Summary of Product Characteristics
LOSARGOOD AM H
(Losartan Potassium 50mg, Amlodipine 5mg and Hydrochlorothiazide 12.5mg Tablets)

1. Name of the medicinal product
LOSARGOOD AM H (Losartan Potassium 50mg, Amlodipine 5mg and Hydrochlorothiazide 12.5mg)

2. Qualitative and quantitative composition
Each Tablet contains 50mg of Losartan Potassium USP, 5mg Amlodipine Besylate USP
eq. to Amlodipine and 12.5mg Hydrochlorothiazide USP.

Excipients of known effect:
Each tablet contains 30.00 mg of lactose monohydrate.
For the full list of excipients see section 6.1.

1. Pharmaceutical form
Tablets
Orange-coloured, round, biconcave-shaped, film coated tablets plain on both sides.

4.CLINICAL PARTICULARS:
4.1 Therapeutic indications
- Hypertension.
- Oedema associated with heart failure.
- Oedema caused by other conditions.

4.2 Posology and method of administration
Posology
The usual recommended dose is once daily.
Per tablet contains amlodipine 5 mg, losartan potassium 50 mg and Hydrochlorothiazide 12.5 mg: Initial: 1 tablet once daily; may increase to 2 tablets daily if the BP control is inadequate after 1-2 wk.

Method of administration
A ready-to-use solution is prepared in 10 ml of sodium chloride 9 mg/ml (0.9 %) solution for injection. For instructions for preparation see section 6.6. The prepared solution may be administered directly or may be administered after mixing it with 100 ml sodium chloride 9 mg/ml (0.9 %) solution for injection or glucose 50 mg/ml (5 %) solution for injection.
The solution obtained should be administered within 12 hours.
The medicinal product should be administered intravenously over 2 - 15 minutes.

4.3 Contraindications
- In patients who are hypersensitive to any component of this product.
- In patients with anuria
- For co administration with aliskiren in patients with diabetes

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4.4 Special warnings and precautions for use

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 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.
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.

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.

Hydrochlorothiazide

Hypotension and electrolyte/fluid imbalance

Symptomatic hypotension may occur in some patients. This was rarely seen in uncomplicated
hypertensive patients, but was more likely in the presence of fluid depletion or electrolyte imbalance.
Therefore, periodic determination of serum electrolytes and creatinine should be performed at
appropriate intervals.
Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (including
hypokalaemia, hyponatraemia, and hypochloraemic alkalosis).
Thiazides may decrease urinary calcium excretion and cause an intermittent and slight elevation of
serum calcium in the absence of known disorders of calcium metabolism. If hypercalcaemia occurs,
further diagnostic tests are necessary.
Marked hypercalcaemia may be evidence of hidden hyperparathyroidism. Thiazides should be
discontinued before carrying out a test for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium, which may result in
hypomagnesaemia.
Hyponatraemia accompanied by neurological symptoms (nausea, weakness, progressive disorientation
and apathy) has been seen in isolated cases.

Potassium

As with all thiazide diuretics, the excretion of potassium which is caused by hydrochlorothiazide is
dose related. At a dose of 12.5 mg/day, the decrease in serum potassium concentrations is on average

0.36 mmol/l after a period of treatment of 6 months. In the case of long-term treatment, the serum potassium concentration has to be established at the start of the treatment and then after 3-4 weeks.
This is then to be monitored every 4–6 months if the potassium balance is not affected by other factors (e.g. vomiting, diarrhoea and changes in renal function).
The monitoring of serum electrolytes is particularly important in elderly people, patients with ascites as a result of cirrhosis of the liver and patients with oedema as a result of nephrotic syndrome.
Concomitant treatment with an oral potassium salt (e.g. KCl) or with a potassium-sparing diuretic can be considered in patients receiving digitalis, in the case of symptoms of coronary heart disease, in patients receiving high doses of a β-adrenergic agonist and in all cases where plasma concentrations are <3.0 mmol/l.
In all cases of combined treatment, the maintenance or normalisation of the serum potassium must be closely monitored. If hypokalaemia is accompanied by clinical symptoms (e.g. muscle weakness, paresis and changes in ECG), the administration of hydrochlorothiazide must be stopped.
Combined treatment consisting of hydrochlorothiazide and a potassium salt or a potassium-sparing diuretic is to be avoided in the case of patients who are also receiving an ACE inhibitor.
<u>Metabolic effects</u>
Just like other diuretics, hydrochlorothiazide can increase the serum uric acid content, but new episodes of gout are only rarely seen with long-term use.
Hydrochlorothiazide must not be used as the medicine of first choice for the long-term treatment of patients with manifest diabetes mellitus. Just as with all thiazide diuretics, glucose tolerance can change during chronic therapy, with the effect being smaller at lower doses. However, diabetes mellitus only rarely occurs during treatment, certainly in the case of patients in whom there are no other predisposing factors. A worsening of the metabolic situation rarely occurs in the case of diabetics.

