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

TRILOSAR

1. Generic Name

Losartan Potassium, Amlodipine and Chlorthalidone Tablets

2. Qualitative and Quantitative composition

TRILOSAR 6.25

Each film coated tablet contains:
Losartan Potassium I.P. ....……50 mg
Amlodipine Besylate I.P. equivalent to Amlodipine…….5 mg
Chlorthalidone I.P. ……..6.25 mg
Excipients…….q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000 and Castor oil.

TRILOSAR 12.5

Each film coated tablet contains:
Losartan potassium I.P. ....……50 mg
Amlodipine Besylate I.P. equivalent to Amlodipine…….5 mg
Chlorthalidone I.P. ……..12.5 mg
Excipients……..q.s.
Colour: Ferric Oxide Yellow NF
The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000, Castor oil and Ferric Oxide Yellow.

3. DOSAGE FORM AND STRENGTH

TRILOSAR 6.25

Dosage Form: Film Coated Tablet
Strength: Losartan potassium 50 mg, Amlodipine 5 mg, Chlorthalidone 6.25mg

TRILOSAR 12.5

Dosage Form: Film Coated Tablet
Strength: Losartan potassium 50 mg, Amlodipine 5 mg, Chlorthalidone 12.5mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

It is used for the treatment of essential hypertension.

4.2 Posology and Method of Administration

Dosage: As directed by the Physician.

Losartan potassium

Posology

Hypertension

The usual starting and maintenance dose is 50 mg once daily for most patients. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. Some patients may receive an additional benefit by increasing the dose to 100 mg once daily (in the morning). Losartan may be administered with other antihypertensive agents, especially with diuretics (e.g. hydrochlorothiazide).

Hypertensive type II diabetic patients with proteinuria ≥ 0.5 g/day

The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response from one month onwards after initiation of therapy. Losartan may be administered with other antihypertensive agents (e.g. diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g. sulfonylureas, glitazones and glucosidase inhibitors).

Heart Failure

The usual initial dose of losartan in patients with heart failure is 12.5 mg once daily. The dose should generally be titrated at weekly intervals (i.e. 12.5 mg daily, 25 mg daily, 50 mg daily, 100 mg daily, up to a maximum dose of 150 mg once daily) as tolerated by the patient.

Reduction in the risk of stroke in hypertensive patients with left ventricular hypertrophy documented by ECG

The usual starting dose is 50 mg of losartan once daily. A low dose of hydrochlorothiazide should be added and/or the dose of losartan should be increased to 100 mg once daily based on blood pressure response.

Special populations

Use in patients with intravascular volume depletion:

For patients with intravascular volume-depletion (e.g. those treated with high-dose diuretics), a starting dose of 25 mg once daily should be considered.

Use in patients with renal impairment and haemodialysis patients:

No initial dosage adjustment is necessary in patients with renal impairment and in haemodialysis patients.

Use in patients with hepatic impairment:

A lower dose should be considered for patients with a history of hepatic impairment. There is no therapeutic experience in patients with severe hepatic impairment. Therefore, losartan is contraindicated in patients with severe hepatic impairment.

Paediatric population

6 months – less than 6 years

The safety and efficacy of children aged 6 months to less than 6 years has not been established.

6 years to 18 years

For patients who can swallow tablets, the recommended dose is 25 mg once daily in patients

>20 to <50 kg. (In exceptional cases the dose can be increased to a maximum of 50 mg once daily). Dosage should be adjusted according to blood pressure response.
In patients >50 kg, the usual dose is 50 mg once daily. In exceptional cases the dose can be adjusted to a maximum of 100 mg once daily. Doses above 1.4 mg/kg (or in excess of 100 mg) daily have not been studied in paediatric patients.
Losartan is not recommended for use in children under 6 years old, as limited data are available in these patient groups.
It is not recommended in children with glomerular filtration rate < 30 ml/min/1.73 m^2, as no data are available.
Losartan is also not recommended in children with hepatic impairment.
Use in Elderly
Although consideration should be given to initiating therapy with 25 mg in patients over 75 years of age, dosage adjustment is not usually necessary for the elderly.

Amlodipine Besilate

Posology

Adults
For both hypertension and angina the usual initial dose is 5 mg Amlodipine once daily which may be increased to a maximum dose of 10 mg depending on the individual patient's response.
In hypertensive patients, Amlodipine has been used in combination with a thiazide diuretic, alpha blocker, beta blocker, or an angiotensin converting enzyme inhibitor. For angina, Amlodipine may be used as monotherapy or in combination with other antianginal medicinal products in patients with angina that is refractory to nitrates and/or to adequate doses of beta blockers.
No dose adjustment of Amlodipine is required upon concomitant administration of thiazide diuretics, beta blockers, and angiotensin-converting enzyme inhibitors.

Special populations

Elderly patients
Amlodipine used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.
Patients with hepatic impairment
Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore, dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.
Patients with renal impairment
Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.
Paediatric population
Children and adolescents with hypertension from 6 years to 17 years of age
The recommended antihypertensive oral dose in paediatric patients ages 6-17 years is 2.5 mg once daily as a starting dose, up-titrated to 5 mg once daily if blood pressure goal is not

achieved after 4 weeks. Doses in excess of 5 mg daily have not been studied in paediatric patients.

Children under 6 years old

No data are available.

Chlorthalidone

The dosage of Chlortalidone should be individually titrated to give the lowest effective dose; this is particularly important in the elderly. Chlortalidone should be taken orally, preferably as a single daily dose at breakfast time.

Adults:

Hypertension

The recommended starting dose is 25mg/day. This is sufficient to produce the maximum hypotensive effect in most patients. If the decrease in blood pressure proves inadequate with 25mg/day, then the dose can be increased to 50mg/day. If a further reduction in blood pressure is required, additional hypertensive therapy may be added to the dosage regime.

Stable, chronic heart failure (NYHA: functional class II /III):

The recommended starting dose is 25 to 50mg/day, in severe cases it may be increased up to 100 to 200mg/day. The usual maintenance dose is the lowest effective dose, eg 25 to 50mg/day either daily or every other day. If the response proves inadequate, digitalis or an ACE inhibitor, or both, may be added. (See "Special warnings and precautions for use").

Oedema of specific origin ("Therapeutic indications")

The lowest effective dose is to be identified by titration and administered over limited periods only. It is recommended that doses should not exceed 50mg/day.

Diabetes insipidus:

Initially 100mg twice daily but reducing where possible to a daily maintenance dose of 50mg.

Children:

The lowest effective dose should also be used in children. For example, an initial dose of 0.5 to 1mg/kg/48hours and a maximum dose of 1.7mg/kg/48hours have been used.

Elderly patients and patients with renal impairment:

The lowest effective dose of Chlortalidone is also recommended for patients with mild renal insufficiency and for elderly patients (see "Pharmacokinetic properties").

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, a reduction in the recommended adult dosage may be needed. Close medical observation is indicated when treating patients of advanced age with chlortalidone.

Chlortalidone and the thiazide diuretics lose their diuretic effect when the creatinine clearance is <30ml/min.

Method of administration

Tablet for oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance, dihydropyridine derivatives, amlodipine or to any of the excipients listed.
- 2nd and 3rd trimester of pregnancy.

- Severe hepatic impairment.
- The concomitant use of losartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2)
- Severe hypotension.
- shock (including cardiogenic shock)
- obstruction of the outflow tract of the left ventricle (e.g., high grade aortic stenosis).
- haemodynamically unstable heart failure after acute myocardial infarction.

4.4 Special Warnings and Precautions for Use

Losartan potassium

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 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.

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-exAmlodipineg 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 ischaemic 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.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS)

There is evidence that the concomitant use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren increases the risk of hypotension, hyperkalaemia, and decreased renal function (including acute renal failure). Dual blockade of RAAS through the combined use of ACE-inhibitors, angiotensin II receptor blockers or aliskiren is therefore not recommended.

If dual blockade therapy is considered absolutely necessary, this should only occur under specialist supervision and subject to frequent close monitoring of renal function, electrolytes and blood pressure. ACE-inhibitors and angiotensin II receptor blockers should not be used concomitantly in patients with diabetic nephropathy.

Amlodipine Besilate

The safety and efficacy of amlodipine in hypertensive crisis has not been established.

Patients with cardiac failure

Patients with heart failure should be treated with caution. In a long-term, placebo controlled study in patients with severe heart failure (NYHA class III and IV) the reported incidence of pulmonary oedema was higher in the amlodipine treated group than in the placebo group. Calcium channel blockers, including amlodipine, should be used with caution in patients with congestive heart failure, as they may increase the risk of future cardiovascular events and mortality.

