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

TRITELSAR

1. Generic Name

Chlorthalidone, Amlodipine & Telmisartan Tablets

2. Qualitative and quantitative composition

TRITELSAR 40

Each film coated tablet contains:

Chlorthalidone I.P.....6.25 mg

Amlodipine Besylate I.P. equivalent to Amlodipine.....5 mg

Telmisartan I.P.....40 mg

Excipients..... q.s.

Colour: Ferric Oxide Red NF

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Red.

TRITELSAR 40 HS

Each film coated tablet contains:

Chlorthalidone I.P.....12.5 mg

Amlodipine Besylate I.P. equivalent to Amlodipine.....5 mg

Telmisartan I.P.....40 mg

Excipients..... q.s.

Colour: Ferric Oxide Yellow NF

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Yellow.

TRITELSAR 80

Each film coated tablet contains:

Chlorthalidone I.P.....6.25 mg

Amlodipine Besylate I.P. equivalent to Amlodipine.....5 mg

Telmisartan I.P.....80 mg

Excipients..... q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000 & Castor Oil.

TRITELSAR 80 HS

Each film coated tablet contains:

Chlorthalidone I.P.....12.5 mg

Amlodipine Besylate I.P. equivalent to Amlodipine.....5 mg

Telmisartan I.P.……80 mg

Excipients……. q.s.

Colour: Ferric Oxide Yellow NF

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Ferric Oxide Yellow & Castor Oil.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength:

TRITELSAR 40

Chlorthalidone I.P 6.25 mg, Amlodipine Besylate I.P. 5 mg and Telmisartan I.P 40 mg

TRITELSAR 40 HS

Chlorthalidone I.P 12.5 mg, Amlodipine Besylate I.P. 5 mg and Telmisartan I.P 40 mg

TRITELSAR 80

Chlorthalidone I.P 6.25 mg, Amlodipine Besylate I.P. 5 mg and Telmisartan I.P 80 mg

TRITELSAR 80 HS

Chlorthalidone I.P 12.5 mg, Amlodipine Besylate I.P. 5 mg and Telmisartan I.P 80 mg

4. Clinical particulars

4.1 Therapeutic indication

Hypertension

Treatment of essential hypertension in adults.

4.2 Posology and method of administration

Dosage: As directed by the Physician

4.3 Contraindications

- Hypersensitivity to dihydropyridine derivatives, amlodipine, chlorthalidone and other sulphonamide derivatives, or to any of the excipients.
- 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.
- Anuria, severe hepatic or renal failure (creatinine clearance <30ml/min), refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia (history of gout or uric acid calculi), hypertension during pregnancy, untreated Addison's disease and concomitant lithium therapy.
- Biliary obstructive disorders

4.4 Special warnings and precautions for use

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

Chlorthalidone

Warnings:

Chlorthalidone 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 ("Contra-indications").

Chlorthalidone 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 Chlorthalidone 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, Chlorthalidone 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), Chlorthalidone should be discontinued.

Combined treatment consamlodipineg of Chlorthalidone 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, Chlorthalidone should be used only under close control in normokalaemic patients with no signs of volume depletion.

Metabolic effects:

Chlorthalidone 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. Chlorthalidone 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.

Chlorthalidone 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.

Amlodipine

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.

Telmisartan

Pregnancy

Angiotensin II receptor antagonists should not be initiated during pregnancy. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started (see sections 4.3 and 4.6).

Hepatic impairment

Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment (see section 4.3) since telmisartan is mostly eliminated with the bile. These patients can be expected to have reduced hepatic clearance for telmisartan. Telmisartan should be used only with caution in patients with mild to moderate hepatic impairment.

Renovascular hypertension

There is an increased risk of severe hypotension and renal insufficiency when patients with bilateral renal artery stenosis or stenosis of the artery to a single functioning kidney are treated with medicinal products that affect the renin-angiotensin-aldosterone system.

Renal impairment and kidney transplantation

When Telmisartan is used in patients with impaired renal function, periodic monitoring of potassium and creatinine serum levels is recommended. There is no experience regarding the administration of Telmisartan in patients with recent kidney transplantation.

Intravascular hypovolaemia

Symptomatic hypotension, especially after the first dose of Telmisartan, may occur in patients who are volume and/or sodium depleted by vigorous diuretic therapy, dietary salt restriction, diarrhoea, or vomiting. Such conditions should be corrected before the administration of Telmisartan. Volume and/or sodium depletion should be corrected prior to administration of Telmisartan.

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.

Other conditions with stimulation of the renin-angiotensin-aldosterone system

In patients whose vascular tone and renal function depend predominantly on the activity of the renin-angiotensin-aldosterone system (e.g. patients with severe congestive heart failure

or underlying renal disease, including renal artery stenosis), treatment with medicinal products that affect this system such as telmisartan has been associated with acute hypotension, hyperazotaemia, oliguria, or rarely acute renal failure (see section 4.8).

Primary aldosteronism

Patients with primary aldosteronism generally will not respond to antihypertensive medicinal products acting through inhibition of the renin-angiotensin system. Therefore, the use of telmisartan is not recommended.

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.

