamidine, terfenadine, vincamine IV).

Calcium salts

Thiazide diuretics may increase serum calcium levels due to decreased excretion. If calcium supplements must be prescribed, serum calcium levels should be monitored and calcium dosage should be adjusted accordingly.

Laboratory Test Interactions

Because of their effects on calcium metabolism, thiazides may interfere with tests for parathyroid function.

Carbamazepine
Risk of symptomatic hyponatreamia. Clinical and biological monitoring is required.
Iodine Contrast Media
In case of diuretic-induced dehydration, there is an increased risk of acute renal failure, especially with high doses of the iodine product. Patients should be rehydrated before the administration.
Amphotericin B (parenteral), corticosteroids, ACTH, stimulant laxatives, or glycyrrhizin (found in liquorice).
Hydrochlorothiazide may intensify electrolyte imbalance, particularly hypokalemia.

16.8 Additional information on special populations
Hepatic impairment
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, as it may cause intrahepatic cholestasis, and since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
It is contraindicated for patients with severe hepatic impairment.
Renal impairment
As a consequence of inhibiting the renin-angiotensin system, changes in renal function including renal failure have been reported (in particular, in patients whose renal function is dependent on the renin- angiotensin-aldosterone system such as those with severe cardiac insufficiency or pre-existing renal dysfunction). As with other medicinal products that affect the renin-angiotensin-aldosterone system, increases in blood urea and serum creatinine have also been reported in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney; these changes in renal function may be reversible upon discontinuation of therapy. Losartan should be used with caution in patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney.
Use in Paediatric patients with renal impairment
Losartan is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2 as no data are available.
Renal function should be regularly monitored during treatment with losartan as it may deteriorate. This applies particularly when losartan is given in the presence of other conditions (fever, dehydration) likely to impair renal function.
Concomitant use of losartan and ACE-inhibitors has shown to impair renal function. Therefore, concomitant use is not recommended
Renal transplantation
There is no experience in patients with recent kidney transplantation.

16.9 Paediatric population
None

16.10 Fertility, pregnancy and lactation

16.10.1 General principles

16.10.2 Women of childbearing potential / Contraception in males and females

Not known

16.10.3 *Pregnancy*

Amlodipine

Although some Dihydropyridines compounds have been found to be teratogenic in animals, data it he rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in pregnancy. Accordingly, amlodipine should not be administered during pregnancy or to women of childbearing potential unless effective contraception is used.

Losartan

The use of losartan is not recommended during the first trimester of pregnancy. The use of losartan is contra-indicated during the 2nd and 3rd trimester of pregnancy.

Epidemiological evidence regarding the risk of teratogenicity following exposure to ACE inhibitors during the first trimester of pregnancy has not been conclusive; however a small increase in risk cannot be excluded. Whilst there is no controlled epidemiological data on the risk with Angiotensin II Receptor Inhibitors (AIIRAs), similar risks may exist for this class of medicinal products. Unless continued AIIRA therapy is considered essential, patients planning pregnancy should be changed to alternative anti-hypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with losartan should be stopped immediately and, if appropriate, alternative therapy should be started.

Exposure to AIIRA therapy during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, and hyperkalemia).

Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.

Hydrochlorothiazide

There is limited experience with hydrochlorothiazide during pregnancy, especially during the first trimester. Animal studies are insufficient.

Hydrochlorothiazide crosses the placenta. Based on the pharmacological mechanism of action of hydrochlorothiazide, its use during second and third trimesters may compromise foeto-placental perfusion and may cause foetal and neonatal effects like icterus, disturbance of electrolyte balance and thrombocytopenia.

Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or preeclampsia due to the risk of decreased plasma volume and placental hypoperfusion, without a beneficial effect on the course of the disease.
Hydrochlorothiazide should not be used for essential hypertension in pregnant women except in rare situations where no other treatment could be used.

16.10.4 ***Lactation***

Amlodipine

Although some Dihydropyridines compounds have been found to be teratogenic in animals, data in the rat and rabbit for amlodipine provide no evidence for a teratogenic effect. There is, however, no clinical experience with the preparation in lactation. Accordingly, amlodipine should not be administered during lactation

Losartan

Because no information is available regarding the use of losartan during breastfeeding, losartan is not recommended and alternative treatments with better established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm infant.