Patients with hepatic impairment

The half-life of amlodipine is prolonged and AUC values are higher in patients with impaired liver function; dosage recommendations have not been established. Amlodipine should therefore be initiated at the lower end of the dosing range and caution should be used, both on initial treatment and when increasing the dose. Slow dose titration and careful monitoring may be required in patients with severe hepatic impairment.

Elderly patients

In the elderly increase of the dosage should take place with care.

Patients with renal impairment

Amlodipine may be used in such patients at normal doses. Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment. Amlodipine is not dialysable.

Chlorthalidone

Warnings:

Chlortalidone should be used with caution in patients with impaired hepatic function or progressive liver disease since minor changes in the fluid and electrolyte balance due to thiazide diuretics may precipitate hepatic coma, especially in patients with liver cirrhosis (see “Contra-indications”).

Chlortalidone should also be used with caution in patients with severe renal disease. Thiazides may precipitate azotaemia in such patients, and the effects of repeated

administration may be cumulative.

Precautions:

Electrolytes:

Treatment with thiazide diuretics has been associated with electrolyte disturbances such as hypokalaemia, hypomagnesaemia, hyperglycaemia and hyponatraemia. Since the excretion of electrolytes is increased, a very strict low-salt diet should be avoided.

Hypokalaemia can sensitise the heart or exaggerate its response to the toxic effects of digitalis.

Like all thiazide diuretics, kaluresis induced by Chlortalidone is dose dependent and varies in extent from one subject to another. With 25 to 50mg/day, the decrease in serum potassium concentrations averages 0.5mmol/l. Periodic serum electrolyte determinations should be carried out, particularly in digitalised patients.

If necessary, Chlortalidone may be combined with oral potassium supplements or a potassium-sparing diuretic (eg triamterene).

If hypokalaemia is accompanied by clinical signs (eg muscular weakness, paresis and ECG alteration), Chlortalidone should be discontinued.

Combined treatment consisting of Chlortalidone and a potassium salt or a potassium-sparing diuretic should be avoided in patients also receiving ACE inhibitors.

Monitoring of serum electrolytes is particularly indicated in the elderly, in patients with ascites due to liver cirrhosis, and in patients with oedema due to nephrotic syndrome. There have been isolated reports of hyponatraemia with neurological symptoms (eg nausea, debility, progressive disorientation and apathy) following thiazide treatment.

For nephrotic syndrome, Chlortalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlortalidone may raise the serum uric acid level, but attacks of gout are uncommon during chronic treatment.

As with the use of other thiazide diuretics, glucose intolerance may occur; this is manifest as hyperglycaemia and glycosuria. Chlortalidone may very seldom aggravate or precipitate diabetes mellitus; this is usually reversible on stopping therapy.

Small and partly reversible increases in plasma concentrations of total cholesterol, triglycerides, or low-density lipoprotein cholesterol were reported in patients during long-term treatment with thiazides and thiazide-like diuretics. The clinical relevance of these findings is a matter for debate.

Chlortalidone should not be used as a first-line drug for long-term treatment in patients with overt diabetes mellitus or in subjects receiving therapy for hypercholesterolaemia (diet or combined).

As with all antihypertensive agents, a cautious dosage schedule is indicated in patients with severe coronary or cerebral arteriosclerosis.

Other effects:

The antihypertensive effect of ACE inhibitors is potentiated by agents that increase plasma renin activity (diuretics). It is recommended that the diuretic be reduced in dosage or withdrawn for 2 to 3 days and/or that the ACE inhibitor therapy be started with a low initial dose of the ACE inhibitor. Patients should be monitored for several hours after the first dose.

4.5 Drugs Interactions

Losartan potassium

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-exAmlodipineg 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, hyperkalaemia, and decreased renal function (including acute renal failure) compared to the use of a single RAAS-acting agent.

Amlodipine Besilate

Effects of other medicinal products on amlodipine

CYP3A4 inhibitors

Concomitant use of amlodipine with strong or moderate CYP3A4 inhibitors (protease inhibitors, azole antifungals, macrolides like erythromycin or clarithromycin, verapamil or diltiazem) may give rise to significant increase in amlodipine exposure resulting in an

increased risk of hypotension. The clinical translation of these PK variations may be more pronounced in the elderly. Clinical monitoring and dose adjustment may thus be required.

CYP3A4 inducers

Upon co-administration of known inducers of the CYP3A4, the plasma concentration of amlodipine may vary. Therefore, blood pressure should be monitored and dose regulation considered both during and after concomitant medication particularly with strong CYP3A4 inducers (e.g. rifampicin, hypericum perforatum).

Administration of amlodipine with grapefruit or grapefruit juice is not recommended as bioavailability may be increased in some patients resulting in increased blood pressure lowering effects.

Dantrolene (infusion)

In animals, lethal ventricular fibrillation and cardiovascular collapse are observed in association with hyperkalemia after administration of verapamil and intravenous dantrolene. Due to risk of hyperkalemia, it is recommended that the co-administration of calcium channel blockers such as amlodipine be avoided in patients susceptible to malignant hyperthermia and in the management of malignant hyperthermia.

Effects of amlodipine on other medicinal products

The blood pressure lowering effects of amlodipine adds to the blood pressure-lowering effects of other medicinal products with antihypertensive properties.

Tacrolimus

There is a risk of increased tacrolimus blood levels when co-administered with amlodipine but the pharmacokinetic mechanism of this interaction is not fully understood. In order to avoid toxicity of tacrolimus, administration of amlodipine in a patient treated with tacrolimus requires monitoring of tacrolimus blood levels and dose adjustment of tacrolimus when appropriate.

Mechanistic Target of Rapamycin (mTOR) Inhibitors

mTOR inhibitors such as sirolimus, temsirolimus, and everolimus are CYP3A substrates. Amlodipine is a weak CYP3A inhibitor. With concomitant use of mTOR inhibitors, amlodipine may increase exposure of mTOR inhibitors.

Cyclosporine

No drug interaction studies have been conducted with cyclosporine and amlodipine in healthy volunteers or other populations with the exception of renal transplant patients, where variable trough concentration increases (average 0% - 40%) of cyclosporine were observed. Consideration should be given for monitoring cyclosporine levels in renal transplant patients on amlodipine, and cyclosporine dose reductions should be made as necessary.

Simvastatin

Co-administration of multiple doses of 10 mg of amlodipine with 80 mg simvastatin resulted in a 77% increase in exposure to simvastatin compared to simvastatin alone. Limit the dose of simvastatin in patients on amlodipine to 20 mg daily.

In clinical interaction studies, amlodipine did not affect the pharmacokinetics of atorvastatin, digoxin or warfarin.

Chlorthalidone

Diuretics potentiate the action of curare derivatives and antihypertensive drugs (e.g. guanethidine, methyldopa, β-blockers, vasodilators, calcium antagonists and ACE

inhibitors).
The hypokalaemic effect of diuretics may be potentiated by corticosteroids, ACTH, ß2 – agonists, amphotericin and carbenoxolone.
It may prove necessary to adjust the dosage of insulin and oral anti-diabetic agents.
Thiazide-induced hypokalaemia or hypomagnesaemia may favour the occurrence of digitalis-induced cardiac arrhythmias (see"Special warnings and precautions for use").
Concomitant administration of certain non-steroidal anti-inflammatory drugs (e.g. indometacin) may reduce the diuretic and antihypertensive activity of Chlortalidone; there have been isolated reports of a deterioration in renal function in predisposed patients.
The bioavailability of thiazide-type diuretics may be increased by anticholinergic agents (eg atropine, biperiden), apparently due to a decrease in gastrointestinal motility and stomach-emptying rate.
Absorption of thiazide diuretics is impaired in the presence of anionic exchange resins such as colestyramine. A decrease in the pharmacological effect may be expected.
Concurrent administration of thiazide diuretics may increase the incidence of hypersensitivity reactions to allopurinol, increase the risk of adverse effects caused by amantadine, enhance the hyperglycaemic effect of diazoxide, and reduce renal excretion of cytotoxic agents (eg cyclophosphamide, methotrexate) and potentiate their myelosuppressive effects.
The pharmacological effects of both calcium salts and vitamin D may be increased to clinically significant levels if given with thiazide diuretics. The resultant hypercalcaemia is usually transient but may be persistent and symptomatic (weakness, fatigue, anorexia) in patients with hyperparathyroidism.
Concomitant treatment with cyclosporin may increase the risk of hyperuricaemia and gout-type complications.
Thiazide and related diuretics can cause a rapid rise in serum lithium levels as the renal clearance of lithium is reduced by these compounds.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

Losartan potassium

Pregnancy

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

The use of losartan is not recommended during the first trimester of pregnancy. The use of losartan is contraindicated 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, hyperkalaemia).
Should exposure to losartan have occurred from the second trimester of pregnancy, ultrasound check of renal function and skull is recommended.
Infants whose mothers have taken losartan should be closely observed for hypotension.
Breastfeeding
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 Besilate

Pregnancy
The safety of amlodipine in human pregnancy has not been established.
In animal studies, reproductive toxicity was observed at high doses.
Use in pregnancy is only recommended when there is no safer alternative and when the disease itself carries greater risk for the mother and foetus.
Breast-feeding
Amlodipine is excreted in human milk. The proportion of the maternal dose received by the infant has been estimated with an interquartile range of 3-7%, with a maximum of 15%. The effect of amlodipine on infants is unknown. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with amlodipine should be made taking into account the benefit of breast-feeding to the child and the benefit of amlodipine therapy to the mother.
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.