Diabetic patients treated with insulin or antidiabetics

In these patients hypoglycaemia may occur under telmisartan treatment. Therefore, in these patients an appropriate blood glucose monitoring should be considered; a dose adjustment of insulin or antidiabetics may be required, when indicated.

Hyperkalaemia

The use of medicinal products that affect the renin-angiotensin-aldosterone system may cause hyperkalaemia.

In the elderly, in patients with renal insufficiency, in diabetic patients, in patients concomitantly treated with other medicinal products that may increase potassium levels, and/or in patients with intercurrent events, hyperkalaemia may be fatal.

Before considering the concomitant use of medicinal products that affect the renin-angiotensin-aldosterone system, the benefit risk ratio should be evaluated.

The main risk factors for hyperkalaemia to be considered are:

- Diabetes mellitus, renal impairment, age (>70 years)

- Combination with one or more other medicinal products that affect the renin-angiotensin-aldosterone system and/or potassium supplements. Medicinal products or therapeutic classes of medicinal products that may provoke hyperkalaemia are salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim.

- Intercurrent events, in particular dehydratation, acute cardiac decompensation, metabolic acidosis, worsening of renal function, sudden worsening of the renal condition (e.g. infectious diseases), cellular lysis (e.g. acute limb ischemia, rhabdomyolysis, extend trauma).

Close monitoring of serum potassium in at risk patients is recommended (see section 4.5).

Sorbitol

This medicinal product contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Telmisartan.

Ethnic differences

As observed for angiotensin converting enzyme inhibitors, telmisartan and the other angiotensin II receptor 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.

Other

As with any antihypertensive agent, excessive reduction of blood pressure in patients with ischaemic cardiopathy or ischaemic cardiovascular disease could result in a myocardial infarction or stroke.

4.5 Drugs interactions

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 ("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 Chlorthalidone; 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.

Amlodipine

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.

Telmisartan

Digoxin

When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. When initiating, adjusting, and discontinuing telmisartan, monitor digoxin levels in order to maintain levels within the therapeutic range.

As with other medicinal products acting on the renin-angiotensin-aldosterone system, telmisartan may provoke hyperkalaemia (see section 4.4). The risk may increase in case of treatment combination with other medicinal products that may also provoke hyperkalaemia (salt substitutes containing potassium, potassium-sparing diuretics, ACE inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicinal products (NSAIDs, including selective COX-2 inhibitors), heparin, immunosuppressives (cyclosporin or tacrolimus), and trimethoprim).

The occurrence of hyperkalaemia depends on associated risk factors. The risk is increased in case of the above-mentioned treatment combinations. The risk is particularly high in combination with potassium sparing-diuretics, and when combined with salt substitutes containing potassium. A combination with ACE inhibitors or NSAIDs, for example, presents a lesser risk provided that precautions for use are strictly followed.

Concomitant use not recommended.

Potassium sparing diuretics or potassium supplements

Angiotensin II receptor antagonists such as telmisartan, attenuate diuretic induced potassium loss. Potassium sparing diuretics e.g. spirinolactone, eplerenone, triamterene, or amiloride, potassium supplements, or potassium-containing salt substitutes may lead to a significant increase in serum potassium. If concomitant use is indicated because of documented hypokalaemia, they should be used with caution and with frequent monitoring of serum potassium.

Lithium

Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors, and with angiotensin II receptor antagonists, including telmisartan. If use of the combination proves necessary, careful monitoring of serum lithium levels is recommended.

Concomitant use requiring caution.

Non-steroidal anti-inflammatory medicinal products

NSAIDs (i.e. acetylsalicylic acid at anti-inflammatory dosage regimens, COX-2 inhibitors and non-selective NSAIDs) may reduce the antihypertensive effect of angiotensin II receptor antagonists.

In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin II receptor antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy and periodically thereafter.

In one study the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC_{0-24} and C_{max} of ramipril and Ramiprilat. The clinical relevance of this observation is not known.

Diuretics (thiazide or loop diuretics)

Prior treatment with high dose diuretics such as furosemide (loop diuretic) and hydrochlorothiazide (thiazide diuretic) may result in volume depletion, and in a risk of hypotension when initiating therapy with telmisartan.

To be taken into account with concomitant use.

Other antihypertensive agents

The blood pressure lowering effect of telmisartan can be increased by concomitant use of other antihypertensive medicinal products.

Clinical trial data has 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 (see sections 4.3, 4.4 and 5.1).

Based on their pharmacological properties it can be expected that the following medicinal products may potentiate the hypotensive effects of all antihypertensives including telmisartan: Baclofen, amifostine. Furthermore, orthostatic hypotension may be aggravated by alcohol, barbiturates, narcotics, or antidepressants.

Corticosteroids (systemic route)

Reduction of the antihypertensive effect.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

Chlorthalidone passes into the breast milk; mothers taking Chlorthalidone should refrain from breast-feeding their infants.

Amlodipine

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.

Telmisartan

Pregnancy

The use of angiotensin II receptor antagonists is not recommended during the first trimester of pregnancy (see section 4.4). The use of angiotensin II receptor antagonists is contraindicated during the second and third trimesters of pregnancy (see sections 4.3 and 4.4).