Hydrochlorothiazide

Hydrochlorothiazide is excreted in human milk in small amounts. Thiazides in high doses causing intense diuresis can inhibit the milk production. The use of Hydrochlorothiazide Comp during breastfeeding is not recommended. If it is used during breastfeeding, doses should be kept as low as possible.

16.4.5 ***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

In preclinical studies, no effects of Hydrochlorothiazide on male and female fertility were observed.

16.11 Effects on ability to drive and use machine

No studies on the reactions on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy, in particular during initiation of treatment or when the dose is increased.

16.12 Undesirable effects

Amlodipine

The following events occurred in <1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship:

Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, peripheral ischemia, syncope, tachycardia, Vasculitis.

Central and Peripheral Nervous System: hypoesthesia, neuropathy peripheral, paraesthesia, tremor, vertigo.

Gastrointestinal: anorexia, constipation, 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 multiform, pruritus, rash, rash erythematous, rash maculo-papular.

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.

Haemapoietic: leukopenia, purpura, thrombocytopenia.

Losartan

Blood and lymphatic system disorders

Uncommon: Anaemia, Henoch-Schönlein purpura, ecchymosis, hemolysis

Immune system disorders

Rare: Anaphylactic reactions, angioedema, urticaria

Metabolism and nutrition disorders

Uncommon: Anorexia, gout

Psychiatric disorders

Common: Insomnia

Uncommon: Anxiety, anxiety disorder, panic disorder, confusion, depression, abnormal dreams, sleep disorder, somnolence, memory impairment

Nervous system disorders

Common: Headache, dizziness

Uncommon: Nervousness, paraesthesia, peripheral neuropathy, tremor, migraine, syncope

Eye disorders

Uncommon: Blurred vision, burning/stinging in the eye, conjunctivitis, decrease in visual acuity

Ear and labyrinth disorders

Uncommon: Vertigo, tinnitus

Cardiac disorders

Uncommon: Hypotension, orthostatic hypotension, sternalgia, angina pectoris, grade II-AV block, cerebrovascular event, myocardial infarction, and palpitation, arrhythmias (atrial fibrillations, sinus Bradycardia, tachycardia, ventricular tachycardia, and ventricular fibrillation).
Vascular disorders
Uncommon: Vasculitis.
Respiratory, thoracic and mediastinal disorders
Uncommon: Decreased libido, impotence.
General disorders and administration site conditions
Common: Asthenia, fatigue, chest pain.
Uncommon: Facial oedema.

Hydrochlorothiazide

System organ class	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	Agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, purpura, thrombocytopenia	uncommon
Immune system disorders	Anaphylactic reaction	rare
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hyperuricemia, hypokalaemia, hyponatreamia	uncommon
Psychiatric disorders	Insomnia	uncommon
Nervous system disorders	Cephalalgia	common
Eye disorders	Transient blurred vision, xanthopsia	uncommon
Vascular disorders	Necrotizing angiitis (Vasculitis, cutaneous Vasculitis)	uncommon
Respiratory, thoracic and mediastinal disorders	Respiratory distress including pneumonitis and pulmonary oedema	uncommon
Gastrointestinal disorders	Sialoadenitis, spasms, stomach irritation, nausea, vomiting, diarrhoea, constipation	uncommon
Hepato-biliary disorders	Icterus (intrahepatic cholestatis), pancreatitis	uncommon
Skin and subcutaneous tissue disorders	Photosensitivity, urticaria, toxic epidermal necrolysis	uncommon
	cutaneous lupus erythematous	not known
Musculoskeletal and connective tissue disorders	Muscle cramps	uncommon
Renal and urinary disorders	Glycosuria, interstitial nephritis, renal dysfunction, renal failure	uncommon
General disorders and administration site	Fever, dizziness	uncommon

conditions		

16.13 Overdose

Amlodipine

Available data suggest that gross over dosage 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.

Administration of activated charcoal to healthy volunteers immediately or up to two hours after ingestion of amlodipine 10mg has been shown to significantly decrease amlodipine absorption.

In humans, experience with intentional overdose is limited. Gastric lavage may be worthwhile in some cases. Clinically significant hypotension due to amlodipine over dosage 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. Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Losartan

(i) Symptoms of intoxication

Limited data are available with regard to overdose in humans. The most likely manifestation of overdose would be hypotension and tachycardia. Bradycardia could occur from parasympathetic (vagal) stimulation.