Chlorthalidone

Diuretics are best avoided for the management of oedema or hypertension in pregnancy as their use may be associated with hypovolaemia, increased blood viscosity and reduced placental perfusion. There have been reports of foetal bone marrow depression, thrombocytopenia, and foetal and neonatal jaundice associated with the use of thiazide diuretics.
Chlortalidone passes into the breast milk; mothers taking Chlortalidone should refrain from breast-feeding their infants.

4.7 Effects On Ability to Drive and Use Machines

Losartan potassium

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.

Amlodipine Besilate

Amlodipine can have minor or moderate influence on the ability to drive and use machines. If patients taking amlodipine suffer from dizziness, headache, fatigue or nausea the ability to react may be impaired. Caution is recommended especially at the start of treatment.

Chlorthalidone

Patients should be warned of the potential hazards of driving or operating machinery if they experience side effects such as dizziness.

4.8 Undesirable Effects

Losartan potassium

Losartan has been evaluated in reported clinical studies as follows:

- In reported controlled clinical trial in > 3,000 adult patients 18 years of age and older for essential hypertension
- In reported controlled clinical trial in 177 hypertensive paediatric patients 6 to 16 years of age
- In reported controlled clinical trial in > 9,000 hypertensive patients 55 to 80 years of age with left ventricular hypertrophy (see LIFE Study)
- In reported controlled clinical trials in > 7,700 adult patients with chronic heart failure (see ELITE I, ELITE II, and HEAAL study)
- In reported controlled clinical trial in > 1,500 type 2 diabetic patients 31 years of age and older with proteinuria (see RENAAL study)

In these reported clinical trials, the most common adverse event was dizziness.

The frequency of adverse reactions listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100, to < 1/10); uncommon (≥ 1/1,000, to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1. The frequency of adverse reactions identified from placebo-controlled clinical studies and post marketing experience

Adverse reaction	**Frequency of adverse reaction by indication**				**Other**
	Hypertension	**Hypertensive patients with left-ventricular hypertrophy**	**Chronic Heart Failure**	**Hypertension and type 2 diabetes with renal disease**	**Post-marketing experience**
Blood and lymphatic system disorders					

anaemia			common		frequency not known
thrombocytopenia					frequency not known
Immune system disorders					
hypersensitivity reactions, anaphylactic reactions, angiooedema*, and vasculitis**					rare
Psychiatric disorders					
depression					frequency not known
Nervous system disorders					
dizziness	common	common	common	common	
somnolence	uncommon				
headache	uncommon		uncommon		
sleep disorders	uncommon				
paraesthesia			rare		
migraine					frequency not known
dysgeusia					frequency not known
Ear and labyrinth disorders					
vertigo	common	common			
tinnitus					frequency not known
Cardiac disorders					
palpitations	uncommon				
angina pectoris	uncommon				
syncope			rare		
atrial fibrillation			rare		
cerebrovascular accident			rare		
Vascular disorders					
(orthostatic)	uncommon		common	common	

hypotension (including dose-related orthostatic effects)‖					
Respiratory, thoracic and mediastinal disorders					
dyspnoea			uncommon		
cough			uncommon		frequency not known
Gastrointestinal disorders					
abdominal pain	uncommon				
obstipation	uncommon				
diarrhoea			uncommon		frequency not known
nausea			uncommon		
vomiting			uncommon		
Hepatobiliary disorders					
pancreatitis					frequency not known
hepatitis					rare
liver function abnormalities					frequency not known
Skin and subcutaneous tissue disorders					
urticaria			uncommon		frequency not known
pruritus			uncommon		frequency not known
rash	uncommon		uncommon		frequency not known
photosensitivity					frequency not known
Musculoskeletal and connective tissue disorders					
myalgia					frequency not known
arthralgia					frequency not known
rhabdomyolysis					frequency not known
Renal and urinary disorders					

renal impairment			common		
renal failure			common		
Reproductive system and breast disorders					
erectile dysfunction / impotence					frequency not known
General disorders and administration site conditions					
asthenia	uncommon	common	uncommon	common	
fatigue	uncommon	common	uncommon	common	
oedema	uncommon				
malaise					frequency not known
Investigations					
hyperkalaemia	common		uncommon†	common‡	
increased alanine aminotransferase (ALT) §	rare				
increase in blood urea, serum creatinine, and serum potassium			common		
hyponatraemia					frequency not known
hypoglycaemia				common	

*****Including swelling of the larynx, glottis, face, lips, pharynx, and/or tongue (causing airway obstruction); in some of these patients angiooedema had been reported in the past in connection with the administration of other medicines, including ACE inhibitors

**Including Henoch-Schönlein purpura

‖Especially in patients with intravascular depletion, e.g. patients with severe heart failure or under treatment with high dose diuretics

†Common in patients who received 150 mg losartan instead of 50 mg

‡In a clinical study conducted in type 2 diabetic patients with nephropathy, 9.9% of patients treated with Losartan tablets developed hyperkalaemia >5.5 mmol/l and 3.4% of patients treated with placebo

§Usually resolved upon discontinuation

The following additional adverse reactions occurred more frequently in patients who received losartan than placebo (frequencies not known): back pain, urinary tract infection, and flu-like symptoms.

Renal and urinary disorders:

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function including renal failure have been reported in patients at risk; these changes in renal

function may be reversible upon discontinuation of therapy.

Paediatric population

The adverse reaction profile for paediatric patients appears to be similar to that seen in adult patients. Data in the paediatric population are limited.

Amlodipine Besilate

Summary of the safety profile

The most commonly reported adverse reactions during treatment are somnolence, dizziness, headache, palpitations, flushing, abdominal pain, nausea, ankle swelling, oedema and fatigue.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very rare	Leukocytopenia, thrombocytopenia
Immune system disorders	Very rare	Allergic reactions
Metabolism and nutrition disorders	Very rare	Hyperglycaemia
Psychiatric disorders	Uncommon	Depression, mood changes (including anxiety), insomnia
	Rare	Confusion
Nervous system disorders	Common	Somnolence, dizziness, headache (especially at the beginning of the treatment)
	Uncommon	Tremor, dysgeusia, syncope, hypoaesthesia, paraesthesia
	Very rare	Hypertonia, peripheral neuropathy
Eye disorders	Common	Visual disturbance (including diplopia)
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia,

		altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Very rare	Hepatitis, jaundice, hepatic enzyme increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria
	Very rare	Angioedema, erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, Quincke oedema, photosensitivity
	Not known	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Common	Ankle swelling, muscle cramps
	Uncommon	Arthralgia, myalgia, back pain
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency
Reproductive system and breast disorders	Uncommon	Impotence, gynaecomastia
General disorders and administration site conditions	Very common	Oedema
	Common	Fatigue, asthenia
	Uncommon	Chest pain, pain, malaise
Investigations	Uncommon	Weight increased, weight decreased

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

<u>Chlorthalidone</u>

Frequency estimate: very rare <0.01%, rare ≤0.01% to ≤0.1%;uncommon ≤0.1% to <1%; common ≤1% to <10%; very common ≥10%.

Electrolytes and metabolic disorders:

Very common: mainly at higher doses, hypokalaemia, hyperuricaemia, and rise in blood lipids.

Common: hyponatraemia, hypomagnesaemia and hyperglycaemia.

Uncommon: gout.

Rare: hypercalcaemia, glycosuria, worsening of diabetic metabolic state.

Very rare: hypochloraemic alkalosis.

Skin:

Common: urticaria and other forms of skin rash.

Rare: photosensitisation.