There are no adequate data from the use of Telmisartan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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 antagonists, similar risks may exist for this class of drugs. Unless continued angiotensin II receptor antagonist therapy is considered essential, patients planning pregnancy should be changed to alternative antihypertensive treatments which have an established safety profile for use in pregnancy. When pregnancy is diagnosed, treatment with angiotensin II receptor antagonists should be stopped immediately, and, if appropriate, alternative therapy should be started.

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

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

Infants whose mothers have taken angiotensin II receptor antagonists should be closely observed for hypotension (see sections 4.3 and 4.4).

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

Chlorthalidone

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

Amlodipine

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.

Telmisartan

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy such as Telmisartan.

4.8 Undesirable effects

Chlorthalidone

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.

Amlodipine

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.

Tabulated list of adverse reactions

The following adverse reactions have been observed and reported during treatment with amlodipine with the following frequencies: 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).

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
	Common	Ankle swelling, muscle cramps

Musculoskeletal and connective tissue disorders	Uncon	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.

Telmisartan

Summary of the safety profile

Serious adverse drug reactions include anaphylactic reaction and angioedema which may occur rarely (≥1/10,000 to <1/1,000), and acute renal failure.

The overall incidence of adverse reactions reported with telmisartan was usually comparable to placebo (41.4 % vs 43.9 %) in controlled trials in patients treated for hypertension. The incidence of adverse reactions was not dose related and showed no correlation with gender, age or race of the patients. The safety profile of telmisartan in patients treated for the reduction of cardiovascular morbidity was consistent with that obtained in hypertensive patients.

The adverse reactions listed below have been accumulated from controlled clinical trials in patients treated for hypertension and from post-marketing reports. The amlodipine also takes into account serious adverse reactions and adverse reactions leading to discontinuation reported in three clinical long-term studies including 21,642 patients treated with telmisartan for the reduction of cardiovascular morbidity for up to six years.

Tabulated list of adverse reactions

Adverse reactions have been ranked under headings of frequency 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).

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

Infections and infestations		

Uncommon: Rare:	Urinary tract infection including cystitis, upper respiratory tract infection including pharyngitis and sinusitis Sepsis including fatal outcome[1]
Blood and the lymphatic system disorders	
Uncommon:	Anaemia
Rare:	Eosinophilia, thrombocytopenia
Immune system disorders	
Rare:	Anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders	
Uncommon: Rare:	Hyperkalaemia Hypoglycaemia (in diabetic patients)
Psychiatric disorders	
Uncommon:	Insomnia, depression
Rare:	Anxiety
Nervous system disorders	
Uncommon: Rare:	Syncope Somnolence
Eye disorders	
Rare:	Visual disturbance
Ear and labyrinth disorders	
Uncommon:	Vertigo
Cardiac disorders	
Uncommon:	Bradycardia
Rare:	Tachycardia
Vascular disorders	

Uncommon:	Hypotension[2], orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon: Very rare:	Dyspnoea, cough Interstitial lung disease[4]
Gastrointestinal disorders	
Uncommon: Rare:	Abdominal pain, diarrhoea, dyspepsia, flatulence, vomiting Dry mouth, stomach discomfort, dysgeusia
Hepato-biliary disorders	
Rare:	Hepatic function abnormal/liver disorder[3]
Skin and subcutaneous tissue disorders	
Uncommon: Rare:	Pruritus, hyperhidrosis, rash Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
Musculoskeletal and connective tissue disorders	
Uncommon: Rare:	Back pain (e.g. sciatica), muscle spasms, myalgia Arthralgia, pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	
Uncommon:	Renal impairment including acute renal failure
General disorders and administration site conditions	
Uncommon: Rare:	Chest pain, asthenia (weakness) Influenza-like illness
Investigations	
Uncommon:	Blood creatinine increased
Rare:	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, blood creatine phosphokinase increased

[1,2,3,4]: for further descriptions, please see sub-section *"Description of selected adverse reactions"*

Description of selected adverse reactions

Sepsis

In the PRoFESS trial, an increased incidence of sepsis was observed with telmisartan compared with placebo. The event may be a chance finding or related to a mechanism currently not known.

Hypotension

This adverse reaction was reported as common in patients with controlled blood pressure who were treated with telmisartan for the reduction of cardiovascular morbidity on top of standard care.

Hepatic function abnormal / liver disorder

Most cases of hepatic function abnormal / liver disorder from post-marketing experience occurred in Japanese patients. Japanese patients are more likely to experience these adverse reactions.

Interstitial lung disease

Cases of interstitial lung disease have been reported from post-marketing experience in temporal association with the intake of telmisartan. However, a causal relationship has not been established.

4.9 Overdose

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 Chlorthalidone. 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.

Amlodipine

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.

Telmisartan

There is limited information available with regard to overdose in humans.

Symptoms

The most prominent manifestations of telmisartan overdose were hypotension and tachycardia; bradycardia dizziness, increase in serum creatinine, and acute renal failure have also been reported.

Management

Telmisartan is not removed by haemodialysis. The patient should be closely monitored, and the treatment should be symptomatic and supportive. Management depends on the time since ingestion and the severity of the symptoms. Suggested measures include induction of emesis and / or gastric lavage. Activated charcoal may be useful in the treatment of overdosage. Serum electrolytes and creatinine should be monitored frequently. If hypotension occurs, the patient should be placed in a supine position, with salt and volume replacement given quickly.