Small, sometimes reversible increases in the plasma concentrations of total cholesterol, triglycerides
or" low-density lipoprotein" cholesterol have been reported in patients in the course of long-term
treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for discussion.
Hydrochlorothiazide is not to be used as the medicine of first choice in the case of patients who are
receiving treatment for hypercholesterolaemia (diet combined therapy).

4.5 Interaction with other medicinal products and other forms of interaction

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 metabolised 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.

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.

Hydrochlorothiazide
The following combinations with Hydrochlorothiazide Orion may require dose adjustments.
Medicinal products associated with potassium loss and hypokalaemia
Simultaneous application of hydrochlorothiazide and medicinal products associated with potassium
loss and hypokalaemia, e.g. kaliuretic diuretics (e.g. furosemide), glucocorticoids, ACTH, laxatives,
carbenoxolone, amphotericin B, penicillin G sodium, salicylic acid and derivatives may enhance the
potassium-depleting effect. The monitoring of potassium level is advised. Use of such combinations

requires caution.
Lithium
Concomitant application of hydrochlorothiazide and lithium may lead to diminished lithium elimination and increased cardiotoxic and neurotoxic effects of lithium. Therefore, co-administration of lithium and hydrochlorothiazide should only be allowed under strict medical supervision and should not be recommended. If this combination proves essential, serum lithium level monitoring is recommended during concomitant use.
Other diuretics, blood pressure lowering drugs, betablockers, nitrates, barbiturates, phenothiazines, tricyclic antidepressive, vasodilators, alcohol
Concomitant application of hydrochlorothiazide and these products may intensify the antihypertensive efficacy of Hydrochlorothiazide
ACE inhibitors (e.g. captopril, enalapril)
When administered concurrently with ACE inhibitors (e.g. captopril, enalapril) severe first-dose hypotension and deterioration of renal function may develop. Treatment with diuretics should therefore be stopped 2–3 days before starting ACE inhibitor therapy to reduce the risk of first-dose hypotension.
Salicylates and other NSAIDs (e.g. indometacin) including selective COX-2 inhibitors
Salicylates and other NSAIDs (e.g. indometacin), including selective COX-2 inhibitors, may diminish antihypertensive and diuretic effects of hydrochlorothiazide.
During simultaneous application of NSAIDs acute renal failure may occur in those patients, who develop hypovolaemia during hydrochlorothiazide therapy. Clinical observations suggest that the risk of hospitalization is doubled in patients treated with NSAIDs and diuretics compared with those who only received diuretics. There are single cases of worsening of renal function, especially in patients with poor pre-existing renal function.
Hydrochlorothiazide may intensify the toxic effects of salicylates on the central nervous system.

4.6 Fertility, pregnancy and lactation

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Losartan

Pregnancy

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.

Lactation

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.

Amlodipine

Although some Dihydropyridines compounds have been found to be teratogenic in animals, data it he rats 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.

Lactation

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.

Hydrochlorothiazide

Pregnancy

There is limited experience with the use of hydrochlorothiazide during pregnancy, particularly during
the first trimester. Animal studies are insufficient. Hydrochlorothiazide crosses the placenta. Based on

pharmacological mechanism of action of hydrochlorothiazide, its use during the second and third
trimester may compromise foeto-placental perfusion and may cause foetal and neonatal effects such
as icterus, disturbance of electrolyte balance and thrombocytopenia.
Hydrochlorothiazide should not be used for gestational oedema, gestational hypertension or pre-
eclampsia, 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 the
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 production of milk. The use of Hydrochlorothiazide during lactation is
not recommended. If Hydrochlorothiazide is used during breast feeding, doses should be kept as low
as possible.