Liver:
Rare: intrahepatic cholestasis or jaundice.
Cardiovascular system:
Common: postural hypotension.
Rare: cardiac arrhythmias.
Central nervous system:
Common: Dizziness.
Rare: paraesthesia, headache.
Gastro-intestinal tract:
Common: loss of appetite and minor gastrointestinal distress.
Rare: mild nausea and vomiting, gastric pain, constipation and diarrhoea.
Very rare: pancreatitis.
Blood:
Rare: Thrombocytopenia, leucopenia, agranulocytosis and eosinophilia.
Other effects:
Common: impotence
Rare: Idiosyncratic pulmonary oedema (respiratory disorders), allergic interstitial nephritis.

4.9 Overdose

Losartan potassium

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. Stabilisation 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 haemodialysis.

Amlodipine Besilate

In humans experience with intentional overdose is limited.

Symptoms

Available data suggest that gross overdosage 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.

Treatment

Clinically significant hypotension due to amlodipine overdosage 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.
Gastric lavage may be worthwhile in some cases. In healthy volunteers the use of charcoal up to 2 hours after administration of amlodipine 10 mg has been shown to reduce the absorption rate of amlodipine.
Since amlodipine is highly protein-bound, dialysis is not likely to be of benefit.

Chlorthalidone

Signs and symptoms: In poisoning due to an overdosage the following signs and symptoms may occur: dizziness, nausea, somnolence, hypovolaemia, hypotension and electrolyte disturbances associated with cardiac arrhythmias and muscle spasms.
Treatment: There is no specific antidote to Chlortalidone. Gastric lavage, emesis or activated charcoal should be employed to reduce absorption. Blood pressure and fluid and electrolyte balance should be monitored and appropriate corrective measures taken. Intravenous fluid and electrolyte replacement may be indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Mechanism of Action

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.

Amlodipine Besilate

Amlodipine is a calcium ion influx inhibitor of the dihydropyridine group (slow channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac and vascular smooth muscle.
The mechanism of the antihypertensive action of amlodipine is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but amlodipine reduces total ischaemic burden by the following two actions.
1) Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. Since the heart rate remains stable, this unloading of the heart reduces myocardial energy consumption and oxygen requirements.
2) The mechanism of action of amlodipine also probably involves dilatation of the main coronary arteries and coronary arterioles, both in normal and ischaemic regions. This dilatation increases myocardial oxygen delivery in patients with coronary artery spasm (Prinzmetal's or variant angina).

Chlorthalidone

Chlortalidone is a benzothiadiazine (thiazide)-related diuretic with a long duration of action.

Thiazide and thiazide-like diuretics act primarily on the distal renal tubule (early convoluted part), inhibiting $NaCl^-$ reabsorption (by antagonising the $Na+Cl^-$ cotransporter) and promoting Ca++ reabsorption (by an unknown mechanism). The enhanced delivery of Na+ and water to the cortical collection tubule and/or the increased flow rate leads to increased secretion and excretion of K+ and H+.

5.2. Pharmacodynamic Properties

Losartan potassium

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

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. Measurement 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 effect on heart rate.

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

LIFE-Study

The Losartan Intervention For Endpoint Reduction in Hypertension [LIFE] study was a randomised, triple-blind, active-controlled study in 9193 hypertensive patients aged 55 to 80 years with ECG-documented left-ventricular hypertrophy. Patients were randomised to once daily losartan 50 mg or once daily atenolol 50 mg. If goal blood pressure (< 140/90 mmHg) was not reached, hydrochlorothiazide (12.5 mg) was added first and, if needed, the dose of losartan or atenolol was then increased to 100 mg once daily. Other antihypertensives, with the exception of ACE-inhibitors, angiotensin II antagonists or beta-blockers were added if necessary to reach the goal blood pressure.

The mean length of follow up was 4.8 years.

The primary endpoint was the composite of cardiovascular morbidity and mortality as measured by a reduction in the combined incidence of cardiovascular death, stroke and myocardial infarction. Blood pressure was significantly lowered to similar levels in the two groups. Treatment with losartan resulted in a 13.0% risk reduction (p=0.021, 95% confidence interval 0.77-0.98) compared with atenolol for patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of stroke. Treatment with losartan reduced the risk of stroke by 25% relative to atenolol (p=0.001, 95% confidence interval 0.63-0.89). The rates of cardiovascular death and myocardial infarction were not significantly different between the treatment groups.

Race

In the LIFE-Study black patients treated with losartan had a higher risk of suffering the primary combined endpoint, i.e. a cardiovascular event (e.g. cardiac infarction, cardiovascular death) and especially stroke, than the black patients treated with atenolol. Therefore the results observed with losartan in comparison with atenolol in the LIFE study with regard to cardiovascular morbidity/mortality do not apply for black patients with hypertension and left ventricular hypertrophy.

RENAAL Study

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan RENAAL study was a controlled clinical study conducted worldwide in 1513 Type 2 diabetic patients with proteinuria, with or without hypertension. 751 patients were treated with losartan.

The objective of the study was to demonstrate a nephroprotective effect of losartan potassium over and above the benefit of lowering blood pressure.

Patients with proteinuria and a serum creatinine of 1.3 – 3.0 mg/dl were randomised to receive losartan 50 mg once a day, titrated if necessary, to achieve blood pressure response, or to placebo, on a background of conventional antihypertensive therapy excluding ACE-inhibitors and angiotensin II antagonists.

Investigators were instructed to titrate the study medication to 100 mg daily as appropriate; 72% of patients were taking the 100 mg daily dose for the majority of the time. Other antihypertensive agents (diuretics, calcium antagonists, alpha- and beta-receptor blockers and also centrally acting antihypertensives) were permitted as supplementary treatment depending on the requirement in both groups. Patients were followed up for up to 4.6 years (3.4 years on average). The primary endpoint of the study was a composite endpoint of doubling of the serum creatinine end-stage renal failure (need for dialysis or transplantation) or death.

The results showed that the treatment with losartan (327 events) as compared with placebo (359 events) resulted in a 16.1% risk reduction (p = 0.022) in the number of patients reaching the primary composite endpoint. For the following individual and combined components of the primary endpoint, the results showed a significant risk reduction in the group treated with losartan: 25.3% risk reduction for doubling of the serum creatinine (p = 0.006); 28.6% risk reduction for end-stage renal failure (p = 0.002); 19.9% risk reduction for end-stage renal failure or death (p = 0.009); 21.0% risk reduction for doubling of serum creatinine or end-stage renal failure (p = 0.01). All-cause mortality rate was not significantly different between the two treatment groups. In this study losartan was generally well tolerated, as

shown by a therapy discontinuation rate on account of adverse reactions that was comparable to the placebo group.

HEAAL Study

The Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL) study was a controlled clinical study conducted worldwide in 3834 patients aged 18 to 98 years with heart failure (NYHA Class II-IV) who were intolerant of ACE inhibitor treatment. Patients were randomised to receive losartan 50 mg once a day or losartan 150 mg, on a background of conventional therapy excluding ACE-inhibitors.

Patients were followed for over 4 years (median 4.7 years). The primary endpoint of the study was a composite endpoint of all-cause death or hospitalisation for heart failure.

The results showed that treatment with 150 mg losartan (828 events) as compared with 50 mg losartan (889 events) resulted in a 10.1% risk reduction (p=0.027, 95% confidence interval 0.82-0.99) in the number of patients reaching the primary composite endpoint. This was mainly attributable to a reduction of the incidence of hospitalisation for heart failure. Treatment with 150 mg losartan reduced the risk of hospitalisation for heart failure by 13.5% relative to 50 mg losartan (p=0.025, 95% confidence interval 0.76-0.98). The rate of all cause death was not significantly different between the treatment groups. Renal impairment, hypotension, and hyperkalaemia were more common in the 150 mg group than in the 50 mg group, but these adverse events did not lead to significantly more treatment discontinuations in the 150 mg group.

ELITE I and ELITE II Studies

In the ELITE Study carried out over 48 weeks in 722 patients with heart failure (NYHA Class II-IV), no difference was observed between the patients treated with losartan and those treated with captopril was observed with regard to the primary endpoint of a long-term change in renal function. The observation of the ELITE I Study, that compared with captopril, losartan reduced the mortality risk, was not confirmed in the subsequent ELITE II Study, which is described in the following.

In the ELITE II Study losartan 50 mg once daily (starting dose 12.5 mg, increased to 25 mg, then 50 mg once daily) was compared with captopril 50 mg three times daily (starting dose 12.5 mg, increased to 25 mg and then to 50 mg three times daily). The primary endpoint of this prospective study was the all-cause mortality.