5. Pharmacological properties

5.1 Mechanism of Action

Chlorthalidone

Chlorthalidone 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^+.

Amlodipine

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).

Telmisartan

Telmisartan is an orally active and specific angiotensin II receptor (type AT_1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT_1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT_1 receptor. Telmisartan selectively binds the AT_1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT_2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects.

5.2 Pharmacodynamicproperties

Chlorthalidone

Chlorthalidone 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+.

In persons with normal renal function, diuresis is induced after the administration of 12.5mg Chlorthalidone. 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, chlorthalidone 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 Chlorthalidone 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 Chlorthalidone 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 chlorthalidone, reduces cerebrovascular (stroke), coronary heart and total cardiovascular morbidity and mortality.

Combined treatment with other antihypertensives 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, Chlorthalidone paradoxically reduces polyuria. The mechanism of action has not been elucidated.

Amlodipine

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

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).

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

Reported 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.

Reported 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.

Telmisartan

In human, an 80 mg dose of telmisartan almost completely inhibits the angiotensin II evoked blood pressure increase. The inhibitory effect is maintained over 24 hours and still measurable up to 48 hours.

Clinical efficacy and safety

Treatment of essential hypertension

After the first dose of telmisartan, the antihypertensive activity gradually becomes evident within 3 hours. The maximum reduction in blood pressure is generally attained 4 to 8 weeks after the start of treatment and is sustained during long-term therapy.

The antihypertensive effect persists constantly over 24 hours after dosing and includes the last 4 hours before the next dose as shown by ambulatory blood pressure measurements.

This is confirmed by trough to peak ratios consistently above 80 % seen after doses of 40 and 80 mg of telmisartan in placebo controlled clinical studies. There is an apparent trend to a dose relationship to a time to recovery of baseline systolic blood pressure (SBP). In this respect data concerning diastolic blood pressure (DBP) are inconsistent.

In patients with hypertension telmisartan reduces both systolic and diastolic blood pressure without affecting pulse rate. The contribution of the medicinal product's diuretic and natriuretic effect to its hypotensive activity has still to be defined. The antihypertensive efficacy of telmisartan is comparable to that of agents representative of other classes of antihypertensive medicinal products (demonstrated in clinical trials comparing telmisartan to amlodipine, atenolol, enalapril, hydrochlorothiazide, and lisinopril).

Upon abrupt cessation of treatment with telmisartan, blood pressure gradually returns to pre-treatment values over a period of several days without evidence of rebound hypertension.

The incidence of dry cough was significantly lower in patients treated with telmisartan than in those given angiotensin converting enzyme inhibitors in clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention

ONTARGET (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial) compared the effects of telmisartan, ramipril and the combination of telmisartan and ramipril on cardiovascular outcomes in 25620 patients aged 55 years or older with a history of coronary artery disease, stroke, TIA, peripheral arterial disease, or type 2 diabetes mellitus accompanied by evidence of end-organ damage (e.g. retinopathy, left ventricular hypertrophy, macro- or microalbuminuria), which is a population at risk for cardiovascular events.

Patients were randomized to one of the three following treatment groups: telmisartan 80 mg (n = 8542), ramipril 10 mg (n = 8576), or the combination of telmisartan 80 mg plus ramipril 10 mg (n = 8502), and followed for a mean observation time of 4.5 years.

Telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6 % and 11.8 % among telmisartan and ramipril treated patients, respectively.

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08), p (non-inferiority) = 0.0004], the primary endpoint in the reference study HOPE (The **H**eart **O**utcomes **P**revention **E**valuation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND randomized ACE-I intolerant patients with otherwise similar inclusion criteria as ONTARGET to telmisartan 80 mg (n=2954) or placebo (n=2972), both given on top of standard care. The mean duration of follow up was 4 years and 8 months. No statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found [15.7 % in the telmisartan and 17.0 % in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)]. There was evidence for

a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95 % CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95 % CI 0.85 - 1.24).

Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan.

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

In the "Prevention Regimen For Effectively avoiding Second Strokes" (PRoFESS) trial in patients 50 years and older, who recently experienced stroke, an increased incidence of sepsis was noted for telmisartan compared with placebo, 0.70 % vs. 0.49 % [RR 1.43 (95 % confidence interval 1.00 - 2.06)]; the incidence of fatal sepsis cases was increased for patients taking telmisartan (0.33 %) vs. patients taking placebo (0.16 %) [RR 2.07 (95 % confidence interval 1.14 - 3.76)]. The observed increased occurrence rate of sepsis associated with the use of telmisartan may be either a chance finding or related to a mechanism not currently known.

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. For more detailed information see above under the heading “Cardiovascular prevention”. 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

The safety and efficacy of Telmisartan in children and adolescents aged below 18 years have not been established.