(ii) Treatment of intoxication

If symptomatic hypotension should occur, supportive treatment should be instituted. Measures are depending on the time of medicinal product intake and kind and severity of symptoms. Stabilization of the cardiovascular system should be given priority. After oral intake, the administration of a sufficient dose of activated charcoal is indicated. Afterwards, close monitoring of the vital parameters should be performed. Vital parameters should be corrected if necessary. Neither losartan nor the active metabolite can be removed by hemodialysis.

Hydrochlorothiazide

The most common signs and symptoms observed are those caused by electrolyte depletion (hypokalemia, hypochloremic, hyponatreamia) and dehydration resulting from excessive diuresis. If digitalis has also been administered, hypokalemia may accentuate cardiac arrhythmias. The degree to which hydrochlorothiazide is removed by hemodialysis has not been established.

17. Pharmacological Properties

17.1 Pharmacodynamic Properties

Amlodipine

Amlodipine is a dihydropyridines calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Experimental data suggest that amlodipine binds to both dihydropyridine and nondihydropyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Amlodipine inhibits calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Negative inotropic effects can be detected in vitro but such effects have not been seen in intact animals at therapeutic doses. Serum calcium concentration is not affected by amlodipine. Within the physiologic pH range, amlodipine is an ionized compound (pKa=8.6), and its kinetic interaction with the calcium channel receptor is characterized by a gradual rate of association and dissociation with the receptor binding site, resulting in a gradual onset of effect.

Amlodipine is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The precise mechanisms by which amlodipine relieves angina have not been fully delineated, but are thought to include the following:

Exceptional Angina: In patients with exceptional angina, Amlodipine reduces the total peripheral resistance (afterload) against which the heart works and reduces the rate pressure product, and thus myocardial oxygen demand, at any given level of exercise.

Vasospastic Angina: Amlodipine has been demonstrated to block constriction and restore blood flow in coronary arteries and arterioles in response to calcium, potassium epinephrine, serotonin, and thromboxane A2 analog in experimental animal models and in human coronary vessels in vitro. This inhibition of coronary spasm is responsible for the effectiveness of Amlodipine in Vasospastic (Prinzmetal's or variant) angina.

Losartan

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.

Hypertension Studies

In controlled clinical studies, once-daily administration of losartan to patients with mild to moderate essential hypertension produced statistically significant reductions in systolic and diastolic blood pressure. Measurements of blood pressure 24 hours post-dose relative to 5 – 6 hours post-dose demonstrated blood pressure reduction over 24 hours; the natural diurnal rhythm was retained. Blood pressure reduction at the end of the dosing interval was 70 – 80% of the effect seen 5-6 hours post-dose.

Discontinuation of losartan in hypertensive patients did not result in an abrupt rise in blood pressure (rebound). Despite the marked decrease in blood pressure, losartan had no clinically significant effects on heart rate.

Losartan is equally effective in males and females, and in younger (below the age of 65 years) and older hypertensive patients.

Hydrochlorothiazide

Hydrochlorothiazide is a thiazide diuretic. The mechanism of the antihypertensive effect of thiazide diuretics is not fully known. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. The diuretic action of hydrochlorothiazide reduces plasma volume, increases plasma renin activity and increases aldosterone secretion, with consequent increases in urinary potassium and bicarbonate loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II and therefore co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with thiazide diuretics.

After oral use, diuresis begins within 2 hours, peaks in about 4 hours and lasts about 6 to 12 hours the antihypertensive effect persists for up to 24 hours.

17.2 Pharmacokinetic Properties:

Amlodipine

After oral administration of therapeutic doses of Amlodipine, absorption produces peak plasma concentrations 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 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. Elimination from the plasma is biphasic with a terminal elimination half-life of about 30–50 hours. Steady-state plasma levels of amlodipine are reached after 7 to 8 days of consecutive daily dosing.

The pharmacokinetics of amlodipine are not significantly influenced by renal impairment. Patients with renal failure may therefore receive the usual initial dose.

Elderly patients and patients with hepatic insufficiency have decreased clearance of amlodipine with a resulting increase in AUC of approximately 40–60%, and a lower initial dose may be required. A similar increase in AUC was observed in patients with moderate to severe heart failure.

Losartan

Absorption

Following oral administration, losartan is well absorbed and undergoes first-pass metabolism, forming an active carboxylic acid metabolite and other inactive metabolites. The systemic bioavailability of losartan tablets is approximately 33%. Mean peak concentrations of losartan and its active metabolite are reached in 1 hour and in 3-4 hours, respectively.