In this study, 3152 patients with heart failure (NYHA Class II-IV) were followed for almost two years (median: 1.5 years) in order to determine whether losartan is superior to captopril in reducing all-cause mortality. The primary endpoint did not show any statistically significant difference between losartan and captopril in reducing all-cause mortality.

In both comparator-controlled (not placebo-controlled) clinical studies on patients with heart failure the tolerability of losartan was superior to that of captopril, measured on the basis of a significantly lower rate of discontinuations of therapy on account of adverse reactions and a significantly lower frequency of cough.

An increased mortality was observed in ELITE II in the small subgroup (22% of all HF patients) taking beta-blockers at baseline.

Dual Blockade of the renin-angiotensin-aldosterone system (RAAS)

Two large randomised, controlled trials (ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and VA NEPHRON-D (The Veterans

Affairs Nephropathy in Diabetes)) have examined the use of the combination of an ACE-inhibitor with an angiotensin II receptor blocker.
ONTARGET was a study conducted in patients with a history of cardiovascular or cerebrovascular disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage. VA NEPHRON-D was a study in patients with type 2 diabetes mellitus and diabetic nephropathy.
These studies have shown no significant beneficial effect on renal and/or cardiovascular outcomes and mortality, while an increased risk of hyperkalaemia, acute kidney injury and/or hypotension as compared to monotherapy was observed. Given their similar pharmacodynamic properties, these results are also relevant for other ACE-inhibitors and angiotensin II receptor blockers.
ACE-inhibitors and angiotensin II receptor blockers should therefore not be used concomitantly in patients with diabetic nephropathy.
ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints) was a study designed to test the benefit of adding aliskiren to a standard therapy of an ACE-inhibitor or an angiotensin II receptor blocker in patients with type 2 diabetes mellitus and chronic kidney disease, cardiovascular disease, or both. The study was terminated early because of an increased risk of adverse outcomes. Cardiovascular death and stroke were both numerically more frequent in the aliskiren group than in the placebo group and adverse events and serious adverse events of interest (hyperkalaemia, hypotension and renal dysfunction) were more frequently reported in the aliskiren group than in the placebo group.

Paediatric Population

Paediatric Hypertension

The antihypertensive effect of losartan was established in a clinical study involving 177 hypertensive paediatric patients 6 to 16 years of age with a body weight > 20 kg and a glomerular filtration rate > 30 ml/min/1.73 m^2. Patients who weighed > 20 kg to < 50 kg received either 2.5, 25 or 50 mg of losartan daily and patients who weighed > 50 kg received either 5, 50 or 100 mg of losartan daily. At the end of three weeks, losartan administration once daily lowered trough blood pressure in a dose-dependent manner.
Overall, there was a dose-response. The dose-response relationship became very obvious in the low dose group compared to the middle dose group (period I: -6.2 mmHg vs. -11.65 mmHg), but was attenuated when comparing the middle dose group with the high dose group (period I: -11.65 mmHg vs. -12.21 mmHg). The lowest doses studied, 2.5 mg and 5 mg, corresponding to an average daily dose of 0.07 mg/ kg, did not appear to offer consistent antihypertensive efficacy.
These results were confirmed during period II of the study where patients were randomised to continue losartan or placebo, after three weeks of treatment. The difference in blood pressure increase as compared to placebo was largest in the middle dose group (6.70 mmHg middle dose vs. 5.38 mmHg high dose). The rise in trough diastolic blood pressure was the same in patients receiving placebo and in those continuing losartan at the lowest dose in each group, again suggesting that the lowest dose in each group did not have significant antihypertensive effect.
Long-term effects of losartan on growth, puberty and general development have not been

studied. The long-term efficacy of antihypertensive therapy with losartan in childhood to reduce cardiovascular morbidity and mortality has also not been established.

In hypertensive (N=60) and normotensive (N=246) children with proteinuria, the effect of losartan on proteinuria was evaluated in a 12-week placebo- and active-controlled (amlodipine) clinical study. Proteinuria was defined as urinary protein/creatinine ratio of ≥0.3. The hypertensive patients (ages 6 through 18 years) were randomised to receive either losartan (n=30) or amlodipine (n=30). The normotensive patients (ages 1 through 18 years) were randomised to receive either losartan (n=122) or placebo (n=124). Losartan was given at doses of 0.7 mg/kg to 1.4 mg/kg (up to maximum dose of 100 mg per day). Amlodipine was given at doses of 0.05 mg/kg to 0.2 mg/kg (up to a maximum dose of 5 mg per day).

Overall, after 12 weeks of treatment, patients receiving losartan experienced a statistically significant reduction from baseline in proteinuria of 36% versus 1% increase in placebo/amlodipine group ($p \leq 0.001$). Hypertensive patients receiving losartan experienced a reduction from baseline proteinuria of -41.5% (95% CI -29.9;-51.1) versus +2.4% (95% CI -22.2; 14.1) in the amlodipine group. The decline in both systolic blood pressure and diastolic blood pressure was greater in the losartan group (-5.5/-3.8 mmHg) versus the amlodipine group (-0.1/+0.8 mmHg). In normotensive children a small decrease in blood pressure was observed in the losartan group (-3.7/-3.4 mmHg) compared to placebo. No significant correlation between the decline in proteinuria and blood pressure was noted, however it is possible that the decline in blood pressure was responsible, in part, for the decline in proteinuria in the losartan treated group.

Long-term effects of losartan in children with proteinuria were studied for up to 3 years in the open-label safety extension phase of the same study, in which all patients completing the 12-week base study were invited to participate. A total of 268 patients entered the open-label extension phase and were re-randomized to losartan (N=134) or enalapril (N=134) and 109 patients had ≥3 years of follow-up (pre-specified termination point of ≥100 patients completing 3 years of follow-up in the extension period). The dose ranges of losartan and enalapril, given according to investigator discretion, were 0.30 to 4.42 mg/kg/day and 0.02 to 1.13 mg/kg/day, respectively. The maximum daily doses of 50 mg for <50 kg body weight and 100 mg>50 kg were not exceeded for most patients during the extension phase of the study.

In summary, the results of the safety extension show that losartan was well-tolerated and led to sustained decreases in proteinuria with no appreciable change in glomerular filtration rate (GFR) over 3 years. For normotensive patients (n=205), enalapril had a numerically greater effect compared to losartan on proteinuria (-33.0% (95%CI -47.2;-15.0) vs -16.6% (95%CI -34.9; 6.8)) and on GFR (9.4 (95%CI 0.4; 18.4) vs -4.0 (95%CI -13.1; 5.0) ml/min/1.73m2)). For hypertensive patients (n=49), losartan had a numerically greater effect on proteinuria (-44.5% (95%CI -64.8; -12.4) vs -39.5% (95%CI -62.5; -2.2)) and GFR (18.9 (95%CI 5.2; 32.5) vs -13.4 (95%CI -27.3; 0.6)) ml/min/1.73m2.

An open label, dose-ranging clinical trial was conducted to study the safety and efficacy of losartan in paediatric patients aged 6 months to 6 years with hypertension. A total of 101 patients were randomized to one of three different starting doses of open-label losartan: a low dose of 0.1 mg/kg/day (N=33), a medium dose of 0.3 mg/kg/day (N=34), or a high dose of 0.7 mg/kg/day (N=34). Of these, 27 were infants which were defined as children aged 6

months to 23 months. Study medication was titrated to the next dose level at Weeks 3, 6, and 9 for patients that were not at blood pressure goal and not yet on the maximal dose (1.4 mg/kg/day, not to exceed 100 mg/day) of losartan.

Of the 99 patients treated with study medication, 90 (90.9%) patients continued to the extension study with follow up visits every 3 months. The mean duration of therapy was 264 days.

In summary, the mean blood pressure decrease from baseline was similar across all treatment groups (change from baseline to Week 3 in SBP was -7.3, -7.6, and -6.7 mmHg for the low-, medium-, and high-dose groups, respectively; the reduction from baseline to Week 3 in DBP was -8.2, -5.1, and -6.7 mmHg for the low-, medium-, and high-dose groups.); however, there was no statistically significant dose-dependent response effect for SBP and DBP.

Losartan, at doses as high as 1.4 mg/kg, was generally well tolerated in hypertensive children aged 6 months to 6 years after 12 weeks of treatment. The overall safety profile appeared comparable between treatment groups.

Amlodipine Besilate

Pharmacotherapeutic group: Calcium channel blockers, selective calcium channel blockers with mainly vascular effects. ATC Code: C08CA01.

In patients with hypertension, once daily dosing provides clinically significant reductions of blood pressure in both the supine and standing positions throughout the 24 hour interval. Due to the slow onset of action, acute hypotension is not a feature of amlodipine administration.

