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

TELSAR A

1. Generic Name

Telmisartan and Amlodipine Tablets I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TELSAR A

Each uncoated bilayered tablet

Contains: Telmisartan I.P. ……. 40 mg

Amlodipine Besilate I.P

Equivalent to Amlodipine …….. 5 mg

Colour: Red Oxide of Iron

The excipients used are Mannitol, SODIUM HYDROXIDE, MEGLUMINE, POLYVINYL PYRROLIDONE (K-30), MAGNESIUM STEARATE, SODIUM STEARYL FUMARATE, FERRIC OXIDE RED.

TELSAR A 80

Each uncoated bilayered tablet Contains:

Telmisartan I.P. ……..…. 80 mg

Amlodipine Besilate I.P

Equivalent to Amlodipine …..…. 5 mg

Excipients……..…….q.s.

Colour: Ferric Oxide USP-NF Yellow

The other ingredients are Lactose, Starch, Light Magnesium Oxide, Croscarmellose Sodium, Polyvinyl Pyrrolidone, Ferric Oxide Yellow, Isopropyl Alchol, Colloidal Silicon Dioxide, Crospovidone and Magnesium Stearate.

3. Dosage form and strength

Dosage Form: Uncoated Bilayered Tablet

Strength: Telmisartan 40/80 mg and Amlodipine 5 mg.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indication

TELSAR A is indicated for the treatment of essential hypertension.

4.2. Posology and Method of Administration

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 foetus.

4.3. Contraindication

Dose: As directed by the physician

Method of administration: Tablet for oral administration.

4.4. Contraindications

- Hypersensitivity to the active substance, dihydropyridine derivatives, amlodipine or to any of the excipients
- Second and third trimesters of pregnancy
- Biliary obstructive disorders
- Severe hepatic impairment
- 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.
- The concomitant use of Telmisartan with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m2)

4.5. Special Warnings and Precautions for Use

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.

Hepatic impairment

Telmisartan is not to be given to patients with cholestasis, biliary obstructive disorders or severe hepatic impairment 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 reported 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.

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.

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.

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 reported 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 dialyzable.

4.6. Drugs Interactions

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. 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 reported study, the co-administration of telmisartan and ramipril led to an increase of up to 2.5 fold in the AUC0-24 and Cmax 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.

Reported 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.

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.

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

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

Telmisartan

Pregnancy

WARNING: FETAL TOXICITY

When pregnancy is detected, discontinue the product as soon as possible.

Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing foetus.

There are no adequate data from the use of Telmisartan in pregnant women. Reported studies in animals have shown reproductive toxicity.

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 reported, 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.

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

Amlodipine

Pregnancy

The safety of amlodipine in human pregnancy has not been established. In reported 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. Reported clinical data are insufficient regarding the potential effect of amlodipine on fertility. In one reported rat study, adverse effects were found on male fertility

4.8. Effects on Ability to Drive and Use Machines

Telmisartan

When driving vehicles or operating machinery it should be taken into account that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy. If patients suffer from dizziness, headache, fatigue or nausea, the ability to react may be impaired. Caution is recommended especially at the start of treatment.

Undesirable Effects

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

The overall incidence of adverse reactions reported was usually comparable to placebo (41.4 % vs 43.9 %) in reported 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 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 reported controlled clinical trials in patients treated for hypertension and from post-marketing reports.

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.

System organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Uncommon	Anaemia
	Rare	Eosinophilia, thrombocytopenia
	Very rare	Leukocytopenia
Immune system disorders	Rare	Anaphylactic reaction, hypersensitivity
	Very rare	Allergic reactions
Metabolism and nutrition disorders	Uncommon	Hyperkalaemia
	Rare	Hyperglycaemia (in diabetic patients)
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, Vertigo
Cardiac disorders	Common	Palpitations
	Uncommon	Arrhythmia (including bradycardia, ventricular tachycardia and atrial fibrillation)
	Very rare	Myocardial infarction
Vascular disorders	Common	Flushing
	Uncommon	Hypotension[2], orthostatic hypotension
	Very rare	Vasculitis
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	Uncommon	Cough, rhinitis
	Very rare	Interstitial lung disease[4]
Gastrointestinal disorders	Common	Abdominal pain, nausea, dyspepsia, flatulence, altered bowel habits (including diarrhoea and constipation)
	Uncommon	Vomiting, dry mouth
	Rare	Stomach discomfort, dysgeusia
	Very rare	Pancreatitis, gastritis, gingival hyperplasia
Hepatobiliary disorders	Rare	Hepatic function abnormal/liver disorder[3]
	Very rare	Hepatitis, jaundice, hepatic enzyme increased*
Skin and subcutaneous tissue disorders	Uncommon	Alopecia, purpura, skin discolouration, hyperhidrosis, pruritus, rash, exanthema, urticaria

	Rare	Angioedema (also with fatal outcome), eczema, erythema, urticaria, drug eruption, toxic skin eruption
	Very rare	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	Uncommon	Arthralgia, myalgia, back pain (e.g. sciatica), pain in extremity, tendon pain (tendinitis like symptoms)
Renal and urinary disorders	Uncommon	Micturition disorder, nocturia, increased urinary frequency, renal impairment including acute renal failure
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
	Rare	Influenza-like illness
Investigations	Uncommon	Weight increased, weight decreased, blood creatinine increased
	Rare	Haemoglobin decreased, blood uric acid increased, hepatic enzyme increased, 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 reported 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

As per reported data, 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

As per reported data, 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

As per reported data, 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.