Distribution

Both losartan and its active metabolite are ≥99% bound to plasma proteins, primarily albumin. The volume of distribution of losartan is 34 litres.

Biotransformation

About 14% of an intravenously- or orally-administered dose of losartan is converted to its active metabolite. Following oral and intravenous administration of ^{14}C-labelled losartan potassium, circulating plasma radioactivity primarily is attributed to losartan and its active metabolite. Minimal conversion of losartan to its active metabolite was seen in about one percent of individuals studied.

In addition to the active metabolite, inactive metabolites are formed.

Elimination

Plasma clearance of losartan and its active metabolite is about 600 ml/min and 50 ml/min, respectively. Renal clearance of losartan and its active metabolite is about 74 ml/min and 26

ml/min, respectively. 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 pharmacokinetics of losartan and its active metabolite are linear with oral losartan potassium doses up to 200 mg.

Following oral administration, plasma concentrations of losartan and its active metabolite decline polyexponentially, with a terminal half-life of about 2 hours and 6-9 hours, respectively. 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. Following an oral dose/intravenous administration of ^{14}C-labelled losartan in man, about 35% / 43% of radioactivity is recovered in the urine and 58%/ 50% in the faeces.

Characteristics in patients

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 hemodialysis patients.

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

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

Pharmacokinetics in Paediatric 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.

Hydrochlorothiazide

Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney. When plasma levels have been followed for at least 24 hours, the plasma half-life has been observed to vary between 5.6 and 14.8 hours. At least 61 percent of the oral dose is eliminated unchanged within 24 hours.

17.3 Preclinical safety Data

Amlodipine

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rats and mice treated with amlodipine maleate in the diet for up to two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 amlodipine mg/kg/day, showed no evidence of a carcinogenic effect of the drug. For the mouse, the highest dose was, on a mg/m2 basis, similar to the maximum recommended human dose of 10 mg amlodipine/day. For the rat, the highest dose was, on a mg/m2 basis, about twice the maximum recommended human dose.

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

There was no effect on the fertility of rats treated orally with amlodipine maleate (males for 64 days and females for 14 days prior to mating) at doses up to 10 mg amlodipine/kg/day (8 times the maximum recommended human dose of 10 mg/day on a mg/m2 basis).

Losartan-Hydrochlorothiazide

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. The toxic potential of the combination of losartan/hydrochlorothiazide was evaluated in chronic toxicity studies for up to six months duration in rats and dogs after oral administration, and the changes observed in these studies with the combination were mainly produced by the losartan component. The administration of the losartan/hydrochlorothiazide combination induced a decrease in the red blood cell parameters (erythrocytes, hemoglobin, and hematocrit), a rise in urea-N in the serum, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, hemorrhages).

There was no evidence of teratogenicity in rats or rabbits treated with the losartan/hydrochlorothiazide combination. Foetal toxicity in rats, as evidenced by a slight increase in supernumerary ribs in the F_1 generation, was observed when females were treated prior to and throughout gestation. As observed in studies with losartan alone, adverse foetal and neonatal reactions, including renal toxicity and foetal death, occurred when pregnant rats were treated with the losartan/hydrochlorothiazide combination during late gestation and/or lactation.

17.4 Environmental Risk Assessment (ERA)
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

18. Pharmaceutical Particulars
18.1 List of excipients
Maize Starch, Microcrystalline Cellulose, Methyl Hydroxy Benzoate, Propyl Hydroxy Benzoate, Sodium Starch Glycollate, Colloidal Silicon dioxide, Talc, Magnesium Stearate, Cross Povidone, Hypermellose, Titanium Dioxide, Talc, Coloring agent.

18.2 Incompatibilities
None

18.3 Shelf life
24 months from the date of manufacturing.

18.4 Special precautions for storage
Store below 30°C. Keep this medicine out of reach of children

18.5 Nature and contents of container
Alu/Alu Blister pack of 10 Tablets, such 3 blisters are packed in printed outer carton along with pack insert.

18.6 Special precautions for disposal and other handling
None

19. Marketing Authorization Holder and Manufacturing Site Addresses
MICRO LABS LIMITED
92, Sipcot Industrial Complex,
Hosur - 635 126 (T.N.)
INDIA

20. Marketing Authorisation Number
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21. Date of First Registration/Renewal of the registration
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22. Date of revision of the text
April 2019

23. DOSIMETRY
Not applicable

24. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Not applicable