In patients with angina, once daily administration of amlodipine increases total exercise time, time to angina onset, and time to 1 mm ST segment depression, and decreases both angina attack frequency and glyceryl trinitrate tablet consumption.

Amlodipine has not been associated with any adverse metabolic effects or changes in plasma lipids and is suitable for use in patients with asthma, diabetes, and gout.

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in an independent, multi-centre, randomized, double-blind, placebo-controlled study of 1997 patients; Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT). Of these patients, 663 were treated with amlodipine 5-10 mg, 673 patients were treated with enalapril 10-20 mg, and 655 patients were treated with placebo, in addition to standard care of statins, beta-blockers, diuretics and aspirin, for 2 years. The key efficacy results are presented in Table 1. The results indicate that amlodipine treatment was associated with fewer hospitalizations for angina and revascularization procedures in patients with CAD.

Table 1. Incidence of significant clinical outcomes for CAMELOT

	Cardiovascular event rates, No. (%)			Amlodipine vs. Placebo	
Outcomes	Amlodipine	Placebo	Enalapril	Hazard Ratio (95% CI)	*P* Value

Primary Endpoint					
Adverse cardiovascular events	110 (16.6)	151 (23.1)	136 (20.2)	0.69 (0.54-0.88)	.003
Individual Components					
Coronary revascularization	78 (11.8)	103 (15.7)	95 (14.1)	0.73 (0.54-0.98)	.03
Hospitalization for angina	51 (7.7)	84 (12.8)	86 (12.8)	0.58 (0.41-0.82)	.002
Nonfatal MI	14 (2.1)	19 (2.9)	11 (1.6)	0.73 (0.37-1.46)	.37
Stroke or TIA	6 (0.9)	12 (1.8)	8 (1.2)	0.50 (0.19-1.32)	.15
Cardiovascular death	5 (0.8)	2 (0.3)	5 (0.7)	2.46 (0.48-12.7)	.27
Hospitalization for CHF	3 (0.5)	5 (0.8)	4 (0.6)	0.59 (0.14-2.47)	.46
Resuscitated cardiac arrest	0	4 (0.6)	1 (0.1)	NA	.04
New-onset peripheral vascular disease	5 (0.8)	2 (0.3)	8 (1.2)	2.6 (0.50-13.4)	.24
Abbreviations: CHF, congestive heart failure; CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack.					

Use in patients with heart failure

Haemodynamic studies and exercise based controlled clinical trials in NYHA Class II-IV heart failure patients have shown that Amlodipine did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction and clinical symptomatology.

A placebo controlled study (PRAISE) designed to evaluate patients in NYHA Class III-IV heart failure receiving digoxin, diuretics and ACE inhibitors has shown that Amlodipine did not lead to an increase in risk of mortality or combined mortality and morbidity with heart failure.

In a follow-up, long term, placebo controlled study (PRAISE-2) of Amlodipine in patients with NYHA III and IV heart failure without clinical symptoms or objective findings suggestive or underlying ischaemic disease, on stable doses of ACE inhibitors, digitalis, and diuretics, Amlodipine had no effect on total cardiovascular mortality. In this same population Amlodipine was associated with increased reports of pulmonary oedema.

Treatment to prevent heart attack trial (ALLHAT)

A randomised double-blind morbidity-mortality study called the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was performed to compare newer drug therapies: amlodipine 2.5-10 mg/d (calcium channel blocker) or lisinopril 10-40 mg/d (ACE-inhibitor) as first-line therapies to that of the thiazide-diuretic,

chlorthalidone 12.5-25 mg/d in mild to moderate hypertension.
A total of 33,357 hypertensive patients aged 55 or older were randomised and followed for a mean of 4.9 years. The patients had at least one additional CHD risk factor, including: previous myocardial infarction or stroke (> 6 months prior to enrollment) or documentation of other atherosclerotic CVD (overall 51.5%), type 2 diabetes (36.1%), HDL-C < 35 mg/dL (11.6%), left ventricular hypertrophy diagnosed by electrocardiogram or echocardiography (20.9%), current cigarette smoking (21.9%).
The primary endpoint was a composite of fatal CHD or non-fatal myocardial infarction. There was no significant difference in the primary endpoint between amlodipine-based therapy and chlorthalidone-based therapy: RR 0.98 95% CI (0.90-1.07) p=0.65. Among secondary endpoints, the incidence of heart failure (component of a composite combined cardiovascular endpoint) was significantly higher in the amlodipine group as compared to the chlorthalidone group (10.2% vs. 7.7%, RR 1.38, 95% CI [1.25-1.52] p<0.001). However, there was no significant difference in all-cause mortality between amlodipine-based therapy and chlorthalidone-based therapy. RR 0.96 95% CI [0.89-1.02] p=0.20.
Use in children (aged 6 years and older)
In a study involving 268 children aged 6-17 years with predominantly secondary hypertension, comparison of a 2.5 mg dose, and 5.0 mg dose of amlodipine with placebo, showed that both doses reduced Systolic Blood Pressure significantly more than placebo. The difference between the two doses was not statistically significant.
The long-term effects of amlodipine on growth, puberty and general development have not been studied. The long-term efficacy of amlodipine on therapy in childhood to reduce cardiovascular morbidity and mortality in adulthood has also not been established.

Chlorthalidone

In persons with normal renal function, diuresis is induced after the administration of 12.5mg Chlortalidone. The resulting increase in urinary excretion of sodium and chloride and the less prominent increase in urinary potassium are dose dependent and occur both in normal and in oedematous patients. The diuretic effect sets in after 2 to 3 hours, reaches its maximum after 4 to 24 hours, and may persist for 2 to 3 days.
Thiazide-induced diuresis initially leads to decreases in plasma volume, cardiac output, and systemic blood pressure. The renin-angiotensin-aldosterone system may possibly become activated.
In hypertensive individuals, chlortalidone gently reduces blood pressure. On continued administration, the hypotensive effect is maintained, probably due to the fall in peripheral resistance; cardiac output returns to pretreatment values, plasma volume remains somewhat reduced and plasma renin activity may be elevated.
On chronic administration, the antihypertensive effect of Chlortalidone is dose dependent between 12.5 and 50mg/day. Raising the dose above 50mg increases metabolic complications and is rarely of therapeutic benefit.
As with other diuretics, when Chlortalidone is given as monotherapy, blood pressure control is achieved in about half of patients with mild to moderate hypertension. In general, elderly and black patients are found to respond well to diuretics given as primary therapy. Randomised clinical trials in the elderly have shown that treatment of hypertension or predominant systolic hypertension in older persons with low-dose thiazide diuretics,

including chlortalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.
Combined treatment with other antihypertensive potentiates the blood-pressure lowering effects. In the large proportion of patients failing to respond adequately to monotherapy, a further decrease in blood pressure can thus be achieved.
In renal diabetes insipidus, Chlortalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

5.3. Pharmacokinetic Properties

Losartan potassium

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 haemodialysis patients. The plasma concentrations of the active metabolite are not altered in patients with renal impairment or in haemodialysis patients.
Neither losartan nor the active metabolite can be removed by haemodialysis.
Pharmacokinetics in 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 Besilate

Absorption, distribution, plasma protein binding***:*** After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. The volume of distribution is approximately 21 l/kg. *In vitro* studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins.
The bioavailability of amlodipine is not affected by food intake.
Biotransformation/elimination
The terminal plasma elimination half-life is about 35-50 hours and is consistent with once daily dosing. Amlodipine is extensively metabolised by the liver to inactive metabolites with 10% of the parent compound and 60% of metabolites excreted in the urine.
Hepatic impairment
Very limited clinical data are available regarding amlodipine administration in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine resulting in a longer half-life and an increase in AUC of approximately 40-60%.
Elderly population
The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. Amlodipine clearance tends to be decreased with resulting increases in AUC and elimination half-life in elderly patients. Increases in AUC and elimination half-life in patients with congestive heart failure were as expected for the patient age group studied.
Paediatric population
A population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving

amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

Chlorthalidone

Absorption and plasma concentration

The bioavailability of an oral dose of 50mg Chlortalidone is approximately 64%, peak blood concentrations being attained after 8 to 12 hours. For doses of 25 and 50mg, Cmax values average 1.5µg/ml (4.4µmol/L) and 3.2µg/ml (9.4µmol/L) respectively. For doses up to 100mg there is a proportional increase in AUC. On repeated daily doses of 50mg, mean steady-state blood concentrations of 7.2µg/ml (21.2µmol/L), measured at the end of the 24 hour dosage interval, are reached after 1 to 2 weeks.