Fertility

There are no human data regarding the effect of hydrochlorothiazide on fertility. In animal studies
hydrochlorothiazide didn't indicate harmful effects on fertility or reproduction

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines 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.

4.8 Undesirable effects

Losartan

Blood and lymphatic system disorders
Uncommon: Anemia, 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.

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, paresthesia, 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.
Haemopoietic: leukopenia, purpura, thrombocytopenia.

Hydrochlorothiazide
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Not known: Non-melanoma skin cancer (Basal cell carcinoma and Squamous cell carcinoma)
Blood and lymphatic system disorders:
Common: Thrombocytopenia (sometimes with purpura)
Uncommon: Leukopenia
Very rare: Agranulocytosis, bone marrow depression, aplastic anaemia, haemolytic anaemia, immune
haemolytic anaemia due to formation of antibodies against hydrochlorothiazide during simultaneous
application of methyldopa
Immune system disorders:
Rare: Hypersensitivity reactions.
Metabolism and nutrition disorders:
Very common: disturbances in the electrolyte- and fluid imbalance, especially hypokalaemia,
hyponatraemia, hypochloraemia and hypercalcaemia; hyperglycaemia and glucosuria in patients
without metabolic problems and those with latent or manifest diabetes mellitus or in patients with
hypokalaemia; hyperuricaemia, resulting in acute gout in pre-disposed patients; elevations of serum
lipids (cholesterol, triglycerides).
Very rare: Hypochloraemic alkalosis
Not known: aggravation of diabetes in patients with manifest diabetes mellitus, manifestation of a
latent diabetes mellitus
Psychiatric disorders:
Rare: sleep disorders, depression
Nervous system disorders
Rare: Paraesthesia, headache, dizziness or dullness.
Eye disorders
Uncommon: Visual disorders (e.g. blurred vision, xanthopsia) impaired secretion of tears, aggravation

of myopia
Not known: Acute myopia, acute angle-closure glaucoma
Cardiac disorders
Common: palpitations
Uncommon Orthostatic hypotension, especially in patients with intravascular volume depletion, e.g.
patients with severe heart failure or under treatment with high dose diuretics (which can be
aggravated
by alcohol, anaesthetics or sedatives).
Rare: Arrhythmias.
Vascular disorders:
Uncommon: Vasculitis (in single cases necrotizing vasculitis)
Respiratory, thoracic and mediastinal disorders
Uncommon: respiratory distress, acute interstitial pneumonia
Very rare: pulmonary oedema with shock, probably due to an allergic reaction
Gastrointestinal disorders
Common: Loss of appetite, gastrointestinal disorders (e.g. nausea, vomiting, diarrhoea, abdominal
cramps and abdominal pain)
Rare: constipation
Hepato-biliary disorders
Uncommon: Pancreatitis, hyperamylasemia, icterus (intrahepatic cholestasis)
Not known: in patients with pre-existing cholelithiasis, anacute cholestasis may develop, jaundice.
Skin and subcutaneous tissue disorders
Uncommon: allergic skin reactions (e.g. pruritus, erythema, photoallergic exanthema, purpura,
urticaria)
Very rare: Angiitis necroticans (vasculitis) and toxic epidermal necrolysis, cutaneous lupus
erythematodes, lupus erythematodes--like reactions, reactivation of cutaneous lupus erythematodes.
Renal und urinary disorders:
Very common: glucosuria
Common: reversible elevation of serum creatinine and urea
Uncommon: interstitial nephritis
Reproductive system and breast disorders
Uncommon: Impotence.
General disorders and administration site conditions:
Uncommon: drug fever

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to National Regulatory Agents.

4.9 Overdose

Losartan

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.

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.

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.