The blood pressure lowering effects of two doses of telmisartan were assessed in 76 hypertensive, largely overweight patients aged 6 to < 18 years (body weight ≥ 20 kg and ≤ 120 kg, mean 74.6 kg), after taking telmisartan 1 mg/kg (n = 29 treated) or 2 mg/kg (n = 31 treated) over a four-week treatment period. By inclusion the presence of secondary hypertension was not investigated. In some of the investigated patients the doses used were higher than those recommended in the treatment of hypertension in the adult population, reaching a daily dose comparable to 160 mg, which was tested in adults. After adjustment for age group effects mean SBP changes from baseline (primary objective) were -14.5 (1.7) mm Hg in the telmisartan 2 mg/kg group, -9.7 (1.7) mm Hg in the telmisartan 1 mg/kg group, and -6.0 (2.4) in the placebo group. The adjusted DBP changes from baseline were -8.4 (1.5) mm Hg, -4.5 (1.6) mm Hg and -3.5 (2.1) mm Hg respectively. The change was dose dependent. The reported safety data from this study in patients aged 6 to < 18 years appeared generally similar to that observed in adults. The safety of long term treatment of telmisartan in children and adolescents was not evaluated.

An increase in eosinophils reported in this patient population has not been recorded in adults. Its clinical significance and relevance is unknown.

These clinical data do not allow to make conclusions on the efficacy and safety of telmisartan in hypertensive paediatric population.

5.3 Pharmacokinetic properties

Chlorthalidone

Absorption and plasma concentration

The bioavailability of an oral dose of 50mg Chlorthalidone 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 chlorthalidone 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 chlorthalidone in whole blood was found in plasma at steady state during treatment with 50mg doses. In vitro, plasma protein binding of chlorthalidone is about 76% and the major binding protein is albumin.

Chlorthalidone crosses the placental barrier and passes into the breast milk. In mothers treated with 50mg chlorthalidone daily before and after delivery, chlorthalidone levels in fetal whole blood are about 15% of those found in maternal blood. Chlorthalidone 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

Chlorthalidone 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 chlorthalidone is excreted by the kidneys, with a mean renal clearance of 60ml/min.

Special patient groups

Renal dysfunction does not alter the pharmacokinetics of chlorthalidone, 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 chlorthalidone 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 chlorthalidone.

Amlodipine

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 reported 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

Reported 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.

Telmisartan

Absorption

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve ($AUC_{0-\infty}$) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

Linearity/non-linearity

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C_{max} and to a lesser extent AUC increase disproportionately at doses above 40 mg.

Distribution

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V_{dss}) is approximately 500 l.

Biotransformation

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate.

Elimination

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The maximum plasma concentration (C_{max}) and, to a smaller extent, the area under the plasma concentration-time curve (AUC), increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Plasma concentrations were higher in females than in males, without relevant influence on efficacy.

After oral (and intravenous) administration, telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound. Cumulative urinary excretion is <1 % of dose. Total plasma clearance (Cl_{tot}) is high (approximately 1,000 ml/min) compared with hepatic blood flow (about 1,500 ml/min).

Paediatric population

The pharmacokinetics of two doses of telmisartan were assessed as a secondary objective in hypertensive patients (n = 57) aged 6 to < 18 years after taking telmisartan 1 mg/kg or 2 mg/kg over a four-week treatment period. Pharmacokinetic objectives included the determination of the steady-state of telmisartan in children and adolescents, and investigation of age related differences. Although the study was too small for a meaningful assessment of the pharmacokinetics of children under 12 years of age, the results are generally consistent with the findings in adults and confirm the non-linearity of telmisartan, particularly for C_{max}.

Gender

Differences in plasma concentrations were observed, with C_{max} and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

Elderly

The pharmacokinetics of telmisartan do not differ between the elderly and those younger than 65 years.

Renal impairment

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations was observed. However, lower plasma concentrations were observed in patients with renal insufficiency undergoing dialysis. Telmisartan is highly bound to plasma protein in renal-insufficient patients and cannot be removed by dialysis. The elimination half-life is not changed in patients with renal impairment.

Hepatic impairment

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability up to nearly 100 %. The elimination half-life is not changed in patients with hepatic impairment.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Chlorthalidone

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of Product Characteristics.

Amlodipine

Reproductive toxicology

Reported 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 reported 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.

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

*Based on patient weight of 50 kg

Telmisartan

In reported preclinical safety studies, doses producing exposure comparable to that in the clinical therapeutic range caused reduced red cell parameters (erythrocytes, haemoglobin, haematocrit), changes in renal haemodynamics (increased blood urea nitrogen and creatinine), as well as increased serum potassium in normotensive animals. In dogs, renal

tubular dilation and atrophy were observed. Gastric mucosal injury (erosion, ulcers or inflammation) also was noted in rats and dogs. These pharmacologically-mediated undesirable effects, known from preclinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, were prevented by oral saline supplementation.

In both species, increased plasma renin activity and hypertrophy/hyperplasia of the renal juxtaglomerular cells were observed. These changes, also a class effect of angiotensin converting enzyme inhibitors and other angiotensin II receptor antagonists, do not appear to have clinical significance.

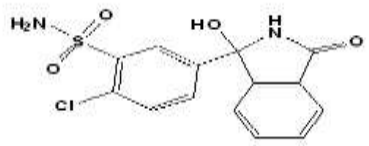
No clear evidence of a teratogenic effect was observed, however at toxic dose levels of telmisartan an effect on the postnatal development of the off springs such as lower body weight and delayed eye opening was observed.

There was no evidence of mutagenicity and relevant clastogenic activity in eported *in vitro* studies and no evidence of carcinogenicity in rats and mice.