*mostly consistent with cholestasis

Exceptional cases of extrapyramidal syndrome have been reported.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9. Overdose

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.

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.

5. Pharmacological properties

5.1. Mechanism of Action

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.

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.

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.

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.

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).

5.2. Pharmacodynamic Properties

Telmisartan

Pharmacotherapeutic group: Angiotensin II Antagonists, plain, ATC Code: C09CA07.

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 agent's representative

of other classes of antihypertensive medicinal products (demonstrated in reported 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 reported clinical trials directly comparing the two antihypertensive treatments.

Cardiovascular prevention

ONTARGET (ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial), a reported clinical trial, 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 reported reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

TRANSCEND, a reported trial, 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 reported "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 reported 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 reported 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 reported 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 reported 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.

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

Amlodipine

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

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

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

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

Use in patients with coronary artery disease (CAD)

The effectiveness of amlodipine in preventing clinical events in patients with coronary artery disease (CAD) has been evaluated in a reported 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.

A 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 reported 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 reported 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 reported 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.

5.3. Pharmacokinetic Properties

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

As per reported data, 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

Reported 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.

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. 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 reported 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

As per reported data, a population PK study has been conducted in 74 hypertensive children aged from 1 to 17 years (with 34 patients aged 6 to 12 years and 28 patients aged 13 to 17 years) receiving amlodipine between 1.25 and 20 mg given either once or twice daily. In children 6 to 12 years and in adolescents 13-17 years of age the typical oral clearance (CL/F) was 22.5 and 27.4 L/hr respectively in males and 16.4 and 21.3 L/hr respectively in females. Large variability in exposure between individuals was observed. Data reported in children below 6 years is limited.

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology 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 offsprings such as lower body weight and delayed eye opening was observed.

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

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.

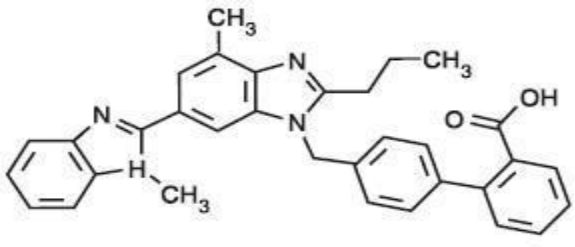
Reported mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

*Based on patient weight of 50 kg

7. DESCRIPTION

Telmisartan

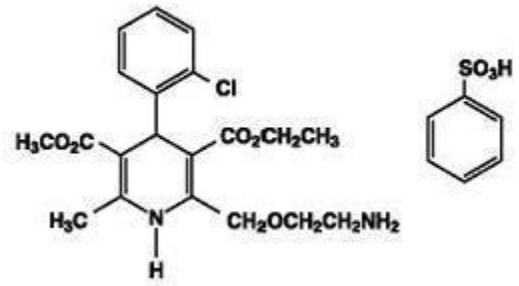
Telmisartan is chemically described as 4'-{[4-methyl-6-(1-methyl-1H-benzimidazol-2-yl)- 2-propyl-1H-benzimidazol-1-yl]methyl}-2-biphenyl-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$, its molecular weight is 514.63, and its structural formula is:



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

Amlodipine

Amlodipine is a besilate salt of amlodipine, a dihydropyridine calcium-channel blocker (CCB). It is freely soluble in methanol; sparingly soluble in ethanol (95%); slightly soluble in 2-propanol and in water. Amlodipine besylate's chemical name is 3-Ethyl-5-methyl (4RS)-2-[(2-aminoethoxy) methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulphonate. Its empirical formula is $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$ and molecular weight is 567.1 and its structural formula is:



TELSAR A

Telmisartan and amlodipine tablet is capsule shaped, biconvex, uncoated, bilayered tablets with plain surface on both sides having white to off white coloured layer that may contain light pink coloured specks on one side and light pink coloured layer with white to off white specks on other side. The excipients used are Mannitol, SODIUM HYDROXIDE, MEGLUMINE, POLYVINYL PYRROLIDONE (K-30), MAGNESIUM STEARATE, SODIUM STEARYL FUMARATE, FERRIC OXIDE RED.

TELSAR A 80

Telmisartan and amlodipine tablet is bilayered, capsule shaped biconvex uncoated tablet one layer with white to off white colour and other layer with light yellow to yellow colour. The excipients used are Lactose, Starch, Light Magnesium Oxide, Croscarmellose Sodium, Polyvinyl Pyrrolidone, Ferric Oxide Yellow, Isopropyl Alchol, Colloidal Silicon Dioxide, Crospovidone and Magnesium Stearate.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

Not Available

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

TELSAR A is available in Strips of 15 tablets.