Distribution

In blood, only a small fraction of chlortalidone is free, due to extensive accumulation in erythrocytes and binding to plasma proteins. Owing to the large degree of high affinity binding to the carbonic anhydrase of erythrocytes, only some 1.4% of the total amount of chlortalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlortalidone is about 76% and the major binding protein is albumin.

Chlortalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlortalidone daily before and after delivery, chlortalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlortalidone concentrations in amniotic fluid and in the maternal milk are approximately 4% of the corresponding maternal blood level.

Metabolism

Metabolism and hepatic excretion into bile constitute a minor pathway of elimination. Within 120 hours, about 70% of the dose is excreted in the urine and the faeces, mainly in unchanged form.

Elimination

Chlortalidone is eliminated from whole blood and plasma with an elimination half-life averaging 50 hours. The elimination half-life is unaltered after chronic administration. The major part of an absorbed dose of chlortalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special patient groups

Renal dysfunction does not alter the pharmacokinetics of chlortalidone, the rate-limiting factor in the elimination of the drug from blood or plasma being most probably the affinity of the drug to the carbonic anhydrase of erythrocytes.

No dosage adjustment is needed in patients with impaired renal function.

In elderly patients, the elimination of chlortalidone is slower than in healthy young adults, although absorption is the same. Therefore, close medical observation is indicated when treating patients of advanced age with chlortalidone.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Losartan potassium

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 Besilate

Reproductive toxicology

Reproductive studies in rats and mice have shown delayed date of delivery, prolonged duration of labour and decreased pup survival at dosages approximately 50 times greater than the maximum recommended dosage for humans based on mg/kg.

Impairment of fertility

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis). In another rat study in which male rats were treated with amlodipine besilate for 30 days at a dose comparable with the human dose based on mg/kg, decreased plasma follicle-stimulating hormone and testosterone were found as well as decreases in sperm density and in the number of mature spermatids and Sertoli cells.

Carcinogenesis, mutagenesis

Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

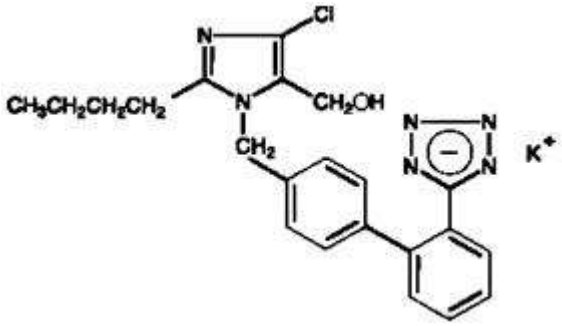
Chlorthalidone

There are no pre-clinical data of relevance to the prescriber.

7. DESCRIPTION

Losartan potassium

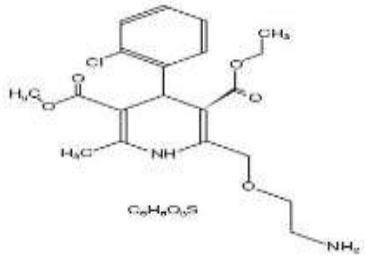
Losartan potassium is a monopotassium salt of 2-butyl-4-chloro-1-[[2´-(1H-tetrazol-5-yl)[1,1´-biphenyl]-4-yl]methyl]-1H-imidazole-5-methanol. Its empirical formula is $C_{22}H_{22}ClKN_6O$ having molecular weight of 461.0, and its structural formula is:



Losartan potassium is a white to off-white crystalline powder. It is freely soluble in water; sparingly soluble in isopropyl alcohol; slightly soluble in acetonitrile.

Amlodipine Besilate

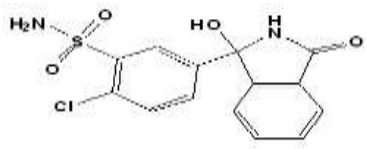
Amlodipine Besilate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene-sulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \bullet C_6H_6O_3S$, and its structural formula is:



Amlodipine Besilate is a white or almost white powder with a molecular weight of 567.1. it is freely soluble in methanol; sparingly soluble in ethanol (95 percent); slightly soluble in 2-propanol and in water.

Chlorthalidone

Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl)benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



Chlorthalidone is a white to yellowish-white, crystalline powder which is soluble in methanol; slightly soluble in ethanol (95%); practically insoluble in water, in ether and in chloroform**.**

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Losartan Potassium, Amlodipine and Chlorthalidone Tablets are white circular shaped

slightly biconvex film coated tablets having plain on both sides.
The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000 and Castor oil.

TRILOSAR 12.5
Losartan Potassium, Amlodipine and Chlorthalidone Tablets are yellow colour, circular shaped slightly biconvex film coated tablets having plain on both sides. The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000, Castor oil and Ferric Oxide Yellow.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TRILOSAR is available in blister pack of 10 tablets.

8.4 Storage and Handing Instructions

Store in a cool & dry place. Protect from light and moisture.

9. PATIENT COUNSELLING INFORMATION

TRILOSAR

Read all of this leaflet carefully before you start taking this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet please tell your doctor or pharmacist.

The information in this leaflet has been divided into the following sections:

9.1 What TRILOSAR is and what it is taken for
9.2 Check before you take TRILOSAR
9.3 How to take TRILOSAR
9.4 Possible side effects
9.5 How to store TRILOSAR

9.6 Further information

9.1 What TRILOSAR is and what it is taken for

TRILOSAR is combination of losartan, amlodipine and chlorthalidone and is used to treat essential hypertension.

9.2 Check before you take TRILOSAR

Do not take TRILOSAR:

- if you are allergic (hypersensitive) to any of the active ingredients or excipients of TRILOSAR
- if you are not passing any urine at all
- if you have severe kidney or liver problems
- if you have low blood levels of potassium which can cause muscle weakness, muscle twitching or abnormal heartbeat
- if you have low blood levels of sodium which can cause tiredness, confusion, muscle twitching, fits or coma
- if you have high blood levels of calcium which can cause loss of appetite, tiredness or muscle weakness
- if you have ever had gout or kidney stones
- if you have Addison's disease (which is a condition where your adrenal gland is not producing enough steroids)
- if you are taking lithium.

If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist before you take TRILOSAR.
if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren

Warnings and precautions

Talk to your doctor, pharmacist, or nurse before taking TRILOSAR
You must tell your doctor if you think you are (or might become) pregnant. TRILOSAR is not recommended in early pregnancy, and must not be taken if you are more than 3 months pregnant, as it may cause serious harm to your baby if used at that stage.
It is important to tell your doctor before taking TRILOSAR:

- if you have had a history of angiooedema (swelling of the face, lips, throat, and/or tongue),
- if you suffer from excessive vomiting or diarrhoea leading to an extreme loss of fluid and/or salt in your body,
- if you receive diuretics (medicines that increase the amount of water that you pass out through your kidneys) or are under dietary salt restriction leading to an extreme loss of fluid and salt in your body,
- if you are known to have narrowing or blockage of the blood vessels leading to your kidneys or if you have received a kidney transplant recently,

- if your liver function is impaired,
- if you suffer from heart failure with or without renal impairment or concomitant severe life threatening cardiac arrhythmias. Special caution is necessary when you are treated with a ß-blocker concomitantly,
- if you have problems with your heart valves or heart muscle,
- if you suffer from coronary heart disease (caused by a reduced blood flow in the blood vessels of the heart) or from cerebrovascular disease (caused by a reduced blood circulation in the brain),
- if you suffer from primary hyperaldosteronism (a syndrome associated with increased secretion of the hormone aldosterone by the adrenal gland, caused by an abnormality within the gland),
- if you are taking any of the following medicines used to treat high blood pressure: an ACE-inhibitor (for example enalapril, lisinopril, ramipril), in particular if you have diabetes-related kidney problems; aliskiren
- Your doctor may check your kidney function, blood pressure, and the amount of electrolytes (e.g. potassium) in your blood at regular intervals.

Do not take TRILOSAR".

Children and adolescents

TRILOSAR has been studied in children. For more information, talk to your doctor.

TRILOSAR is not recommended for use in children suffering from kidney or liver problems, as limited data are available in these patient groups. TRILOSAR is not recommended for use in children under 6 years old, as it has not been shown to work in this age group.

Take special care with TRILOSAR

Before you take TRILOSAR tell your doctor if:

- you suffer from any other liver or kidney problems
- you are on a low-salt diet
- you suffer from diabetes mellitus (increased levels of sugar in the blood)
- you have high cholesterol levels
- if you have recently had an anaesthetic
- you are elderly.

If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist before you take TRILOSAR.

Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines as they may interfere with TRILOSAR: other treatments for high blood pressure or heart problems such as: - ACE inhibitors (for example, lisinopril)	adrenocorticotropic hormone (ACTH) - used to treat a number of different conditions, including ulcerative colitis, Crohn's disease and rheumatoid arthritis

- beta blockers (for example propranolol hydrochloride) - methyldopa - vasodilators (for example baseman) - calcium channel blockers (for example amlodipine) - guanethidine	
corticosteroids such as prednisolone or betamethasone - used to treat allergic and inflammatory diseases and immune reactions	anticholinergics such as atropine sulphate or hyoscine butyl bromide - for abdominal or stomach spasms or cramps
cytotoxic agents such as cyclophosphamide or methotrexate - used to treat cancer	colestyramine - used to reduce cholesterol levels and prevent heart disease
asthma treatments such as salbutamol or formoterol	amantadine - used to treat Parkinson's disease or viral infections
amphotericin - used to treat infections	allopurinol - used to treat gout
carbenoxolone - used to treat ulcers	calcium salts or vitamin D - used for replacement therapy
insulin and other treatments for diabetes such as chlorpropamide or glibenclamide	non-steroidal anti-inflammatories (NSAIDs) such as aspirin or indometacin - used for pain relief or rheumatism
digoxin - for an irregular heartbeat	ciclosporin - used to treat rheumatic disease or skin complaints or after a transplant
lithium - used to treat mental illness	

Driving and using machines

If you feel dizzy when you start taking these tablets, do not drive or work with machinery until these effects have worn off.

9.3 How to take TRILOSAR

Always take TRILOSAR exactly as your doctor has told you to.

It is important to take your tablets at the right time. You should check with your doctor or pharmacist if you are not sure.

Your doctor will choose a suitable starting dose for your particular condition and monitor your progress. If necessary, this dose can be increased or reduced.

Whilst you are taking TRILOSAR, your doctor may want to carry out a number of tests from time to time. This is quite usual and nothing to worry about.

If you are not sure how many tablets to take, ask your doctor or pharmacist. Do not stop taking your tablets suddenly. Ask your doctor first.

Dosage in special patient groups

The doctor may advise a lower dose, especially when starting treatment in certain patients such as those treated with diuretics in high doses, in patients with liver impairment, or in patients over the age of 75 years. The use of TRILOSAR is not recommended in patients with severe hepatic impairment.

Administration

The tablets should be swallowed whole with a glass of water. You should try to take your daily dose at about the same time each day. It is important that you continue to take TRILOSAR until your doctor tells you otherwise.

What to do if you take more TRILOSAR than you should

If you accidentally take too many tablets, or someone else takes any of your medicine, you should tell your doctor immediately or contact your nearest accident and emergency department because you may need urgent treatment. Show any left-over medicines or the empty packet to the doctor. Symptoms of overdose are low blood pressure, increased heartbeat, possibly decreased heartbeat.

If you forget to take TRILOSAR

If you accidentally miss a daily dose, just take the next dose as normal. Do not take a double dose to make up for a forgotten tablet. If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

9.4 Possible side effects

Do not worry. Like all medicines, TRILOSAR can cause side effects, although not everyone gets them.

If you get any of the following tell your doctor or pharmacist immediately as they may tell you to stop taking TRILOSAR:

- muscles feel weak or will not work properly
- irregular heartbeat.

A severe allergic reaction (rash, itching, swelling of the face, lips, mouth or throat that may cause difficulty in swallowing or breathing).

Very common side effects (that affect more than 1 person in 10)

- low blood levels of potassium which can cause muscle weakness, muscle twitching or abnormal heartbeat This is a serious but rare side effect, which affects more than 1 out of 10,000 patients but fewer than 1 out of 1,000 patients. You may need urgent medical attention or hospitalisation.

The following side effects have been reported with TRILOSAR

- increased blood levels of uric acid
- increased blood levels of cholesterol.

Common side effects (that affect less than 1 person in 10)

- low levels of sodium which can cause tiredness, confusion, muscle twitching, fits or coma
- low levels of magnesium
- high blood sugar levels which can cause tiredness, weakness or feeling thirsty
- nettle rash
- skin rash
- low blood pressure (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics),
- dizziness
- loss of appetite
- upset stomach
- impotence in men.
- debility,
- fatigue
- too little sugar in the blood (hypoglycaemia),
- too much potassium in the blood (hyperkalaemia),
- changes in kidney function including kidney failure,
- reduced number of red blood cells (anaemia),
- increase in blood urea, serum creatinine and serum potassium in patients with heart failure.

Uncommon side effects (that affect less than 1 person in 100)

- gout which causes pain and swelling in the joints.
- somnolence,
- headache,
- sleep disorders,
- feeling of increased heart rate (palpitations),
- severe chest pain (angina pectoris),
- shortness of breath (dyspnoea),
- abdominal pain,
- obstipation,
- diarrhoea,
- nausea,
- vomiting,

- hives (urticaria),
- itching (pruritus),
- rash,
- localised swelling (oedema),
- cough.

Rare side effects (that affect less than 1 person in 1000)

- increased calcium in the blood which can cause agitation, sore eyes, abdominal pain
- sugar in the urine (this would show up when your doctor or nurse tests your urine)
- worsening of diabetes
- yellowing of the skin or eyes caused by liver or blood problems (jaundice)
- increased sensitivity of your skin to sunlight
- abnormal heartbeat the symptoms of which include palpitations and fainting
- pins and needles
- headache
- feeling or being sick
- stomach pain
- constipation
- diarrhoea
- reduction in blood platelets which increases the risk of bruising or bleeding
- severe reduction in the number of white blood cells which makes infection more likely
- an abnormally high amount of eosinophils (type of white blood cell) in the blood
- breathing problems
- problems with your kidneys.
- hypersensitivity,
- angiooedema,
- inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura),
- numbness or tingling sensation (paraesthesia),
- fainting (syncope),
- very rapid and irregular heartbeat (atrial fibrillation),
- brain attack (stroke),
- inflammation of the liver (hepatitis),
- elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

Not known (frequency cannot be estimated from the available data):

- reduced number of thrombocytes,
- migraine,
- liver function abnormalities,
- muscle and joint pain,
- flu-like symptoms,
- back pain and urinary tract infection,
- increased sensitivity to the sun (photosensitivity),

- unexplained muscle pain with dark (tea-coloured) urine (rhabdomyolysis),
- impotence,
- inflammation of the pancreas (pancreatitis),
- low levels of sodium in the blood (hyponatraemia),
- depression,
- generally feeling unwell (malaise),
- ringing, buzzing, roaring, or clicking in the ears (tinnitus),
- disturbed taste (dysgeusia).

Side effects in children are similar to those seen in adults.

Very rare side effects (that affect less than 1 person in 10 000)

- low levels of chloride in the blood, symptoms include dry mouth, thirst, gastrointestinal disturbances (including nausea, vomiting), weakness, lethargy, drowsiness, restlessness, seizures, confusion, headache, muscle pains or cramps, hypotension
- inflammation of the pancreas which causes severe stomach and back pain.

If any of the side effects gets worse, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

9.5 How to store TRILOSAR

Store in a cool & dry place. Protect from light and moisture.
Keep all medicines out of reach of children

9.6 What TRILOSAR looks like and contents of the pack

The active substance in TRILOSAR are Losartan Potassium, Amlodipine and Chlorthalidone.

TRILOSAR 6.25

The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000 and Castor oil.

TRILOSAR 12.5

The excipients used are Ethylcellulose, Acetone, Starch, Microcrystalline Cellulose, Povidone K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Talc, Magnesium Stearate, Croscarmellose Sodium, Sodium Lauryl Sulphate, HPMC E15, Methylene Chloride, Titanium Dioxide, Polyethylene Glycol 6000, Castor oil and Ferric Oxide Yellow.

What TRILOSAR looks like

TRILOSAR 6.25

Losartan Potassium, Amlodipine and Chlorthalidone Tablets are white circular shaped slightly biconvex film coated tablets having plain on both sides.

TRILOSAR 12.5

Losartan Potassium, Amlodipine and Chlorthalidone Tablets are yellow colour, circular shaped slightly biconvex film coated tablets having plain on both sides.

Pack Sizes:

TRILOSAR is available in blister pack of 10 tablets.

10. DETAILS OF MANUFACTURER

Manufactured in India by:
GKM New Pharma
Spl. Type Plot No. 5, 6,7 & 8, PIPDIC,
Electronic Park, Thirubuvanai, Puducherry – 605107.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Lic No. 09 13 2634 issued on 15.06.2015

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
IN/TRILOSAR 50 , 5, 6.25, 12.5 mg/AUG-20/01/PI