7. Description

Chlorthalidone

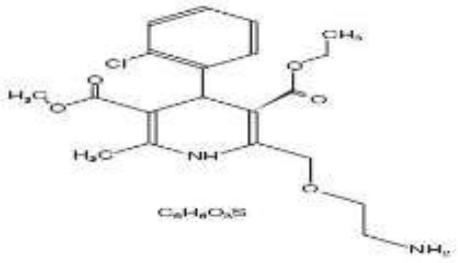
Chlorthalidone is chemically described as (RS)-2-chloro-5-(1-hydroxy-3-oxoisoindolin-1-yl) benzenesulphonamide. Its empirical formula is $C_{14}H_{11}ClN_2O_4S$ with a molecular weight of 338.76. The structural formula for chlorthalidone is:



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.

Amlodipine Besilate

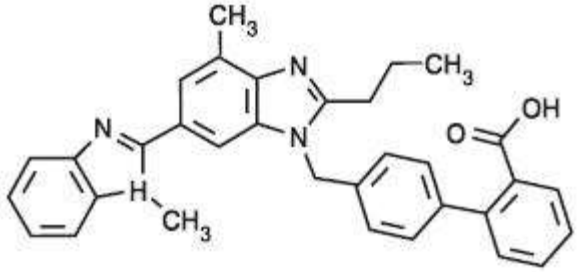
Amlodipine Besilate is chemically described as 3-Ethyl-5-methyl (±)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzene-sulphonate. Its molecular formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$, and its structural formula is:



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.

Telmisartan

Telmisartan is chemically described as 4'-{[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and its structural formula is:



Telmisartan is a white to off-white crystalline powder. It is sparingly soluble in dichloromethane; slightly soluble in methanol; practically insoluble in water.

TRITELSAR 40

Chlorthalidone, Amlodipine and Telmisartan Tablets are Brick red coloured, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Red.

TRITELSAR 40 HS

Chlorthalidone, Amlodipine and Telmisartan Tablets are pale yellow coloured, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Yellow.

TRITELSAR 80

Chlorthalidone, Amlodipine and Telmisartan Tablets are White circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000 & Castor Oil.

TRITELSAR 80 HS

Chlorthalidone, Amlodipine and Telmisartan Tablets are pale yellow coloured, circular shaped, slightly biconvex, film coated tablets having plain on both sides. The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Ferric Oxide Yellow & Castor Oil.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not Available

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

TRITELSAR is available in strip of 10 Tablets.

8.4 Storage and handing instructions

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

Keep all medicines out of reach of children

9. Patient Counselling Information

Package leaflet: Information for the user

TRITELSAR

Chlorthalidone, Telmisartan and Amlodipine

Read all of this leaflet carefully before you start taking this medicine because it Contains important information for you.

- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What TRITELSAR is and what it is used for

9.2 What you need to know before you take TRITELSAR

9.3 How to take TRITELSAR

9.4 Possible side effects

9.5 How to store TRITELSAR

9.6 Contents of the pack and other information

9.1 What TRITELSAR is and what it is used for

TRITELSAR is combination of Telmisartan, Amlodipine and Chlorthalidone Telmisartan belongs to a class of medicines known as angiotensin II receptor antagonists. Angiotensin II is a substance produced in your body which causes your blood vessels to narrow, thus increasing your blood pressure. Telmisartan blocks the effect of angiotensin II so that the blood vessels relax, and your blood pressure is lowered. Amlodipine belongs to a group of medicines called calcium antagonists. Chlorthalidone belongs to a group of medicines called thiazide diuretics. Thiazide diuretics help to reduce the amount of water in your body. They do this by increasing the amount of water that you pass as urine. They are sometimes called 'water tablets'.

TRITELSAR is used for treatment of essential hypertension in adults.

9.2 What you need to know before you take TRITELSAR

Do not take TRITELSAR

- If you are allergic to Telmisartan, Amlodipine and Chlorthalidone or any other ingredients of this medicine.

- If you are more than 3 months pregnant. (It is also better to avoid TRITELSAR in early pregnancy
- if you have severe liver problems such as cholestasis or biliary obstruction (problems with
- Drainage of the bile from the liver and gall bladder) or any other severe liver disease.
- If you have severe low blood pressure (hypotension).
- If you have narrowing of the aortic heart valve (aortic stenosis) or cardiogenic shock (a condition where your heart is unable to supply enough blood to the body).
- If you suffer from heart failure after a heart attack.
- if you have diabetes or impaired kidney function and you are treated with a blood pressure lowering medicine containing aliskiren.

  If any of the above applies to you, tell your doctor or pharmacist before taking TRITELSAR.

  If you are not passing any urine at all
- 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.

Warnings and precautions

Talk to your doctor before taking TRITELSAR if you are suffering or have ever suffered from any of the following conditions or illnesses:

- Kidney disease or kidney transplant.
- Renal artery stenosis (narrowing of the blood vessels to one or both kidneys).
- Liver disease.
- Heart trouble.
- Raised aldosterone levels (water and salt retention in the body along with imbalance of various blood minerals).
- Low blood pressure (hypotension), likely to occur if you are dehydrated (excessive loss of body water) or have salt deficiency due to diuretic therapy ('water tablets'), low-salt diet, diarrhoea, or vomiting.
- Elevated potassium levels in your blood.
- Diabetes.