Hydrochlorothiazide

Symptoms of intoxication

Symptoms which can occur after ingestion are acute fluid loss, gastrointestinal symptoms, polyuria or oliguria, dizziness and impaired consciousness. As a result of severe hypokalemia:

muscle weakness, fatigue, concentration disorders, dullness, cardiac arrhythmias, hypotension and coma. As a result of acute hyponatraemia: agitation, headache, pain or cramps, and convulsions.
Treatment of intoxication
Treatment consists of the inducement of vomiting, the repeated administration of activated charcoal and the drinking of large amounts. Gastric lavage, where necessary (only useful shortly after intake).
Maintenance of the fluid and electrolyte balance. Potassium suppletion, where necessary. Further symptomatic treatment.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Losartan

Pharmacodynamic group: Angiotensin II receptor blockers
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.

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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.

Amlodipine

Pharmacodynamic group: Dihydropyridine Derivatives
ATC Code: C08CA01
Amlodipine 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. 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.

Hydrochlorothiazide
Pharmacotherapeutic group: Low-ceiling diuretics, thiazides – Thiazides, plain – Hydrochlorothiazide,
ATC code: C03AA03.
Thiazide diuretics particularly exert their effect in the distal part of the renal tubule by inhibiting
NaCl resorption (by antagonism of the Na+Cl carrier). The increased amount of Na+ and water in the
ductus colligens (collecting duct) and/or the increased filtration rate results in an increase in the
secretion and excretion of K+ and H+.
In people with normal renal function, diuresis is already promoted after administration of 12.5 mg of
hydrochlorothiazide. The resulting increase in the urinary excretion of sodium and chloride and the
relatively small increase in potassium in the urine are dose related. The diuretic and natriuretic effect
is noticeable after 1–2 hours following the oral administration of hydrochlorothiazide, reaches its
maximum after 4–6 hours and can last for 10–12 hours.
Thiazide-induced diuresis initially results in a decrease in plasma volume, the cardiac minute volume
and systemic blood pressure. The renin-angiotensin-aldosterone system can be activated. The
hypotensive effect continues to be maintained with the continuation of the medication, probably as a
result of the decrease in peripheral resistance; the cardiac minute volume returns to the original value
and the plasma volume remains somewhat lower.
With long-term administration, the antihypertensive effect of hydrochlorothiazide is dose related
between 12.5 and 50 mg a day. The maximum hypotensive effect is usually reached at 50 mg a day in
most patients. Increasing the dose to above 50 mg/day increases the metabolic complications and is
rarely necessary from a therapeutic point of view.
If given as a monotherapy, hydrochlorothiazide appears to produce a good effect in around 40–50% of patients, just like other diuretics. In general, elderly people and black people appear to respond well to diuretics as the primary therapy.
Combined treatment with other antihypertensive agents increases the blood

pressure lowering effect.
In a large proportion of patients who show an unsatisfactory response to a monotherapy, a further
decrease in blood pressure can be achieved in this way.
As thiazide diuretics such as hydrochlorothiazide reduce Ca+ excretion, these are used in order to
prevent the recurrence of renal calcium oxalate stones in patients with idiopathic normocalcaemic
hypercalciuria.
With long-term treatment, users of thiazide diuretics appear to have a significantly higher mineral
content in their bones than non-users.
In nephrogenic diabetes insipidus, hydrochlorothiazide reduces the volume of urine and increases the
osmolality of the urine.

5.2 Pharmacokinetic properties

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 liters.

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.

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.

Hydrochlorothiazide
Absorption
The absorption of hydrochlorothiazide administered as hydrochlorothiazide tablets amounts in total to
around 70% of the dose. However, variations in absorption as a result of fasting or the intake of food
are of little clinical significance. The absorption of hydrochlorothiazide is reduced in patients who
suffer from cardiac decompensation.
In the therapeutic domain, the bioavailability and maximum concentration are directly proportional to
the dose. After continuous administration, the pharmacokinetics of hydrochlorothiazide do not change
and the average concentration is around 100 ng/ml at a dose of 75 mg a day every day for six weeks.
Distribution
Hydrochlorothiazide accumulates in erythrocytes and reaches a maximum concentration around 4
hours after oral administration. After 10 hours, the concentration in the erythrocytes is around three
times higher than in the plasma. Binding to plasma proteins of around 40–70% has been reported and
the apparent volume of distribution can be estimated to be 5–6 l/kg.
Hydrochlorothiazide crosses the placenta and, in the umbilical cord, reaches a concentration which
approaches the concentration in the plasma of the mother. The medicinal product accumulates in the
amniotic fluid, where the concentration can be nineteen times the concentration in the umbilical cord.
Hydrochlorothiazide is excreted in the maternal milk.
Elimination