8.4. Storage and Handing Instructions

TELSAR A

Store at a temperature not exceeding 30°C, protected from light and moisture.

Keep out of reach of children.

TELSAR A 80

Store protected from light and moisture. At a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

TELSAR A

Telmisartan and Amlodipine

Read all of this leaflet carefully before you start using 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. See section 9.4.

What is in this leaflet?

9.1 What TELSAR A is and what it is used for

TELSAR A Is combination of Telmisartan and Amlodipine. 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.

TELSAR A is used to for the treatment of essential hypertension.

9.2 What you need to know before you take TELSAR A Do not take TELSAR A

- If you are allergic to TELSAR A or any other ingredients of this medicine
- If you are more than 3 months pregnant. (It is also better to avoid TELSAR A 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 TELSAR A.

Warnings and precautions

Talk to your doctor before taking TELSAR A 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 TELSAR A:

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 TELSAR A".

If you are taking digoxin.

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

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

Other medicines and TELSAR A

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 TELSAR A:

- 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 orIbuprofen), heparin, immunosuppressive (e.g. cyclosporin or tacrolimus), and the antibiotic Trimethoprim.
- Diuretics ('water tablets'), especially if taken in high doses together with TELSAR A, may lead to excessive loss of body water and low blood pressure (hypotension).
- If you are taking an ACE-inhibitor or aliskiren (see also information under the headings "Do not take TELSAR A" and "Warnings and precautions").
- Digoxin.
- 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)

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

TELSAR A 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 TELSAR A.

TELSAR A 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 TELSAR A.

Pregnancy and breast-feeding

Pregnancy

You must tell your doctor if you think you are (or might become) pregnant. Your doctor will normally advise you to stop taking TELSAR A before you become pregnant or as soon as you know you are pregnant and will advise you to take another medicine instead of TELSAR A. TELSAR A is not recommended in pregnancy, and must not be taken without consultation of doctor..

Breast-feeding

Tell your doctor if you are breast-feeding or about to start breast-feeding. TELSAR A is not recommended for mothers who are breast-feeding and your doctor may choose another treatment for you if you wish to breast-feed, especially if your baby is new-born, or was born prematurely.

Driving and using machines

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

9.3 How to take TELSAR A

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You can take TELSAR A with or without food. The tablets should be swallowed with some water or other non-alcoholic drink. It is important that you take TELSAR A every day until your doctor tells you otherwise. If you have the impression that the effect of TELSAR A is too strong or too weak, talk to your doctor or pharmacist.

Dose: As directed by Physician

If you take more TELSAR A 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 TELSAR A

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 stop taking TELSAR A

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 pharmacist.

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 inflammatory Response), 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

Possible side effects of TELSAR A

Very common: may affect more than 1 in 10 people

Oedema (fluid retention)

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

Low blood pressure (hypotension) in users treated for reduction of cardiovascular events.

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

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

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

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 TELSAR A.

However, it is not known whether TELSAR A was the cause.

9.5 How to store

TELSAR A

Store at a temperature not exceeding 30°C, protected from light and moisture.

TELSAR A 80

Store protected from light and moisture. At a temperature not exceeding 30°C.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this

medicine.

9.6 Contents of the pack and other information What TELSAR A contains

The active substance are Telmisartan and Amlodipine.

Each tablet contains 40/80 mg Telmisartan and Amlodipine 5 mg.

TELSAR A

The other ingredients The excipients used are Mannitol, SODIUM HYDROXIDE, MEGLUMINE, POLYVINYL PYRROLIDONE (K-30), MAGNESIUM STEARATE, SODIUM STEARYL FUMARATE, FERRIC OXIDE RED.

TELSAR A 80

The other ingredients are Lactose, Starch, Light Magnesium Oxide, Croscarmellose Sodium, Polyvinyl Pyrrolidone, Ferric Oxide Yellow, Isopropyl Alchol, Colloidal Silicon Dioxide, Crospovidone and Magnesium Stearate.

10. DETAILS OF MANUFACTURER

TELSAR A

Manufactured by:

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East
District, Gangtok. Sikkim-737 135.

OR

Manufactured in India by:

Ravenbhel Biotech

EPIP, SIDCO, Kartholi

Bari Brahmana, Jammu-181133

TELSAR A 80

Manufactured in India by:

Hetero Labs Limited (Unit – II)

Village Kalyanpur, Chakkan Road, Baddi,

Tehsil, Solan Distt. Himachal Pradesh 173205.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

TELSAR A

Mfg Licence No.: M/563/2010 issued on 13.03.2019

OR

Mfg Licence No.: JK/01/11-12/192 issued on 25.05.2018.

TELSAR A 80

Mfg Licence No.: MNB/09/780 issued on 03.07.2018.

12. DATE OF REVISION

July 2022

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ TELSAR A 40, 80mg JUL-22/02/PI