Talk to your doctor before taking TRITELSAR:

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. See also information under the heading "Do not take TRITELSAR".

- If you are taking digoxin.
- 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.

You must tell your doctor if you think you are (or might become) pregnant. TRITELSAR 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.

In case of surgery or anaesthesia, you should tell your doctor that you are taking TRITELSAR.

TRITELSAR may be less effective in lowering the blood pressure in black patients.

Other medicines and TRITELSAR

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other Medicines. Your doctor may need to change the dose of these other medicines or take other Precautions. In some cases, you may have to stop taking one of the medicines. This applies especially to the medicines listed below taken at the same time with TRITELSAR:

- Lithium containing medicines to treat some types of depression.
- Medicines that may increase blood potassium levels such as salt substitutes containing potassium, potassium-sparing diuretics (certain 'water tablets'), ACE inhibitors, angiotensin II receptor antagonists, NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen), heparin, immunosuppressives (e.g. cyclosporin or tacrolimus), and the antibiotic
- Trimethoprim.
- Diuretics ('water tablets'), especially if taken in high doses together with TRITELSAR, may lead to excessive loss of body water and low blood pressure (hypotension).
- ketoconazole, itraconazole (anti-fungal medicines)
- Ritonavir, indinavir, nelfinavir (so called protease inhibitors used to treat HIV)
- Rifampicin, erythromycin, clarithromycin (antibiotics)
- Hypericum perforatum (St. John's Wort)

- Verapamil, diltiazem (heart medicines)
- Dantrolene (infusion for severe body temperature abnormalities)
- Tacrolimus, sirolimus, temsirolimus, and everolimus (medicines used to alter the way your immune system works)
- Simvastatin (cholesterol lowering medicine)
- Cyclosporine (an immunosuppressant) ACE inhibitors (for example, lisinopril)
- beta blockers (for example propranolol hydrochloride)
- methyldopa
- vasodilators (for example bosentan)
- calcium channel blockers (for example amlodipine)
- guanethidine
- adrenocorticotropic hormone (ACTH) - used to treat a number of different conditions, including ulcerative colitis, Crohn's disease and rheumatoid arthritis
- 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

The effect of TRITELSAR may be reduced when you take NSAIDs (non-steroidal anti-inflammatory medicines, e.g. aspirin or ibuprofen) or corticosteroids.

TRITELSAR may increase the blood pressure lowering effect of other medicines used to treat high blood pressure or of medicines with blood pressure lowering potential (e.g. baclofen, amifostine).

Furthermore, low blood pressure may be aggravated by alcohol, barbiturates, narcotics or Antidepressants. You may notice this as dizziness when standing up. You should consult with your doctor if you need to adjust the dose of your other medicine while taking TRITELSAR.

TRITELSAR with food and drink

Grapefruit juice and grapefruit should not be consumed by people who are taking **Amlodipine**. This is because grapefruit and grapefruit juice can lead to an increase in the blood levels of the active ingredient amlodipine, which can cause an unpredictable increase in the blood pressure lowering effect of TRITELSAR.

Pregnancy and breast-feeding

Pregnancy

Do not take TRITELSAR if you are pregnant or trying to become pregnant. Do not take TRITELSAR if you are breast-feeding because TRITELSAR passes into breast milk and could harm your baby. Ask your doctor or pharmacist for advice before taking any medicine..

Driving and using machines

Some people feel dizzy or tired when taking TRITELSAR. If you feel dizzy or tired, do not drive or operate machinery.

9.3 How to take TRITELSAR

Always take this medicine exactly as your doctor has told you. 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.

Dose: As directed by Physician

If you take more TRITELSAR than you should

If you accidentally take too many tablets, contact your doctor, pharmacist, or your nearest hospital emergency department immediately.

If you forget to take TRITELSAR

Do not worry. If you forget to take a tablet, leave out that dose completely. Take your next dose at the right time. Do not take a double dose to make up for a forgotten dose

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

If you stop taking TRITELSAR

Your doctor will advise you how long to take this medicine. Your condition may return if you stop using this medicine before you are advised.

If you have any further questions on the use of this medicine, ask your doctor or

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious and need immediate medical attention

You should see your doctor immediately if you experience any of the following symptoms:

Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatoryresponse), rapid swelling of the skin and mucosa (angioedema); these side effects are rare (may affect up to 1 in 1,000 people) but are extremely serious and patients should stop taking the medicine and see their doctor immediately. If these effects are not treated they could be fatal. Visit your doctor **immediately** if you experience any of the following side effects after taking this medicine.

- Sudden wheeziness, chest pain, shortness of breath or difficulty in breathing
- Swelling of eyelids, face or lips
- Swelling of the tongue and throat which causes great difficulty breathing
- Severe skin reactions including intense skin rash, hives, reddening of the skin over your whole body, severe itching, blistering, peeling and swelling of the skin, inflammation of mucous membranes (Stevens Johnson Syndrome, toxic epidermal necrolysis) or other allergic reactions
- Heart attack, abnormal heart beat
- Inflamed pancreas which may cause severe abdominal and back pain accompanied with feeling very unwell
- muscles feel weak or will not work properly
- irregular heartbeat.

