

**Size: 280 (L) x 420 (H) mm  
Folding size: 35 x 150 mm  
Drg. No. : 9918020-006  
Carton size: 46 x 28 x 106 mm**

**Front side  
Paper 35-45 gsm**

280 mm

130 mm

150 mm



**LOSARTAN POTASSIUM  
HYDROCHLOROTHIAZIDE  
AMLODIPINE**

**AMLOZAAR-H**

50 mg/12.5 mg/5 mg Film Coated Tablet

ANTIHYPERTENSIVE

**PRODUCT NAME**  
AMLOZAAR-H

**DOSAGE FORM AND STRENGTH:**

Amlodipine 5 mg, Losartan Potassium 50 mg and Hydrochlorothiazide 12.5 mg Tablets

**PHARMACOLOGIC CATEGORY:** Calcium channel blockers, Angiotensin II antagonists and diuretics

**PRODUCT DESCRIPTION**

Yellow coloured, circular, biconvex film-coated tablets with a breakline on one surface

**FORMULATION/COMPOSITION:**

Each film-coated tablet contains:  
Losartan Potassium USP ..... 50 mg  
Amlodipine Besilate BP equivalent to Amlodipine ..... 5 mg  
Hydrochlorothiazide BP ..... 12.5 mg

**PHARMACODYNAMICS/PHARMACOKINETICS:**

**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<sub>1</sub>) 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<sub>1</sub> 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<sub>1</sub> 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 fall within three days to the baseline values.

Both losartan and its principal active metabolite have a far greater affinity for the AT<sub>1</sub>-receptor than for the AT<sub>2</sub>-receptor. The active metabolite is 10- to 40- times more active than losartan on a weight for weight basis.

**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.

**Pharmacokinetics:**

**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 <sup>14</sup>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 <sup>14</sup>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.

**INDICATIONS:**

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

**DOSAGE AND MODE / ROUTE 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.

**CONTRAINDICATIONS & PRECAUTION(S), WARNING(S)**

**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

**PRECAUTIONS & WARNINGS:**

**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**

**Angioedema.** Patients with a history of Angioedema (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 hyperkalaemia 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.

**Heart failure**

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.

**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 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<sup>2</sup> 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,**

Size: 280 (L) x 420 (H) mm

Folding size: 35 x 150 mm

Drg. No. : 9918020-006

Carton size: 46 x 28 x 106 mm

**Back side****Paper 35-45 gsm**

280 mm

150 mm

130 mm

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 hypo perfusion, 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.

**Lactation**

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.

**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.

**Immunosuppressants**

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 fluclozole (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, sulfapyrazone 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 sulfapyrazone 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 hyperuricaemia 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, hydroquinidine, disopyramide).
- Class III antiarrhythmic (e.g. dofetilide, ibutilide).
- Some antipsychotics (e.g. thioridazine, chlorpromazine, levomepromazine, trifluoperazine, cyamemazine, sulpiride, sultopride, Amisulpride, tiapride, pimozide, haloperidol, droperidol).
- Others (e.g. bepridil, cisapride, diphenanil, erythromycin IV, halofantrin, mizolastine, 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 hyponatraemia. 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.

**ADVERSE 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, gastritis, 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.

**Haemopoietic:** 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, hyperuricaemia, hypokalaemia, hyponatraemia	uncommon
Psychiatric disorders	Insomnia	uncommon
Nervous system disorders	Cephalgia	common
Eye disorders	Transient blurred vision, xanthopsia	uncommon
Ear and labyrinth disorders	N	

<b>MICRO LABS LIMITED, BANGALORE, INDIA</b>					
1	Product Name	Amlozaar-H		<u>Colours Used</u>	
2	Strength	50 mg, 12.5 and 5 mg		 BLACK	
3	Component	Leaflet			
4	Category	Export - Philippines			
5	Dimension	280 (L) x 420 (H) mm			
6	Artwork Code	EXG-ML01I-1201/A			
7	Pharma Code	264			
8	Reason for Change	Size and New Regulation text		<u>Colours not for Printing</u>  Keylines	
Prepared by (DTP)		Checked by (PD)	<b>Approved by</b>		
Sign	Kantharaju L.		Head CQA	Head Production/ Packing (Site)	Head QC (Site)
Date	09-11-2022				Head QA (Site)