Hydrochlorothiazide is eliminated from plasma with an elimination half-life of on average 9.5 to 13
hours in the terminal elimination phase. Within 72 hours, 60–80% of an oral dose is excreted in the
urine, 95% in an unchanged form and around 4% in the form of the hydrolysate 2-amino-4-chloro-m-
benzene disulphonamide (ACBS). Up to 24% of an oral dose is excreted in the faeces and a negligible amount is excreted via bile.
In elderly patients, the “steady-state” concentration of hydrochlorothiazide is elevated and systemic
clearance is significantly decreased compared with younger patients. For this reason, it is necessary
that the treatment of elderly patients take place under strict supervision.
In patients with renal impairment (creatinine clearance between 30 and around 70 ml/min), the rate of
urinary excretion is reduced and a higher maximum plasma concentration and AUC are observed. The average elimination half-life is twice as long.
Hepatic diseases do not have a significant influence on the pharmacokinetics of hydrochlorothiazide
however caution is recommended when hydrochlorothiazide is administered to patients with liver
disease

5.3 Preclinical safety data

Losartan

Preclinical data reveal no special hazard for humans based on conventional studies of general pharmacology, genotoxicity and carcinogenic potential. In repeated dose toxicity studies, the administration of losartan induced a decrease in the red blood cell parameters (erythrocytes, haemoglobin, haematocrit), a rise in urea-N in the serum and occasional rises in serum creatinine, a decrease in heart weight (without a histological correlate) and gastrointestinal changes (mucous membrane lesions, ulcers, erosions, haemorrhages). Like other substances that directly affect the renin-angiotensin system, losartan has been shown to induce adverse reactions on the late foetal development, resulting in foetal death and malformations.

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).

Hydrochlorothiazide
Animal sub chronic and chronic toxicity studies in dogs and rats revealed no marked results except
changes in electrolyte balance. In vitro and in vivo mutagenicity assays for gene and chromosomal
mutations showed negative results. Long-term carcinogenicity studies with hydrochlorothiazide in rats and mice showed no relevant elevations of tumor amount in the dosage groups. In animal studies,
hydrochlorothiazide crosses the placenta. Animal studies showed no effects on fertility in rats and no
teratogenic effects in rats, mice and rabbits.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Ingredients
1.	Lactose
2.	Microcrystalline Cellulose
3.	Maize Starch
4.	H.P.M.C
5.	Purified Water
6.	Purified Talc
7.	Colloidal Anhydrous Silica
8.	Cross Povidone
9.	Magnesium Stearate
10.	Iso-Propyl Alcohol
11.	Titanium Dioxide
12.	Colour: Sunset Yellow
13.	Mono-Propylene Glycol

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 months.

Summary of Product Characteristics
LOSARGOOD AM H
(Losartan Potassium 50mg, Amlodipine 5mg and Hydrochlorothiazide 12.5mg Tablets)

6.4 Special precautions for storage
Store at the temperature not exceeding 30°C. Protect from light and moisture. Keep medicines out of reach of children.

6.5 Nature and contents of container
1 Alu-Alu Blister of 10 Tablets, such 3 Blisters packed in Printed Carton with Insert

6.6 Special precautions for disposal and other handling
No special requirements

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

ZAIN PHARMA LTD.
Plot No: 209/13741, Colchester Park,
Go-Down No.1, 2, 3, Off Mombasa Road,
Behind Nice and Lovely House,
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8. Marketing Authorization Number:
H2025/CTD12489/26435

9. Date of First <Registration> / Renewal of The <Registration>
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10. Date of Revision of the Text:
8/12/2025