Possible side effects of TRITELSAR

Very common: may affect more than 1 in 10 people

- Oedema (fluid retention)
- low blood levels of potassium which can cause muscle weakness, muscle twitching or abnormal heartbeat
- increased blood levels of uric acid
- increased blood levels of cholesterol.

Common side effects (may affect up to 1 in 10 people):

- Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.
- 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
- Dizziness
- loss of appetite
- upset stomach
- impotence in men.

Uncommon side effects (may affect up to 1 in 100 people):

- Urinary tract infections,
- upper respiratory tract infections (e.g. sore throat, inflamed sinuses, common cold), deficiency in red blood cells (anaemia),

- high potassium levels,
- difficulty falling asleep,
- feeling sad (depression),
- fainting (syncope),
- feeling of spinning (vertigo),
- slow heart rate (bradycardia),
- low blood pressure (hypotension) in users treated for high blood pressure,
- dizziness on standing up (orthostatic hypotension),
- shortness of breath, cough,
- abdominal pain, diarrhoea,
- discomfort in the abdomen, bloating,
- vomiting, itching,
- increased sweating,
- drug rash, back pain, muscle cramps, muscle pain (myalgia),
- kidney impairment including acute kidney failure,
- pain in the chest, feeling of weakness and increased level of creatinine in the blood.
- Ringing in the ears
- Sneezing/running nose caused by inflammation of the lining of the nose (rhinitis)
- Cough
- Dry mouth, vomiting (being sick)
- Hair loss, increased sweating, itchy skin, red patches on skin, skin discoloration
- Disorder in passing urine, increased need to urinate at night, increased number of times of passing urine
- Inability to obtain an erection, discomfort or enlargement of the breasts in men
- Weight increase or decrease
- gout which causes pain and swelling in the joints.

Rare side effects (may affect up to 1 in 1,000 people):

- Sepsis* (often called "blood poisoning", is a severe infection with whole-body inflammatory response which can lead to death),
- low platelet count (thrombocytopenia),
- severe allergic reaction (anaphylactic reaction),
- allergic reaction (e.g. rash, itching, difficulty breathing,
- wheezing,
- swelling of the face or low blood pressure),
- Swelling of the gums

- low blood sugar levels (in diabetic patients),
- feeling anxious,
- somnolence,
- impaired vision,
- fast heart beat (tachycardia),dry mouth,
- upset stomach,
- taste disturbance (dysgeusia),
- abnormal liver function (Japanese patients are more likely to experience this side effect), rapid swelling of the skin and mucosa which can also lead to death (angioedema also with fatal outcome),
- eczema (a skin disorder), redness of skin, hives (urticaria),
- severe drug rash, joint pain (arthralgia),
- pain in extremity,
- tendon pain,
- flulike-illness,
- decreased haemoglobin (a blood protein),
- increased levels of uric acid,
- increased hepatic enzymes or creatine phosphokinase in the blood.
- Inflammation of blood vessels, often with skin rash
- Confusion
- 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
- breathing problems
- Problems with your kidneys.

Very rare side effects (may affect up to 1 in 10,000 people):

Progressive scarring of lung tissue (interstitial lung disease) **.

- Excess sugar in blood (hyperglycemia)
- A disorder of the nerves which can cause muscular weakness, tingling or numbness
- Swelling of the gums
- Abdominal bloating (gastritis)
- Abnormal liver function, inflammation of the liver (hepatitis), yellowing of the skin (jaundice), liver enzyme increase which may have an effect on some medical tests
- Increased muscle tension
- Inflammation of blood vessels, often with skin rash
- Sensitivity to light
- Disorders combining rigidity, tremor, and/or movement disorders
- 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.

* The event may have happened by chance or could be related to a mechanism currently not known.

** Cases of progressive scarring of lung tissue have been reported during intake of TRITELSAR.

However, it is not known whether TRITELSAR was the cause.

9.5 How to store TRITELSAR

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

Keep all medicines out of reach of children

9.6 Contents of the pack and other information

What TRITELSAR contains

The active substance is Telmisartan and Amlodipine and Chlorthalidone.

TRITELSAR 40

Chlorthalidone…6.25mg, Amlodipine….5mg and Telmisartan….40mg

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Red.

TRITELSAR 40 HS

Chlorthalidone…12.5mg, Amlodipine….5mg and Telmisartan….40mg

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC

E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Castor Oil & Ferric Oxide Yellow.

TRITELSAR 80

Chlorthalidone…6.25mg, Amlodipine….5mg and Telmisartan….80mg.

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000 & Castor Oil.

TRITELSAR 80 HS

Chlorthalidone…12.5mg, Amlodipine….5mg and Telmisartan….80mg

The excipients used are Starch, Microcrystalline Cellulose, PVP K30, Isopropyl Alcohol, Aerosil, Sodium Starch Glycolate, Croscarmellose sodium, Magnesium Stearate, HPMC E15, Methylene chloride, Talc, Titanium Dioxide, PEG 6000, Ferric Oxide Yellow & Castor Oil.

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/ TRITELSAR 6.25/12.5/6.25/12.5,5,40/40/80/80mg/May -20/01/PI